CLINICAL STUDY PROTOCOL
Protocol CDI-CS-002

BAL101553

An open-label Phase 1/2a study of oral BAL101553 in adult patients with advanced solid tumors and in adult patients with recurrent or progressive glioblastoma or high-grade glioma

PROTOCOL APPROVAL	
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Function:	**Name:**
Project Physician:	Thomas Kaindl, MD
Clinical Pharmacologist:	[redacted]
Project Statistician:	[redacted]
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

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Protocol Number/Version:	CDI-CS-002 / Version 11.0
Study title:	An open-label Phase 1/2a study of oral BAL101553 in adult patients with advanced solid tumors and in adult patients with recurrent or progressive glioblastoma or high-grade glioma
Compound:	BAL101553
Phase of development:	Phase 1/2a
Date:	1 July 2021
Project Physician:	Thomas Kaindl, MD
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

Name/Title	**Date**	**Signature**
Thomas Kaindl, MD Project Physician	2 JUL 2021	Thomas Kaindl

[redacted]

Protocol Synopsis

TITLE	An open-label Phase 1/2a study of oral BAL101553 in adult patients with advanced solid tumors and in adult patients with recurrent or progressive glioblastoma or high-grade glioma.
SPONSOR	Basilea Pharmaceutica International Ltd, Switzerland
STUDY PHASE	Phase 1/2a
OBJECTIVES	**Phase 1 dose escalation portion** ***Primary objectives*** To determine the maximum tolerated dose (MTD) and to characterize dose-limiting toxicities (DLTs) of daily oral BAL101553, administered to adults with advanced or recurrent solid tumors who have failed standard therapy, or for whom no effective standard therapy is available, and to patients with recurrent or progressive glioblastoma (GBM) or high-grade glioma. ***Secondary objectives*** • To evaluate the safety and tolerability of daily oral BAL101553. • To evaluate BAL101553 and BAL27862 pharmacokinetics (PK). • To assess the anti-tumor activity of daily oral BAL101553 in cancer patients. **Phase 2a dose expansion portion (Simon's two-stage design)** ***Primary objective*** To determine the efficacy of daily oral BAL101553 in patients with recurrent GBM whose tumor tissue is positive for end-binding protein 1 (EB1) based on immunohistochemistry (IHC) based on the objective response rate as per RANO criteria. A tissue-screening program adhering to local standards in selected countries will be established to support the identification of potential patients. ***Secondary objectives*** • To evaluate the efficacy of BAL101553 based on overall survival (OS), progression-free survival (PFS) and the proportion of patients with PFS at 6 months after start of study drug treatment (PFS6). • To evaluate the safety and tolerability of daily oral BAL101553. • To evaluate BAL101553 and BAL27862 pharmacokinetics (PK). **Phase 2a dose expansion portion (Surgical cohort)** If futility is rejected in Stage 1 of the Simon's two-stage study portion, a parallel cohort will be initiated in up to 6 patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862. Details of this Surgical cohort will be provided in a separate protocol amendment. ***Exploratory objectives (Phase 1 and Phase 2a portions)*** • To assess the use of biomarkers to characterize pharmacodynamic effects of daily oral BAL101553. • To explore the potential utility of biomarkers in blood and/or tumor tissue as predictive biomarkers.

STUDY DESIGN	Single-agent, open-label, Phase 1/2a study in two parts: 1) Phase 1 dose escalation portion – an accelerated 3+3 titration design will be used to determine the respective MTDs in patients with: a. advanced or recurrent solid tumors b. recurrent or progressive GBM or high-grade glioma 2) Phase 2a expansion portion (Simon's two-stage design) – to obtain efficacy data in patients with recurrent GBM whose tumor tissue is positive for EB1, and to further characterize the safety and tolerability of BAL101553 at the recommended Phase 2 dose (RP2D). A single-arm Simon's two-stage design will be used. The null hypothesis that the true objective response rate is 14% in patients with measurable disease at baseline will be tested against a one-sided alternative. In the first stage, 9 evaluable patients will be accrued. If there are 1 or fewer responses in these 9 evaluable patients, the study will be stopped. Otherwise, 10 additional evaluable patients will be accrued for a total of 19. The null hypothesis will be rejected if 6 or more responses are observed in 19 patients. This design yields a type I error rate of 3.7% and power of 81% when the true response rate is 40%. Patients with non-measurable disease at baseline will only contribute to the assessment of secondary endpoints. Phase 2a expansion portion (Surgical cohort) – will be performed as a single-arm study if futility is rejected in Stage 1 of the Simon's two-stage study portion, and includes 6 patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862. Details of this Surgical cohort will be provided in a separate protocol amendment. Note: For changes to patient-related study procedures in response to the COVID-19 pandemic, see Section 5.2.
PLANNED NUMBER OF PATIENTS	• Phase 1 dose escalation portion (enrollment completed): 26 patients with advanced or recurrent solid tumors and 28 patients with recurrent or progressive GBM or high-grade glioma. • Phase 2a expansion portion (Simon's two-stage design): Up to 34 evaluable patients with recurrent GBM whose tumor tissue is positive for EB1. This includes up to 19 patients with measurable disease and up to 15 patients with non-measurable disease at baseline. • Phase 2a expansion portion (Surgical cohort): 6 evaluable patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862.
NUMBER OF CENTERS/LOCATIONS	• Phase 1 dose escalation portion (enrollment completed): 2 – 6 study centers in the UK • Phase 2a dose expansion portion (Simon's two-stage design): Up to 20 study centers in the UK, Switzerland, Germany, and potentially other countries • Phase 2a dose expansion portion (Surgical cohort): Up to 20 study centers in the UK, Switzerland, and potentially other countries
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 28 days prior to the start of treatment. Screening evaluations will be performed within 15 days prior to start of treatment.

INCLUSION CRITERIA (cont.)

1. Age 18 years or older.
2. Patients who have in the:
   <u>Phase 1</u> dose escalation portion either of the following:
   a. a histologically- or cytologically-confirmed advanced or recurrent solid tumor, who failed standard therapy, or for whom no effective standard therapy is available to them.*
   b. histologically-confirmed GBM or high-grade glioma, with progressive or recurrent disease after prior radiotherapy, with or without chemotherapy. This will also include patients with histologically-confirmed low-grade glioma who present with unequivocal evidence by imaging of transformation to high-grade glioma/GBM.

   *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.

   <u>Phase 2a</u> dose expansion portion (Simon's two-stage design):
   Recurrent, histologically confirmed, GBM with tumor tissue positive for EB1 by IHC as determined by central laboratory testing; eligible are patients with de novo GBM after prior radical chemoradiotherapy or secondary GBM after prior chemotherapy or radiotherapy; patients must be neurologically stable, without progression of neurologic symptoms, within 15 days prior to starting study drug.

   <u>Phase 2a</u> dose expansion portion (Surgical cohort):
   Recurrent GBM with planned re-resection. Details of the inclusion criteria for the Surgical cohort will be provided in a separate protocol amendment if futility is rejected in Stage 1 of the Simon's two-stage study portion.
3. **Phase 1 dose escalation portion:**
   Patients with advanced solid tumors must have measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) documented within 35 days prior to starting study drug, or non-measurable prostate or ovarian cancer that can be followed by prostate specific antigen (PSA) or cancer antigen-125 (CA-125), documented within 15 days prior to starting study drug.
   Patients with glioblastoma or high-grade glioma must have measurable disease, defined by contrast-enhancing MRI, within 15 days prior to starting study drug. Patients with previous low-grade glioma that progressed after prior radiotherapy (with or without chemotherapy) and are found to have high-grade glioma/GBM by biopsy or imaging are also eligible.
   Phase 2 a dose expansion portion (Simon's two-stage design):
   Patients with recurrent glioblastoma must be evaluable per RANO, defined by contrast-enhancing MRI, within 15 days prior to starting study drug.
4. Life expectancy ≥ 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).

*All listed laboratory parameters, and cardiac troponin (see Exclusion criterion 13), must be included in the study-specific pharmacy prescription chart. During the study, all parameters applicable for any study visit must be reviewed by the investigator and the pharmacy prior to dispensing of any study medication.

6. Patients with advanced solid tumors must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and patients with recurrent or progressive glioblastoma must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
7. Female patients who are not pregnant or breast-feeding and meet one of the following conditions:
   - Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient.
   - Post-hysterectomy and/or post-bilateral salpingectomy or ovariectomy.
   - Congenital or acquired condition that prevents childbearing.
   - 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)
     - intrauterine hormone-releasing system (IUS)
     - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
     - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
     - total heterosexual abstinence

     * The hormonal contraception method must be supplemented with a barrier method (preferably male condom).
8. Male patients must agree not to donate sperm from the first dose of study drug until 90 days after the end of treatment. Male patients, without a vasectomy or other conditions resulting in azoospermia and with a partner of childbearing potential, must agree to use condoms during the study and for at least 90 days after the end of treatment. 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), 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, prior to study-specific screening procedures. 10. Patients must be able and willing to comply with the required food intake restrictions.
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 who have received chemotherapy, radiotherapy, immunotherapy, or investigational agents within 4 weeks (2 weeks for single fraction of palliative radiotherapy, 6 weeks for nitrosoureas or mitomycin C) prior to starting study drug, or who 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 recurrent or progressive GBM or high-grade glioma who have: received radiotherapy within 6 weeks (Phase 1) or 12 weeks (Phase 2a), unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field, or there is histological confirmation of unequivocal tumor progression; received administration of prior anti-tumor chemotherapy within 4 weeks, or within 6 weeks for nitrosoureas; undergone surgical resection within 4 weeks (Phase 2a: 2 weeks) or a stereotactic biopsy/core biopsy within 1 week prior to starting study drug. 2. Patients who have had prior exposure to BAL101553. 3. Inability to swallow oral medication. 4. Increase in steroid dose in GBM or high-grade glioma patients within 5 days prior to first study-drug administration or requirement for > 6 mg/day dexamethasone or equivalent for symptom control. 5. 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). 6. Symptomatic brain metastases or leptomeningeal disease, indicative of active disease, in patients with advanced or recurrent solid tumors. 7. Peripheral neuropathy ≥ CTCAE grade 2. 8. Known human immunodeficiency virus (HIV) infection. 9. Known acute or chronic hepatitis B or hepatitis C infection. 10. Systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg at the screening visit.

	11. Blood pressure (BP) combination treatment with more than two antihypertensive medications. 12. Any history of cerebral hemorrhage, cerebral aneurysm, or ischemic stroke; or a history of transient ischemic attack within 24 months prior to screening in patients with advanced or recurrent solid tumors. Acute intratumoral hemorrhage in patients with recurrent or progressive GBM or high-grade glioma, considered by the study Investigator to be clinically significant. • Patients with MRI or CT demonstrating old hemorrhage or subacute bleed after a neurosurgical procedure (biopsy or resection) will be eligible for treatment. 13. 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 institutional ULN. • Congestive heart failure of New York Heart Association class III or IV. 14. 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. 15. 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. 16. 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 30 days after the last dose of study drug in both sexes.
INVESTIGATIONAL PRODUCT	BAL101553 hard capsule.

DOSE / ROUTE / REGIMEN	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, see Section 5.6). In the Phase 2a portion of the study patients with recurrent glioblastoma must have evaluable disease, defined by contrast-enhancing MRI, within 15 days prior to starting study drug. BAL101553 capsules will be given to fasted patients once or twice daily (depending on observed pharmacokinetics and clinical safety), continuously, until disease progression, unacceptable toxicity, or another reason for withdrawal from study drug occurs (see Section 4.4). A treatment cycle will be defined as one 28-day treatment period; there will be no treatment-free interval between treatment cycles. **Administration** Oral as hard capsules. **Phase 1 dose escalation portion (enrollment completed)** The starting daily dose of BAL101553 in patients with advanced or recurrent solid tumors was 2 mg/day BAL101553 (corresponding to approximately 1 mg/m^2), based on Good Laboratory Practice (GLP) toxicology studies. Dose cohorts comprised three patients per cohort, unless a drug-related DLT was observed in any patient, at which point the cohort was expanded [up] to six patients. For all cohorts, dose increments between cohorts, ranging from 30–100%, were based on the extent and severity of observed drug toxicity. Patients with recurrent or progressive GBM or high-grade glioma are analyzed as part of a separate dose-escalation scheme. The starting dose for the first GBM/glioma cohort was 8 mg/day and was based on the observed clinical safety in completed solid-tumor patient dose cohorts. Dose escalation was performed in fasted patients using an accelerated 3+3 titration design (see Table 3 and Section 3.1.2.1). Details of the dose escalation process are provided in Section 3.2.1 (including intrapatient dose escalation). DLT definitions are provided in Section 3.2.2. The starting dose rationale is described in Section 1.5.3. The MTD was defined as the highest dose level below the MAD with an acceptable tolerability profile. The MTD was different in patients with advanced or recurrent solid tumors (i.e. 16 mg/day) and patients with recurrent or progressive GBM/high-grade glioma (i.e. 30 mg/day). Dose escalation and MTD determination were primarily based on the occurrence of DLT during Cycle 1, however, also included a clinical review of all relevant available data from the current and previous dose cohorts. At least six patients were to be treated at the MTD dose level in the dose escalation portion of this study. **Phase 2a dose expansion portion** Up to 34 evaluable patients with recurrent GBM whose tumor tissue is positive for EB1 will be enrolled, in a Simon's two-stage design and will receive daily oral BAL101553 at the RP2D of 25 mg/day. A daily dose of 25 mg is recommended for the Phase 2a portions based on the following considerations: • Phase 1 data suggest an increased probability to experience certain DLTs when exposure exceeds approximately 2375 h*ng/mL

- At 30 mg/day, the MTD declared in GBM and high-grade glioma patients, 28% of patients are expected to exceed this threshold, while at 25 mg/day only 12% of patients are expected to exceed this threshold
- Long-term disease stabilizations and objective response were only seen at 25 mg/day and 30 mg/day
- The daily dose of 25 mg seems to offer the best safety – efficacy ratio in GBM patients

Sponsor approval of dosing new patients and recommendations for dose delays or dose modifications (Phase 1 and Phase 2a portions of the 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 (Phase 1 portion) or a DLT equivalent (Phase 2a portion), 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. 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 3.2.5.2 and Table 6).

  In the Phase 2a portion of the study, patients will be treated at the RP2D of 25 mg/day in a q24h dosing regimen (see Section 1.5.4). The dose may be reduced based on the severity of events to either 20 mg/day, 15 mg/day, or 10 mg/day (see Section 3.2.5.2).
- In Phase 1, patients who experience drug-related AEs which lead them to miss more than five doses within any 28-day cycle, or lead to a delay of more than 14 days in the commencement of the subsequent cycle, should be discontinued from the study. Such events will be considered a DLT if they occur during Cycle 1.
- In Phase 2a, patients who experience drug-related AEs which lead them to miss more than seven doses within any 28-day cycle, should receive a dose reduction (see Section 3.2.5.2), or should be discontinued from the study.

Detailed study visit and assessment schedules for the Phase 1 portion and the Phase 2a portion are provided respectively in Table 8 and Table 9 (Section 5.1).

DURATION OF PATIENT PARTICIPATION	In the Phase 1 portion of the study, each patient will be scheduled to receive at least two 28-day treatment cycles. In the Phase 2a portion of the study (Simon's two-stage design), each patient will be scheduled to receive at least 6 weeks of study treatment, and to have a subsequent RANO assessment. Patients with an objective response or stable disease may continue to receive BAL101553 until disease progression or unacceptable toxicity occurs. Reasons for discontinuation of treatment will be recorded and may include: • Adverse event. • Abnormal laboratory value. • Abnormal test procedure result. • Missing more than five (Phase 1) or seven (Phase 2a) doses in a cycle, or causing a delay in the start of a subsequent cycle by more than 14 days (Phase 1), due to toxicity. • Intercurrent illness that prevents further administration of treatment. • Death. • Withdrawal of consent. • Withdrawn from the study at Investigator discretion. • Protocol violation and/or non-compliance. • Lost to follow-up. • New cancer treatment/therapy. • Administrative reasons. A patient must be discontinued from the study treatment if any of the following events occur: • Disease progression. (In the Phase 2a portion of the study, patients with a mixed response, e.g., a reduction in target lesion area but an increase in non-target disease or occurrence of new lesions, may continue on study treatment if their clinical condition is stable or improving) • Drug-related AE(s) in Phase 1 which lead(s) to missing greater than five doses within any 28-day cycle, or lead(s) to a delay of more than 14 days in the commencement of the subsequent cycle. • Requirement for more than two dose level reductions in a patient. • Recurrence of the same toxicity, with the same or worse severity, in a patient who had a dose reduction due to toxicity. • Requirement for other anticancer therapy. • Grade 4 hypertension. • Recurrent QTcF > 500 ms or QTcF increase from baseline > 60 ms. • Pregnancy
ASSESSMENTS OF:	
SAFETY / TOLERABILITY	The severity of AEs will be described using the National Cancer Institute CTCAE v4.03 (Phase 1) and v5.0 (Phase 2a) criteria. Safety evaluations will include analysis of AEs, laboratory assessments (hematology, biochemistry, cardiac troponin, coagulation, urinalysis), pregnancy testing in women of childbearing potential, ECG, transthoracal echocardiography, chest X-ray (Phase 1)/computed tomography (CT)/MRI, vital signs, ECOG performance status, physical examination, and evaluation of concomitant medications.

PHARMACOKINETICS	PK variables calculated from 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. Total 24-h urinary excretion of BAL101553 and BAL27862.
EFFICACY	**Phase 1 dose escalation portion:** In patients with advanced or recurrent solid tumors, evaluation of disease progression and response in patients with measurable disease will be assessed by RECIST criteria v1.1. In patients with ovarian or prostate cancer with non-measurable disease, response will be evaluated by the CA-125 Rustin criteria or the PSA Working Group 2 criteria, respectively. For patients with recurrent or progressive GBM or high-grade glioma, evaluation of disease progression and response will be assessed by contrast-enhanced MRI, based on the RANO criteria. Clinical progression of the tumor disease will also be considered as progressive disease. **Phase 2a dose expansion portion (Simon's two-stage design):** For patients with recurrent GBM, evaluation of disease progression and response will be assessed by contrast-enhanced MRI, based on the RANO criteria. Clinical progression of the tumor disease will also be considered as progressive disease. Primary endpoint is ORR with OS, PFS, and the proportion of patients with PFS at 6 months as main secondary endpoints.
BIOMARKER ANALYSIS	In patients with advanced or recurrent solid tumors, exploratory biomarkers obtained from blood will include circulating tumor cells [CTCs], circulating endothelial cells [CECs], and circulating endothelial progenitor cells [CEPs]. In patients with recurrent GBM, exploratory biomarkers obtained from blood will include CTCs and other circulating biomarkers (OCBs; e.g., extracellular vesicles, circulating tumor DNA, circulating tumor RNA or proteins). Malignant pleurocentesis or paracentesis fluid (when available during routine clinical course), filter cards for dried-blood-spot analysis, tumor biopsies (if feasible and safe and if patients are willing to undergo biopsy), and archival tumor blocks (collected from all patients when available) will also be analyzed.
STATISTICAL ANALYSIS	**Analysis populations** Patients enrolled to the study with solid tumors, and those enrolled with GBM/high-grade glioma, will be analyzed as separate populations. The MTD-determining population will consist of patients who have received at least one dose of BAL101553 and experienced a DLT, or received at least 24 of the scheduled 28 doses of BAL101553 for q24h administration, or at least 48 of the scheduled 56 doses of BAL101553 for q12h administration, in Cycle 1 without a DLT; and have been observed for ≥ 28 days following the first dose and have been evaluated for safety. The full analysis population (FAP) includes patients who received at least one dose of BAL101553, and will be used for analyses; the safety population (FAP with at least one post-baseline safety assessment) will be used for the overall analysis of safety; the PK population (FAP with at least one post-baseline PK assessment) will be used to assess PK, and the efficacy-evaluable population (EEP; patients in Phase 2a who had at least one post-baseline RANO assessment after having received at least 6 weeks of study treatment) will be used to evaluate efficacy.

DLT, MAD, and MTD recommendation

The number of patients experiencing DLT and the type of DLT will be listed by dose cohort (separately for patients with advanced or recurrent solid tumors and those with recurrent or progressive GBM or high-grade glioma). The MAD is defined as the dose level at which DLT are observed in ≥ two of [up to] six patients evaluable patients during treatment Cycle 1 (i.e., in a regular or expanded dose cohort, respectively). The MTD is defined as the highest dose level below the MAD with an acceptable tolerability profile.

Adverse events

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

Laboratory evaluations

The frequency of laboratory abnormalities will be displayed by worst CTCAE grade and by dose cohort 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

Objective response rate and disease control rate will be presented by dose cohort and by disease subgroups, as appropriate. Progression-free survival and OS will be listed by patient and dose group. In the Phase 2a portion of the study (Simon's two-stage design), median OS and PFS, and the proportion of patients with PFS6 will be analyzed.

Pharmacokinetic analysis

Listings, and descriptive analysis of PK variables by cohort including arithmetic and geometric mean, coefficient of variations, standard deviation, minimum, maximum, and median.

Biomarker analysis

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

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AE	Adverse event
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
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-t}	Area under the concentration-time curve from time zero to time (t)
$AUC_{0-\tau}$	Area under the concentration-time curve from time zero to time (τ); where tau is the length of the dosing interval
BP	Blood pressure
bpm	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
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
CK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case report/record form
CRO	Clinical research organization
CT	Computed tomography
CTC(s)	Circulating tumor cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day (of a treatment cycle)
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
EB1	End-binding protein 1
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEP	Efficacy evaluable population
F	Bioavailability
FAP	Full analysis population
FSH	Follicle stimulating hormone
GBM	Glioblastoma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	Hour(s)

hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	Highest non-severely toxic dose
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
MAD	Maximum administered dose
MGMT	O^6-methylguanine-DNA methyltransferase
min	Minute(s)
MRI	Magnetic resonance imaging
ms	milliseconds
MTA	Microtubule targeting agent
MTD	Maximum tolerated dose
N	Number
NRT	No relevant toxicity
OCB(s)	Other circulating biomarker(s)
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression-free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PSA	Prostate specific antigen
q12h	Twice daily
q24h	Once daily
QTcF	QT interval corrected for heart rate (Fridericia correction)
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
RT	Radiotherapy
SAE	Serious adverse event
SBP	Systolic blood pressure
$t_{½}$	Terminal elimination half-life
T_{max}	Time to maximum plasma concentration
TMZ	Temozolomide
ULN	Upper limit of normal
Vc	Volume of distribution in the plasma (central) compartment
Vz/F	Volume of distribution in the terminal phase divided by the bioavailability

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 ((Prota 2014).

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 an autoradiography study in mice ((Schmitt-Hoffmann 2009).

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. BAL27862 is also active against temozolomide sensitive and resistant glioblastoma lines. 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. 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.

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, further indicating a potential to combine BAL101553 with radiotherapy 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 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, glioblastoma and breast, colorectal, prostate, ovarian, pancreatic, hepatobiliary and gastric cancer specimens.

In glioblastoma (GBM) models, BAL101553 has shown anticancer activity as a single agent, as well as in combination with radiotherapy (RT) and with radiochemotherapy. 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. In an orthotopic GBM model (GBM6) with reduced sensitivity to 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 (Tuma 2016).

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 IVadministration 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 cleavege of BAL101553 to BAL27862 occurs both in the incubation medium and intracellularly, and that BAL27862 is highly permeable.

A dedicated 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 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 clinical 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

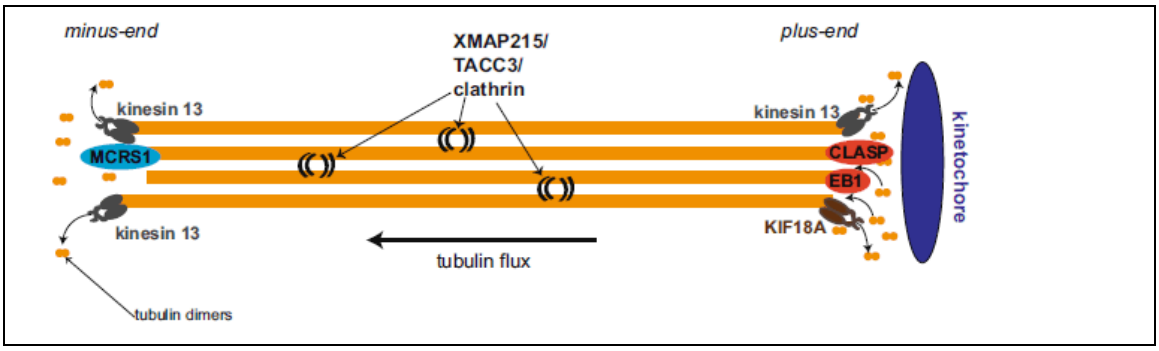
Several possible prognostic factors or surrogate markers for BAL101553 activity have been proposed. These include the number of circulating tumor cells (CTCs), circulating endothelial cells (CECs), circulating endothelial progenitor cells (CEPs), and expression of specific proteins detectable in blood 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.

1.3.4.1 End-binding protein 1

Recent non-clinical data have identified end-binding protein 1 (EB1) as a response-predictive biomarker in rodent glioblastoma models.

EB1 protein is the prototypic member of microtubule plus-end tracking proteins (+TIPs) controlling microtubule dynamics (see Figure 1). EB1 links microtubules to several cellular structures, such as kinetochores and the cell cortex, and participates in microtubule-mediated cell functions, such as cell division, migration, and morphogenesis.

Figure 1 EB1 localization on microtubules

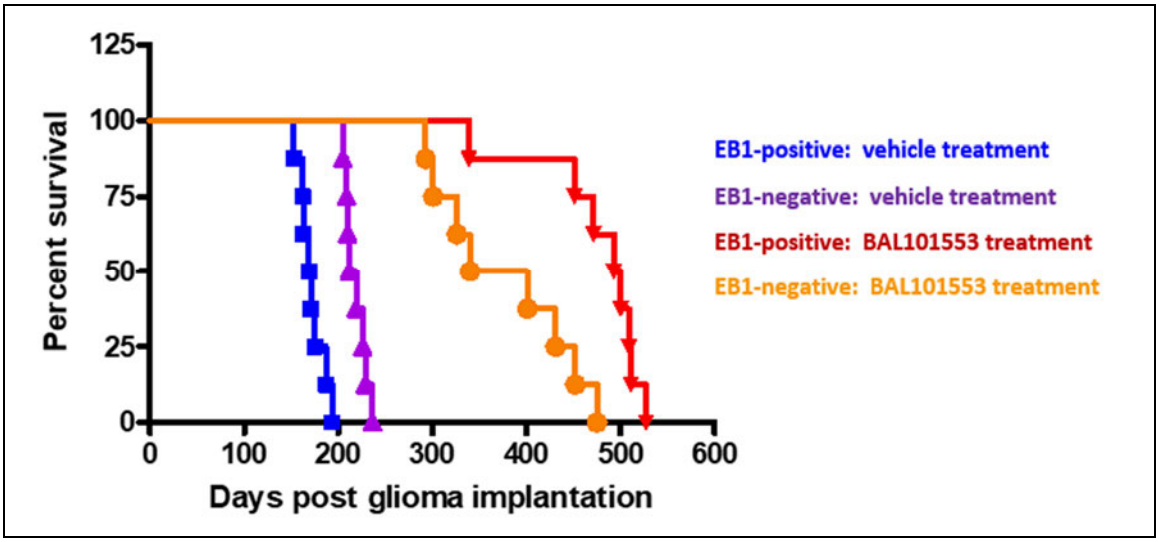


Source: (Meunier 2016)

When overexpressed in GBM, EB1 is involved in GBM progression, and has been reported to predict poor overall- and progression-free survival (PFS). *In vitro* data have shown that EB1 proteins sensitize microtubules to the action of microtubule-interacting agents by promoting microtubule catastrophes (Mohan 2014, Bergès 2014).

EB1 has been shown to be a predictive biomarker of response to BAL101553 (Bergès 2016). In an orthotopic mouse model based on GBM 6 (a stem-cell-like GBM cell line), tumors with high EB1 expression showed a shorter survival compared to EB1-downregulated tumors when the animals were administered placebo. Conversely, when BAL101553 was administered, mice with EB1-high tumors showed a significantly longer survival than those with EB1-downregulated tumors (see Figure 2). This survival benefit was attributed to the action of BAL101553 on GBM stem-like cells, with inhibition of endothelial differentiation and induction of astrocytic differentiation in GBM6 tumor cells (Bergès 2018).

Figure 2 EB1-expression dependent survival in a GBM6 mouse model



These non-clinical data, together with the observation of an exceptionally long-lasting response observed in a patient with GBM in the Phase 1 portion of study CDI-CS-002 (see Section 1.5.2.2.2), and recently generated data on the prevalence of EB1-positive GBM based on retrospective tissue analyses in clinical GBM samples (see Section 1.5.2.2.2) form the basis for assessing the effects of BAL101553 in patients with EB1-positive GBM in the Phase 2a portion of this study.

To further explore and refine the biomarker strategy related to BAL101553, both in terms of baseline (predictive) or on-treatment (pharmacodynamic) biomarkers, additional biomarkers are to be considered, including β-tubulin variant III, 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 $p21^{CIP1}$) or transcription factors such as C-MYC.

Accordingly, blood samples, and, when possible, tumor biopsies , 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

There are 4 clinical studies with BAL101553 that have been completed or are ongoing. The status and main safety and efficacy outcomes from these studies are summarized in Table 1.

Initially BAL101553 was administered as a 2-hour weekly infusion (Study CDI-CS-001), however based on the C_{max}-related vascular toxicity observed with BAL101553 using a 2-hour infusion regimen, and considering that non-clinical data suggest exposure (AUC) rather than C_{max} as the determinant of antitumor efficacy, the 2-hour infusion regimen was not further pursued in the clinical development program. Instead, a study program was initiated that limits the maximum plasma concentration, including in the current study (CDI-CS-002), and in a Phase 1 study in newly diagnosed glioblastoma (in combination with radiotherapy, CDI-CS-004/ABTC 1601, NCT 03250299), both of which investigate a daily oral administration of BAL101553, and in a third study (CDI-CS-003, NCT02895360) using weekly 48-hour infusions.

It has been demonstrated in these clinical studies that neither daily oral administration of BAL101553 nor a 48-hour intravenous administration are associated with vascular toxicity. Both forms of administration present a different BAL101553 safety profile compared to the 2-hour infusion regimen. The safety profile of daily oral or 48-hour IV administration is mainly characterized by dose-limiting toxicities of hallucinations, hyponatremia, and gait disturbance, and provides an at least two-fold higher AUC at MTD dose levels compared to a 2-hour infusion (Joerger 2019, (Lopez 2018).

In study CDI-CS-002, different MTD levels were determined for patients with advanced solid tumors (16 mg/day) and patients with recurrent GBM / high-grade glioma (30 mg/day). The reason for this is unknown, but there were significant differences in age, time since diagnosis of first relapse, and prior duration of cancer treatment, which might explain different tolerance levels. A higher tolerance of patients with GBM / high-grade glioma is also observed when comparing the number of frequent drug-related AEs in Table 2 and the percentage of patients experiencing toxicities of CTCAE grade ≥ 3 (11% vs 38%, see Appendix 3).

Table 1 Demographics in CDI-CS-002

		Advanced solid tumor	Recurrent GBM/ high grade glioma
Gender	**M/F**	10/16	16/12
Age	**Mean (years)**	62.3	49.7
Time between first relapse and C1D1	**Median (days)**	771	282
Prior cancer treatment duration (without hormonal therapy)	**Median (days)**	561	234

When comparing frequent drug-related AEs and DLTs, the safety profile is largely consistent between daily oral and 48-hour IV administration (see Table 2).

Table 2 BAL101553 Clinical trial programme overview and status

Study (NCT number)	**CDI-CS-001 NCT01397929**	**CDI-CS-002* NCT02490800**		**CDI-CS-003* NCT02895360**		**CDI-CS-004* NCT 03250299**
Patient population	Advanced solid tumors	Advanced solid tumors	Recurrent GBM/ high grade glioma (n=20 GBM, n=8 high-grade glioma)	Advanced solid tumors	Recurrent GBM Platinum-resistant ovarian cancer	Newly diagnosed GBM (plus radiotherapy
Enrollment	**N=73**	**N=26**	**N=28**	**N=20**	**N=23**	**N=14**
Status	P1/P2a Completed	P1 Completed	P1 Completed	P1 Completed	P2a Completed	P1 **Ongoing**
Dosing schedule	2-hour IV D1,8,15, q28d	Daily oral	Daily oral	48-hour IV D1,8,15, q28d	48-hour IV D1,8,15, q28d	Daily oral
Dose levels	15, 30, 45, 60, 80 mg/m^2	2, 4, 8, 16, 20, 30, mg/day	8, 15, 20, 25, 30, 35 mg/day	30, 45, 70, 90 mg/m^2	70 mg/m^2	4, 6, 8 mg/day
MTD	30 mg/m^2	16 mg/day	30 mg/day	70 mg/m^2		
Most frequent drug-related adverse events (≥ 10%)	nausea (42%) vomiting (34%) hypertension (33%) fatigue (32%) diarrhea (30%) decreased appetite (18%) neuropathy peripheral (18%) pyrexia (12%) headache (11%)	fatigue (31%) diarrhea (19%) hyponatremia (19%) constipation (15%) lethargy (15%) nausea (15%) decreased appetite (12%) hallucination (12%) hypertension (12%)	fatigue (18%) nausea (18%) anaemia (11%) diarrhea (11%)	fatigue (35%) decreased appetite (20%) hyponatremia (15%) nausea (15%) pyrexia (15%) abdominal pian (10%) diarrhea (10%) hallucination (10%) myalgia (10%) neuropathy peripheral (10%)	fatigue (22%) muscle spasm (17%) abdominal pian (13%)	fatigue (46%) nausea (38%) ALT increased (23%) anaemia (23%) diarrhea (23%) hyponatremia (23%) anorexia (15%) lymphocyte count decreased (15%) platelet count decreased (15%) seizure (15%) vomiting (15%)
DLTs or DLT equivalent	Reduced mobility, Gait disturbance, myocardial injury	G3/4 Hypo-natremia G2 Hallucinations	G2 Fatigue and depression G2/3 Gait disturbances, hallucinations, confusion	G3 Hyponatremia G3 Neutopenia, G2 hallucinations, and G2 ataxia, G3 hypotension; (G3 peripheral neuropathy)	-	G4 Aseptic meningoencephalitis (Dose level reduction due to DLT observed in first patient treated)
Best efficacy result	1 PR (Ampullary cancer)	More SD at higher doses	1 PR (GBM)	1 PR (Ovarian cancer)	1 PR (GBM)	Not applicable

*Data are from an unlocked, partially-monitored clinical database (accessed on 24 February 2020 [CDI-CS-002], 7 March 2020 [CDI-CS-003], and 5 March 2020 [CDI-CS-004]).

1.5 Rationale for study CDI-CS-002

1.5.1 Summary of study design

This oral administration Phase 1/2a study is divided into two sequential parts, with different designs:

- The first part (dose-escalation portion) was a single-agent, open-label, multicenter, multiple ascending dose escalation study using an accelerated 3+3 titration design, and was carried out in 26 patients with advanced or recurrent solid tumors and in 28 patients with recurrent or progressive GBM (n=20) or high-grade glioma (n=8); patients from these two groups were enrolled into separate dose cohorts, and enrollment in both cohorts is completed and MTDs have been defined (see Table 1).
- The second part (expansion portion at the RP2D) is a Simon's two-stage, single-agent, open-label, non-comparative, multicenter, fixed-dose study to be carried out in up to 34 evaluable patients with recurrent GBM whose tumor tissue is positive for EB1 on IHC. A tissue screening program adhering to local standards in selected countries will be established to support the identification of potential patients. Patients with non-measurable disease at baseline, who are therefore unevaluable for ORR (the primary endpoint), will contribute to the assessment of secondary endpoints. If futility is rejected in Stage 1 (9 evaluable patients) then the study will proceed to Stage 2 (10 evaluable patients). At this stage a parallel cohort will be initiated in up to 6 patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862. Details of this Surgical cohort will be provided in a separate protocol amendment pending the results of a non-clinical study to assess any potential effects of BAL101553 on wound healing.

1.5.2 Study design rationale

1.5.2.1 Phase 1 dose escalation portion

Cohort 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 (Chen 2009, (Ivy 2010). The proposed study design limits 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 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 cohort allows 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 therapeutic dose.The Phase 2a expansion portion of the study is intended to confirm the tolerability of BAL101553 at the RP2D, and to provide

additional information about its safety and efficacy in patients with recurrent GBM whose tumor tissue is positive for EB1.

1.5.2.2 Phase 2 dose expansion portion

1.5.2.2.1 Simon's two-stage design

The study design of the Phase 2a portion of this study is a Simon's two-stage design which provides a reliable method for minimizing the number of patients enrolled to each stage if the approach of using EB1 as a biomarker for patient selection is futile. This design also provides for clear go/no go decision criteria.

The sample size rationale of the Phase 2a portion (9 patients in Stage 1 with a minimum of 2 patients with an objective response to move on to Stage 2, and 10 patients in Stage 2 with a minimum total of 6 out of 19 patients with an objective response) is based on the following clinical rationale:

- The null hypothesis of a 14% ORR can be based on historical data obtained with lomustine in a recurrent setting of GBM. Lomustine has been used as standard of care comparator in recent GBM studies in a first-recurrence setting (i.e., after surgery and subsequent radiochemotherapy) with ORRs between 3% (vs 5% with regorafenib) (Lombardi 2019) and 14% (vs 41.5% with lomustine plus bevacizumab) (Wick 2017). This range of objective response rate in recent clinical trials is consistent with historical reports of on ORR of 8% with the use of temozolomide in a recurrent GBM setting (Brada 2001).
- The alternative hypothesis is that BAL101553 will provide an ORR of 40%, which would be considered an indicator of significant benefit over the expected response to standard of care (i.e., 3–14%).

The use of a single-arm, non-comparative design is considered an efficient design to obtain a proof-of-concept that a stratification of patients to treatment with BAL101553 based on EB1-positivity by IHC in GBM tissue is a clinically beneficial approach. It also takes feasibility aspects of the study into account considering the low prevalence of EB1-positivity in GBM of approximately 2–4% (see Section 1.5.2.2.2).

The nominal overall response rate in the Phase 1 portion of the study in GBM (n=20) or high-grade glioma (n=8) patients was 5% for GBM patients (1 partial response in an EB1-positive patient out of 20 GBM patients) and was 0% for high -grade glioma patients (0/8 patients). This relatively low response rate does not support further exploration of BAL101553 in an unselected GBM patient population.

Available GBM tissue samples from nine of the 20 patients who received BAL101553 in the Phase 1 dose escalation portion of study CDI-CS-002 have been stained for EB1. One patient with an exceptional response (see Section 1.5.2.2.2) showed strong positive EB1 staining in his GBM tissue. All available GBM tissues from the other eight non-responding patients in study CDI-CS-002 were weak or negative for EB1.

Using the ORR as the primary endpoint for the Simon´s two-stage design means that patients must have measurable disease at baseline. However, some patients with recurrent GBM may have non-measurable disease, with lesions that are too small to be measured (less than 1 cm in both perpendicular dimensions), lesions that lack contrast enhancement

(non-enhancing disease), or lesions that contain a poorly-defined margin that cannot be measured or segmented with confidence (Ellingson 2017).

These patients will be included in the study, recognizing that EB1-positive GBM is very rare, that these patients are expected to have a similar benefit-risk profile related to BAL101553 as patients with measurable disease, and that these patients may add to the assessment of the main secondary endpoints (OS, PFS) which will be used as primary endpoints in a potential Phase 2 / Phase 3 development of BAL101553 in patients with EB1-positive GBM.

1.5.2.2.2 Rationale for patient selection in Phase 2a (Simon's two-stage design)

The selection of patients for the Phase 2a study based on EB1 expression in GBM tissue is supported by the following considerations:

- One patient with GBM in the Phase 1 portion of study CDI-CS-002 showing an exceptional, long-lasting profound partial response. [redacted]. Figure 3 shows examples of EB1 staining from the exceptional responder and from 4 non-responding patients.
- Results of retrospective GBM tissue micro array (TMA) analyses:
  - TMA from the University of Bern (n=248 patients): This TMA included up to 12 tissue spots per patient (up to 4 tissue spots each from the tumor center, the tumor infiltration front and from normal brain tissue). EB1-positivity on a patient level was defined if EB1 staining was seen in at least 75% of tumor spots from the tumor center and this resulted in a EB1-positive rate of 4%.
  - TMA from the Institute of Cancer Research in the UK (n=354 patients): This TMA included a single GBM tissue spot per patient, and showed an EB1-positive rate of 2%.

  The determined prevalence of EB1-positive GBM in a range of 2–4% is considered sufficient for a biomarker driven enrollment strategy.
- Pre-existing non-clinical data supporting EB1 as a response-predictive biomarker for BAL101553 in GBM in mouse models (see Section 1.3.4.1).
- The need for gaining a better understanding of the molecular underpinnings in exceptional responders has recently been highlighted by a dedicated initiative of the US National Cancer Institute (Exceptional Responders Initiative; NCI 2020), and the

Phase 2a portion of this study is designed to assess the utility of EB1 as a response-predictive biomarker for GBM patients in this context.

A tissue screening program using IHC and adhering to local standards in selected countries will be established to support the identification of potential patients.

Assuming a prevalence of EB1-positive GBM of 2-4%, screening of GBM tissues from 25 – 50 GBM patients is required to identify one EB1-positive case.

EB1-tissue staining using IHC has been performed to date at the University of Basel in a retrospective manner using a Ventana discovery platform. For the Phase 2a portion of this study, a dedicated Clinical Trial Assay is being developed on a platform for clinical use in cooperation with an experienced clinical research organization. This Clinical Trial Assay is expected to be available in June 2020. Details of the EB1-tissue staining methodology are provided in Appendix 4, and will be specified in a dedicated laboratory manual.

If futility is rejected in stage 1, tumor tissue levels of BAL27862 will be determined in an additional cohort of up to 6 patients with planned re-resection of recurrent GBM (see Section 1.5.2.2.3). Details of this Surgical cohort will be provided in a separate protocol amendment.

Figure 3 EB1-expression in GBM tissue from an exceptional responder compared to non-responding patients

1.5.2.2.3 Surgical cohort

If futility is rejected in stage 1 of the Phase 2a Simon's two-stage design in patients with EB1-positive recurrent GBM, tumor tissue levels of BAL27862 will be determined in an additional cohort of up to 6 patients with planned re-resection of recurrent GBM. Details of this Surgical cohort will be provided in a separate protocol amendment pending the results of a non-clinical study in a rabbit animal model to assess any potential effects of BAL101553 on wound healing.

The physicochemical properties of BAL27862 (the active moiety of BAL101553) and available data in rodents from an autoradiography study ((Schmitt-Hoffmann 2009) suggest that BAL27862 penetrates the brain in a 1:1 ratio compared to plasma. The brain penetration of BAL27862 is further supported by central nervous side effects that were consistently observed in clinical studies at high exposures with BAL101553 such as visual hallucinations which were reversible within a few days, consistent with the plasma half-life of BAL27862 which is in a range of 12–24 hours.

However, a definitive assessment of the brain penetration of BAL27862 in humans is considered important, prior to entering a potential Phase 3 program in GBM. Therefore, it is planned to initiate a Surgical cohort in patients undergoing planned re-resection of recurrent GBM once an initial proof of concept has been achieved regarding the efficacy of BAL101553 in patients with EB1-positive GBM in the Stage 1 of the Simon's two-stage Phase 2 a expansion portion of study CDI-CS-002, and once pre-clinical data from a wound-healing study are available. The data from a pre-clinical wound-healing study are considered important, considering that BAL27862 has shown vascular disrupting effects when using dose regimens that result in high Cmax levels, i.e when using a 2-hour infusion regimen.

1.5.3 Starting dose rationale (Phase 1 dose escalation portion)

For patients with solid tumors, the starting dose of 2 mg/day of BAL101553 capsules was determined in accordance with ICH Guideline S9 Non-clinical evaluation for anticancer pharmaceuticals. The starting dose level was primarily based on the highest non-severely toxic dose (HNSTD) from repeated oral toxicity studies (4-week GLP studies) in rats and dogs and was then modified to a more conservative dosing approach taking expected accumulation and PK, safety, and efficacy data from the clinical study CDI-CS-001 (IV BAL101553 given over 2 hours on Days 1, 8 and 15 of an every 28-day treatment cycle) into consideration (see Appendix 1).

Patients with recurrent or progressive GBM or high-grade glioma were treated in a separate dose cohort, using the same dose-escalation rules as described for patients with advanced or recurrent solid tumors. The starting dose of daily oral BAL101553 in patients with GBM or high-grade glioma was 8 mg/day, a dose level already established as safe in solid tumor patients. The optional twice daily dosing regimen was not implemented in Phase 1.

1.5.4 Recommended Phase 2 dose (Phase 2a expansion portion)

A daily dose of 25 mg is recommended for Phase 2 based on the following considerations (see Appendix 3):

- Phase 1 data suggest an increased probability to experience certain DLTs when exposure exceeds approximately 2375 h*ng/mL
- At 30 mg/day, the MTD declared in GBM and high-grade glioma patients, 28% of patients are expected to exceed this threshold, while only 12% of patients are expected to exceed this threshold at 25 mg/day of BAL101553
- Long-term disease stabilizations and objective response were only seen at 25 mg/day and 30 mg/day
- The daily dose of 25 mg seems to offer the best potential benefit-risk ratio in GBM patients

2 OBJECTIVES OF THE STUDY

Phase 1 dose escalation portion

2.1 Primary objectives

The primary objectives of the Phase 1 dose escalation portion of this study are to determine the maximum tolerated dose (MTD) and to characterize dose-limiting toxicities (DLT) of daily oral BAL101553, administered to adults with advanced or recurrent solid tumors who have failed standard therapy or for whom no effective standard therapy is available, and to patients with recurrent or progressive GBM or high-grade glioma.

2.2 Secondary objectives

The secondary objectives of the Phase 1 dose escalation portion are:

- To evaluate the safety and tolerability of daily oral BAL101553.
- To evaluate BAL101553 and BAL27862 pharmacokinetics.
- To assess the anti-tumor activity of daily oral BAL101553 in cancer patients.

Phase 2a dose expansion portion (Simon's two-stage design)

2.3 Primary objective

The primary objective of the Phase 2a dose expansion portion of this study is to determine the efficacy of daily oral BAL101553 in patients with recurrent GBM whose tumor tissue is positive for EB1 based on immunohistochemistry (IHC) based on the objective response rate as per RANO criteria. A tissue screening program adhering to local standards in selected countries will be established to support the identification of potential patients.

2.4 Secondary objectives

The secondary objectives of the Phase 2a dose expansion portion are:

- To evaluate the efficacy of BAL101553 based on OS, PFS, and the proportion of patients with PFS at 6 months after start of study drug treatment (PFS6).
- To evaluate the safety and tolerability of daily oral BAL101553.
- To evaluate BAL101553 and BAL27862 pharmacokinetics.

Phase 2a dose expansion portion (Surgical cohort)

If futility is rejected in Stage 1 of the Simon's two-stage study portion, a parallel cohort will be initiated in up to 6 patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862. Details of this Surgical cohort will be provided in a separate protocol amendment.

2.5 Exploratory objectives (Phase 1 and Phase 2a portions)

The exploratory objectives of the study are to assess the use of biomarkers to characterize pharmacodynamic effects of daily oral BAL101553, and 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

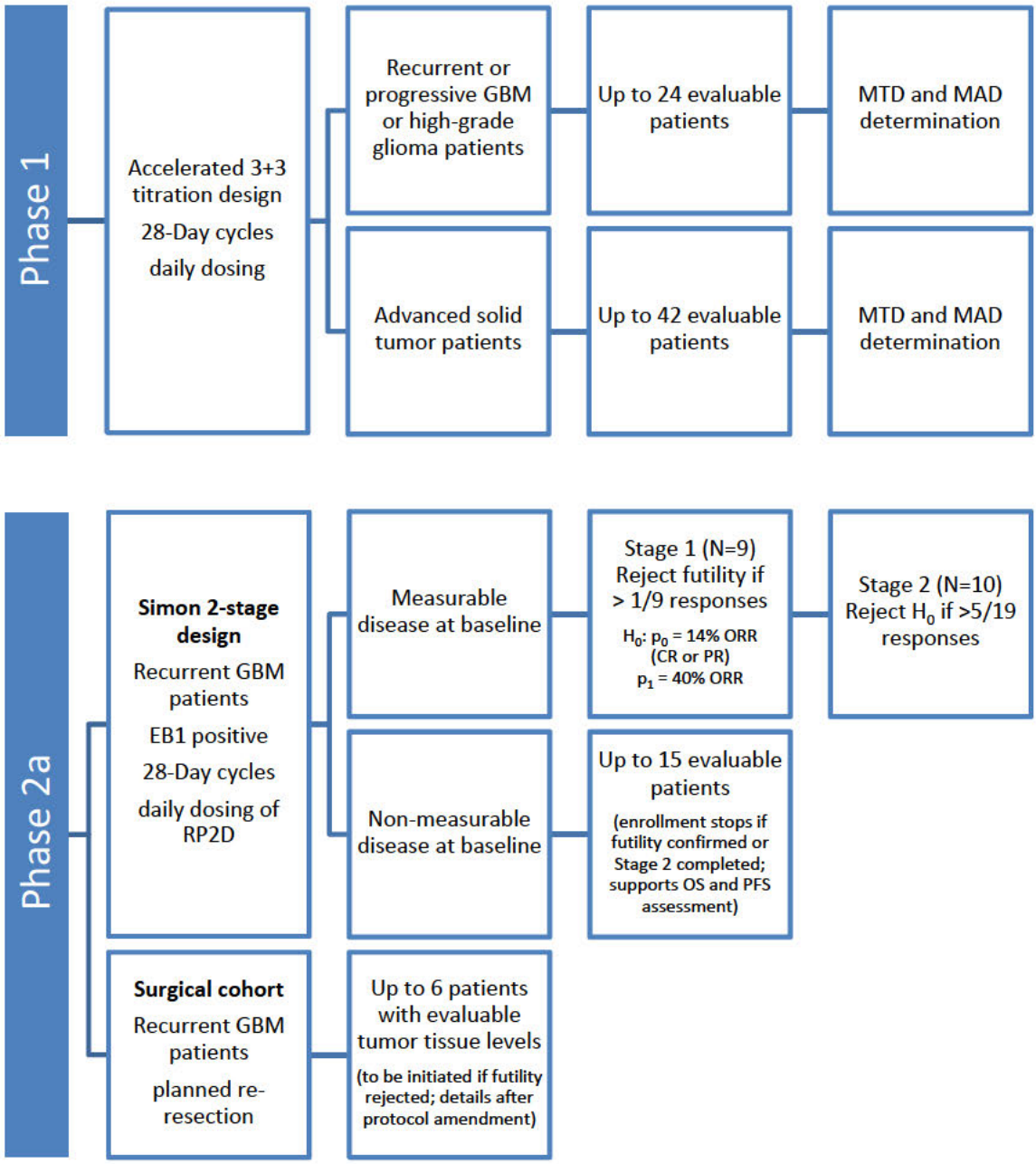
This is a single-agent, open-label, multicenter, Phase 1/2a study for daily oral BAL101553 comprised of two parts:

1. Phase 1 dose-escalation portion: an accelerated 3+3 titration design will be used to determine the respective MTDs in patients with:
   a. advanced or recurrent solid tumors (up to 42 evaluable patients)
   b. recurrent or progressive GBM or high-grade glioma (up to 24 evaluable patients)
2. Phase 2a expansion portion: using a Simon's two-stage design to obtain efficacy data for BAL101553 administered at the RP2D to patients with recurrent GBM whose tumor tissue is positive for EB1, as determined by central laboratory testing using an appropriately validated immunohistochemistry Clinical Trial Assay, and to further characterize the safety and tolerability of BAL101553 at the RP2D (up to 34 evaluable patients).

   A separate sub-study may investigate tumor tissue levels of BAL27862 in up to six evaluable patients with a planned re-resection of recurrent GBM if futility is rejected in stage 1 of the Phase 2a Simon's two-stage design and pending the results of a non-clinical study to assess any potential effects of BAL101553 on wound healing. Details of this Surgical cohort will be provided in a separate protocol amendment.

An overview of the study protocol design is presented in Figure 4.

Figure 4 Schematic overview of study design



3.1.1 Treatment cycles

Each treatment cycle will comprise 28 days of continuous, daily oral BAL101553 administration to patients in a fasted state. Section 3.2.6 describes the planned treatment duration.

Treatment may be administered on an inpatient or outpatient basis.

In the Phase 1 dose-escalation portion 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 3.1.2 and 4.5).

In the Phase 2a dose expansion portion of the study, patients with measurable disease at baseline will be replaced if they could not complete at least one post-baseline RANO assessment after at least 6 weeks of study treatment (see Sections 3.1.3 and 4.5).

3.1.2 Dose escalation (Phase 1)

Patients will be enrolled in sequential dose cohorts, which will comprise three to six patients, with each successive cohort given an increased dose of BAL101553 using a flat-fixed dosing approach. Initially, oral capsules will be administered once daily (q24h) in the morning before breakfast on an empty stomach, with patients remaining nil-by-mouth, except for water and prescribed medications, for 4 h before and 1 h after each dose. Splitting of the assigned daily dose via implementation of a twice-daily dosing regimen (q12h) is permitted, e.g., a 30 mg daily dose may be administered as 15 mg twice daily. Only one regimen may be administered within a given dose cohort; however, the same daily dose may be administered concurrently to two parallel dose cohorts as a once-daily and twice-daily regimen. The rationale for allowing distribution of the daily dose is that the C_{max} would be reduced, which has the potential to further improve tolerability and to extend the therapeutic window.

Each treatment cycle will consist of daily oral BAL101553 administration for 28 consecutive days. Patients will be allowed to receive repeated 28-day treatment cycles until the occurrence of progressive disease, or unacceptable toxicity. For each dose cohort, new patients will be recruited and evaluated for safety, pharmacokinetics, pharmacodynamic effects, and for antitumor activity.

3.1.2.1 Planned dose escalation levels

Cohort size is variable, and will be expanded if patients experience specific Common Terminology Criteria for Adverse Events version 4.03 (CTCAE)-graded toxicity. Dose cohort escalation will be performed using an accelerated 3+3 titration design and will be based upon the occurrence of BAL101553-related toxicities (DLTs) during Cycle 1 of treatment.

The BAL101553 starting dose level will be 2 mg/day (see section 1.5.3) in patients with advanced or recurrent solid tumors.

For patients with recurrent or progressive GBM or high-grade glioma, the starting dose will be at least one dose level below the dose level that has already been demonstrated to be safe and well tolerated in patients with advanced or recurrent solid tumors.

Dose level escalation will proceed in 100% increments for successive dose cohorts until observation of drug-related AEs of CTCAE grade 2 or higher, during the first treatment cycle. Table 3 provides provisional doses for the first four dose levels, depending on observed toxicity.

Dose level escalation will be performed according to the following provisions:

- 100% dose increments (dose doubling): If no DLTs occurred AND no more than 1 out of 3 patients experienced BAL101553-related AEs ≥ grade 2, the dose will be doubled for the subsequent dose cohort.
- 50% dose increments: If (at least) two out of three patients have experienced BAL101553-related AEs ≥ CTCAE grade 2 at a given dose level, but no DLT has occurred, the dose will be increased by 50% for the subsequent dose cohorts, until a DLT is observed.
- ~30% dose increments: Once a DLT has occurred in (at least) one patient, the dose will be increased by ~30% for all subsequent dose cohorts until the MAD level is reached (see Table 4).

If BAL101553-related AEs occur which do not meet the definitions above, but which are considered significant based on a consensus decision of the Study Investigators and the Sponsor, a more conservative dose escalation approach may be implemented, e.g., dose increments of 50% or ~30% rather than 100%, or dose increments of ~30% rather than 50%, or a switch to q12h dosing.

Cohort dose levels will be rounded to the nearest whole number. Dose levels of ≥ 25 mg/day will be rounded to the nearest 5 mg.

Early toxicity

In the case of observation of DLTs at the starting dose level for the solid-tumor patients (2 mg/day), Cohort 1 will be expanded to [up to] 6 patients. If ≥ two of these six patients experience a DLT, the dose for the subsequent cohort will be decreased to 0.5 mg/m^2/day (approx. -50%, Appendix 2, Table 19). To achieve these dose levels, a flexible dose regimen will be implemented (Appendix 2, Table 20). Dose escalation will then be performed according to Appendix 2, Table 19. A summary of the rules governing dose escalation decisions is presented in Appendix 2, Table 21. Once the original starting dose level is reached, the Investigator will implement inter-cohort dose escalation increments of 33–50%, based on observed toxicities. At this point, a decision to continue with the flexible dose regimen, or to switch to a fixed dose regimen, will be made by the Investigator in conjunction with the Sponsor.

In the case of observation of DLTs at the starting dose level for the GBM/glioma patients, Cohort 1 will be expanded to [up to] six patients. If ≥ two of these six patients experience DLT(s), the dose for the subsequent cohort will be decreased by one level, down to the next-lowest level tested in solid-tumor patients.

Table 3 Cohorts 1–4: Dose escalation levels for patients with solid tumors

Cohort 1	**Dose level (mg/day)**	**2**						**2**		
	Cohort 1 toxicity	No relevant toxicity (NRT)						Grade 2 toxicity in ≥ 2 of 3 pts (G2)*		
Cohort 2	% change in dose	+ 100%						+ 50%		
	Dose level (mg/day)	**4**						**3**		
	Cohort 2 toxicity	NRT			G2		DLT	NRT/G2		DLT
Cohort 3	% change in dose	+100%			+50%		+30%	+50%		+30%
	Dose level (mg/day**)**	**8**			**6**		**5**	**5**		**4**
	Cohort 3 toxicity	NRT	G2	DLT	NRT/G2	DLT	NRT/G2/DLT	NRT/G2	DLT	NRT/G2/DLT
Cohort 4	% change in dose	+100%	+50%	+30%	+50%	+30%	+30%	+ 50%	+ 30%	+ 33%
	Dose level	**16**	**12**	**10**	**9**	**8**	**6**	**8**	**6**	**5**

pts=patients; DLT=dose limiting toxicity; NRT=no relevant toxicity; G2=Grade 2 toxivity in ≥ 2 of 3 patients.
Dose escalation for Cohorts 5 onwards may proceed as above (in the absence of ≥ grade 2 CTCAE toxicity), or a more conservative approach may be taken (30–50% increments).

*In the event that a DLT occurs at the starting dose, see Appendix 2.

3.1.2.2 Dose escalation criteria

Table 4 presents a summary of the rules governing escalation decisions. Escalation mainly depends on the occurrence of DLTs, which are described in detail in Section 3.2.2. Briefly, dose escalation to determine the MAD and MTD will be primarily based on whether DLTs are observed during the first 28-day treatment cycle (Cycle 1) of each dose cohort. However, the dose cohort escalation decisions must also include a clinical review of all relevant available data from the current and previous dose cohorts, and will not be solely based on Cycle 1 DLT information. Dose escalation and enrollment of a new cohort will require consultation and agreement between Investigators and the Sponsor, 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 process for dose escalation decisions is described in more detail in Section 3.2.3.

The number of patients required to evaluate a dose level/dose cohort refers to patients who are considered evaluable for DLT assessment (see definition in Section 3.1.2.3).

Each dose cohort will utilize an accelerated 3+3 dose escalation design. The MAD will be defined as the dose level at which DLT are observed during treatment Cycle 1 in ≥ two of [up to] six patients (> 33%). The MTD will be defined as the highest tested dose below the MAD with an acceptable tolerability profile. MTD and/or MAD may be different for patients with advanced or recurrent solid tumors and patients with recurrent or progressive GBM/high-grade glioma.

If any BAL101553-related DLT is observed, the cohort in which the toxicity occurred will be expanded [up] to six patients. If no other patients (i.e., ≤ one of the six patients) experience a DLT at this level, three patients will be enrolled at the next dose level (see Table 3). If any further patients (i.e., ≥ two of the six patients) experience a DLT, the dose escalation must be stopped and this dose will be declared the MAD. Furthermore, at least three additional patients must be enolled at the next lowest dose level, if only three patients were previously treated at that dose. If a DLT is observed in any patient in Cohort 1, the cohort will be expanded [up to] six patients. If ≥ two of these six patients experience DLT(s), the dose for the subsequent cohort will be decreased as detailed above.

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 in a new dose cohort 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 3.2.5.2.

Table 4 Dose escalation criteria

Number of patients with treatment-related 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 0 of these 3 patients (total of 1 of the 6 patients) experience DLT, enter 3 patients at the next higher dose level[2]. – If ≥ 1 of these 3 patients (total of ≥ 2 of the 6 patients) experience DLT, then dose escalation is stopped, and this dose is declared the MAD. At least 3 additional patients must be enrolled at the next lowest dose level[2] if only 3 patients were treated previously at that dose, to determine the MTD.
≥ 2 of 3 patients with DLT	Dose escalation must be stopped. This dose level will be declared the MAD. At least 3 additional patients must be enrolled at the next lowest dose level[2] if only 3 patients were treated previously at that dose, to determine the MTD.

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 cohort.
- ≥ 2 of [up to] 6 patients with DLT in a cohort 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 3 and Appendix 2 for descriptions of provisional dose levels.

3.1.2.3 Evaluable patient population for MTD-determination

The evaluable patient population for MTD-determination (MTD-determining population) will consist of patients who have been observed for ≥ 28 days following the first dose of BAL101553, have been evaluated for safety, and meet one the following criteria during the first 28-day treatment cycle (Cycle 1):

- Received at least one dose of BAL101553 and has experienced a DLT.
- Received at least 24 of the scheduled 28 daily doses for q24h administration, or at least 48 of the scheduled 56 doses for q12h administration (> 85% of the target dose in treatment Cycle 1), of BAL101553 without experiencing a DLT (including the ability to initiate treatment Cycle 2).

The correct dose must be given as described in Section 6.5.

Patients who do not meet these minimum requirements are ineligible for the MTD-determining population and will be replaced by recruitment of additional patients (see Section 4.5).

Up to 42 evaluable patients with advanced or recurrent solid tumors and up to 24 patients with recurrent or progressive GBM/high-grade glioma are planned to be enrolled in this phase of the study (see Section 3.3), with the actual enrollment determined by the number of cohorts and the degree of cohort expansion required. At least six evaluable patients must be treated at the MTD dose level in the dose escalation phase of the study, both in the group of patients with advanced or recurrent solid tumors and in the group of patients with recurrent or progressive GBM/high-grade glioma; dose-escalation cohorts will be independent for the solid-tumor and GBM/high-grade glioma patient groups.

BAL101553 treatment will be continued in patients enrolled in the dose escalation phase until disease progression, occurrence of unacceptable toxicity or until the Investigator or patient decides to withdraw from the study (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 8 and Section 5.6) 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 3.2.5.1). Intra-patient dose escalation should begin as the first dose of a subsequent cycle.

3.1.3 Expansion portion (Phase 2a)

Once the MTD has been defined, additional patients will be enrolled and treated at the RP2D dose of 25 mg/day (see Section 1.5.4). Enrolled patients will be evaluated for safety, pharmacokinetics, pharmacodynamic effects, and for antitumor activity.

At a minimum, a cumulative safety evaluation will be performed at the time of stage transition (see Section 8.3.2) and after approximately, 5 and 15 patients of the Simon's two-stage design have completed their first 28-day cycle, or have discontinued treatment. These evaluations will be performed by a committee comprising a minimum of:

- The Co-ordinating Investigators or delegates of each country
- The Sponsor's Project Physician (or qualified delegate)
- An external/independent cardiologist

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

Patients who withdraw prior to their post-baseline RANO assessment after having received at least 6 weeks of study treatment will be replaced by enrollment of additional patients (see Section 3.2.6 and Section 4.5).

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 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. Patients with a mixed response, e.g. a reduction in target lesion area but an increase in non-target disease or occurrence of new lesions, may continue on study treatment if their clinical condition is stable or improving. From Cycle 6 onwards, the interval between MRI scans may be extended from 8 weeks to 12 weeks. Section 5.6 provides criteria for assessing response, stable disease, and disease progression.

3.1.4 Food and beverage

BAL101553 is to be taken in the fasted state in the morning before breakfast. 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.

3.2 Treatment plan

3.2.1 Dose escalation scheme

Table 3 presents the planned dose escalation scheme, including the percent increases between the planned doses and the planned number of patients to be enrolled in each cohort. Table 4 presents the criteria for dose escalation and cohort size at each dose level. Section 3.1.2 provides a detailed description of the rules governing dose escalation and cohort size as presented in Table 3 and Table 4.

Cohorts of patients will receive increasing dose levels of BAL101553 until the MAD is reached. For each cohort, new patients will be recruited.

After the planned number of patients have completed at least one cycle of BAL101553 in a given dose cohort and have been evaluated for safety, the Investigators and Sponsor will decide whether to proceed to the next higher dose level. The procedure for dose escalation decisions is described in Section 3.2.3. Briefly, DLT occurring in Cycle 1 will be primarily considered in the dose escalation decision, however, the dose escalation decisions must be based on a clinical review of all relevant available safety data.

The dose levels listed in Table 3 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).
- In addition, splitting of the assigned daily dose via implementation of a twice-daily dosing regimen (q12h) may be implemented; e.g., a 30 mg daily dose may be administered as 15 mg twice daily. Only one regimen may be administered within a given dose cohort; however, the same daily dose may be administered concurrently to two parallel dose cohorts as a once-daily and twice-daily regimen.

3.2.2 Dose-limiting toxicity

Whenever possible, AEs will be graded according to the National Cancer Institute CTCAE v4.03 (Phase 1) or v5.0 (Phase 2a). DLT will be defined as any one of the AEs shown in Table 5 which occur during the first 28-day treatment cycle (Cycle 1) and if considered to be at least possibly related to BAL101553.

Table 5 Overview of dose-limiting toxicities

Toxicity	CTCAE 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 or baseline if baseline was abnormal) for > 7 days, or grade 4 (> 20 × ULN or baseline if baseline was abnormal) for any duration.
Cardiac	• Grade 3 QTc interval prolongation (QTcF > 500 ms or > 60 ms change from baseline). • Hypertension-related DLT: – Any recording of SBP > 220 mmHg or DBP > 110 mmHg; or – ≥ Grade 3 Hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) that cannot be controlled to Grade 2 Hypertension within 6 weeks of initiation or modification of antihypertensive treatment; or – BAL101553 treatment discontinuation due to hypertension that cannot be controlled – Grade 4 Hypertension Note: The need for administration of new antihypertensive medication or modification to more intensive antihypertensive medication will not be considered as DLT.
Other AEs	• AEs leading in Phase 1 to missing > 5 doses in Cycle 1, or causing a delay in the start of Cycle 2 by > 14 days. • 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 AE.
Exceptions	• The following 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.

3.2.3 Dose escalation decisions and patient enrollment

3.2.3.1 Responsibilities

Determinations of DLT, as well as decisions to escalate the study drug dose for each cohort or to expand enrollment in cohorts will be made by the Investigators in collaboration with the Sponsor (or Sponsor's named representative).

3.2.3.2 Consultation

At scheduled intervals, and *ad hoc* as needed, the Investigators and Sponsor 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 cohort will be reviewed. Safety information from patients in later cycles, updated safety data from ongoing/completed patients from previous cycles (including intra-patient dose escalation), pharmacokinetic data and efficacy information must also be considered. DLT which occurred in Cycle 1 of the current dose cohort 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 both the Sponsor and Principal Investigators.

After reaching consensus the Investigators and Sponsor will select the actual dose for the next cohort of patients, based on the planned dose escalation levels (see Table 3) or intermediate levels as a guide.

Dose escalation in a new cohort must not occur before completion of the first treatment cycle in the preceding cohort, where completion means either occurrence of DLT, or administration to the planned number of patients of at least 24 of the scheduled 28 doses in the case of a once-daily regimen, or at least 48 out of the scheduled 56 doses in the case of a twice-daily regimen; 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.

Other dosing decisions will be taken as described in Section 3.2.5.

3.2.3.3 Enrollment

Following each consultation and dose escalation decision, the Principal Investigators of all study centers must be notified by the Sponsor of the daily dose (in mg/day) and the dosing regimen (i.e., q24h or q12h) to be given to patients in the new dose cohort. Investigators must not enroll patients into a new cohort 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 h of informed consent); when a patient is scheduled for their first dosing (at least 24 h prior to the scheduled dosing), after administration of the first dose (within 24 h after dosing) and when a patient discontinues treatment (within 24 h 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 cohort size and the post-dose observation periods as described in Section 3.1.2.2.

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.

3.2.4 Fixed-dose treatment at the RP2D

In Phase 2a, patients will be treated at the RP2D of 25 mg/day in a q24h dosing regimen (see Section 1.5.4). The dose may be reduced based on the severity of events to either 20 mg/day, 15 mg/day, or 10 mg/day. Dosing of any new patients may only be started after approval by the Sponsor.

3.2.5 Dose modifications

3.2.5.1 Dose increases (Phase 1 portion only)

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 the 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 higher dosing cohort have completed their first treatment cycle with acceptable tolerability and a decision has been taken to start dosing in the subsequent dose cohort. 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 will 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 cohort for MTD determination, and DLT occurring after a dose increase will not be counted in the formal computation of DLT incidence for any cohort. However, DLT reported after dose increases may be taken into account in dose escalation decisions (Section 3.2.3).

No dose increases are permitted in the Phase2a portion of the study.

3.2.5.2 Dose reductions and dose delays due to adverse events

When a patient experiences a DLT (in the Phase 1 portion of the study) or a DLT equivalent event (in the Phase 2a portion of the study), treatment with BAL101553 must be interrupted until recovery to ≤ CTCAE grade 1 or baseline. If the patient continues in the study, subsequent doses of BAL101553 will be reduced by one dose level in the Phase 1 portion of the study. In the Phase 2a portion of the study the dose will be reduced from the RP2D of 25 mg/day to 20 mg/day or 15 mg/day, depending on the severity of the event. Non-DLT events may also require dose delays and/or dose reductions, or study discontinuation.

In the Phase 1 portion of the study, Cycle 1 will be regarded as complete if there is administration of at least 24 of the scheduled 28 doses of BAL101553 in the case of a q24h regimen, or at least 48 out of the scheduled 56 doses of BAL101553 in the case of a q12h regimen, with recovery of toxicity to permit initiation of Cycle 2 with a maximum delay of 14 days.

Table 6 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 2 AEs and any dose modifications in a timely fashion.

Deviations from the visit schedule by ± 3 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 in the Phase 1 portion of the study. In the Phase 2a portion of the study a maximum of two dose reductions are permitted with the initial dose reduction from the RP2D of 25 mg/day to either 20 mg/day or 15 mg/day depending on the severity of the event and the second dose reduction from 20 mg/day to 15 mg/day or 10 mg/day or from 15 mg/day to 10 mg/day. 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.

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

If, after interruption of treatment and resolution, treatment is re-initiated at the same dose level according to the criteria in Table 6, 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 7.2.5 and 7.2.6.

Table 6 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 1 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 criteria below	Resolution of DLT[1] to ≤ CTCAE grade 1 (or baseline) and criteria 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	≤ 3.0 × ULN[2]	> 5.0 × ULN[2] (any duration)	> 5.0 × ULN[2] for > 7 days	≤ 3.0 × ULN[2]	(No specific criteria)
Total bilirubin (TB)	≤ 1.5 (2.0)[2] × ULN[2]	> 2.0 × ULN[2]	> 2.0 × ULN[2]	≤ 1.5 (2.0)[2] × ULN[2]	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
Blood pressure[6]	SBP <160 and DBP <100 mmHg	SBP ≥180 or DBP ≥110 mmHg[7]	Hypertension-related DLT	SBP <160 and DBP <100 mmHg	Grade 4 Hypertension
Other toxicity[8]	≤ 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] Or baseline if baseline was abnormal.
[3] Consider neurology consultation if neurotoxicity occurs.
[4] Despite appropriate medication/management.
[5] See Section 5.5.5: requires ECG monitoring, clinical assessment, blood sampling for PK assessment and increased ECG monitoring at next dosing.
[6] SBP must be < 140 mmHg and DBP must be < 90 mmHg prior to dosing on Cycle 1 Day 1.
[7] If not normalized on the same day.
[8] Grade 3 fatigue; grade 3/4 alkaline phosphatase elevations, asymptomatic hypophosphatemia, or lymphopenia; do not require dose delays/modifications unless considered clinically significant.

3.2.6 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 withdrawal 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. 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 Phase 1 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. Patients in the Phase 2 a expansion portion of the study (Simon's two-stage design, Section 3.1.3) will be replaced if they could not complete at least one post-baseline RANO assessment after having received at least 6 weeks of study treatment. Section 4.5 describes the replacement of patients who do not complete these minimum numbers of 28-day treatment cycles.

3.2.7 Missed-dose management

If a dose of BAL101553 is missed due to reasons other than toxicity, the missed dose can be taken later in the same day, as long as the patient is able to observe the 4 h pre- and 1 h post-dose fast. If the patient cannot follow the fasting guidelines, or cannot take the dose for reasons other than toxicity, the dose will not be replaced (i.e., patients should not take more than one day's dose on any given calendar day). For a twice-daily regimen, the minimum time between the two administrations of BAL101553 within the same day should be 8 h. Should a patient miss a scheduled dose due to vomiting, the patient should not re-take the dose and should wait until their next scheduled dose. If more than four doses (once-daily dosing) or more than 8 doses (twice-daily dosing) are missed in one cycle (i.e., > 15%), the patient may resume treatment as scheduled, but will be ineligible for MTD determination (See Table 7).

Table 7 Missed-dose outcomes (Phase 1)

Number of missed doses		Outcome
Once-daily dosing	**Twice-daily dosing**	
Any number of doses due to a DLT	Any number of daily doses due to a DLT	• Patient must stop treatment • Patient may continue treatment at a lower dose, depending on the observed toxicity • Patient is eligible for MTD evaluation
≤ 4 for any reason (other than a DLT)	≤ 8 for any reason (other than a DLT)	• Patient may continue dosing schedule • Patient is eligible for MTD evaluation
≥ 5 for reasons other than toxicity	≥ 9 for reasons other than toxicity	• Patient may continue dosing schedule • Patient is not eligible for MTD evaluation
> 5 due to toxicity (constitutes a DLT if in Cycle 1)	> 5 due to toxicity (constitutes a DLT if in Cycle 1)	• Patient must stop treatment • Patient may continue treatment at a lower dose, depending on the observed toxicity • Patient is eligible for MTD evaluation

3.3 Number of patients

Up to 88 evaluable patients will be enrolled in the study.

The dose escalation portion of the study is completed. Dosed were 26 patients with advanced or recurrent solid tumors and 28 patients with recurrent or progressive GBM or high-grade glioma. In each of the groups 24 patients were evaluable for MTD assessment. Up to 34 evaluable patients with recurrent GBM whose tumor tissue is positive for EB1 and up to 6 evaluable patients with planned re-resection of recurrent GBM are expected to be treated in the expansion portion.

Assuming approximately 25% non-evaluability rate, up to 104 patients may be enrolled in total.

3.4 Study centers

Four investigational centers participated in the dose escalation portion designed to characterize the MTD, and up to twenty investigational centers will participate in the expansion portion in patients treated at the RP2D.

4 STUDY POPULATION

4.1 Target population

Consenting patients with histologically or cytologically confirmed advanced or recurrent solid tumors who failed standard therapy, or for whom no effective standard therapy is available (Phase 1); or with recurrent or progressive GBM or high-grade glioma (Phase 1); or recurrent GBM with tumor tissue positive for EB1 (Phase 2a); or with planned re-resection of recurrent GBM (Phase 2a); who meet the inclusion/exclusion criteria, will be eligible for enrollment into the study.

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 28 days prior to the start of treatment. Screening evaluations will be performed within 15 days prior to start of treatment.

1. Age 18 years or older.
2. Patients who have in the:
   Phase 1 dose escalation portion either of the following:
   a. a histologically- or cytologically confirmed advanced or recurrent solid tumor, who failed standard therapy, or for whom no effective standard therapy is available to them*
   b. histologically-confirmed GBM or high-grade glioma, with progressive or recurrent disease after prior radiotherapy, with or without chemotherapy. This will also include patients with histologically-confirmed low-grade glioma who present with unequivocal evidence by imaging of transformation to high-grade glioma/GBM.

   * 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.

   Phase 2a dose expansion portion (Simon's two-stage design):

   Recurrent, histologically confirmed, GBM with tumor tissue positive for EB1 by IHC as determined by central laboratory testing; eligible are patients with de novo GBM after prior radical chemoradiotherapy or secondary GBM after prior chemotherapy or radiotherapy; patients must be neurologically stable, without progression of neurologic symptoms, within 15 days prior to starting study drug.

   Phase 2a dose expansion portion (Surgical cohort):

   Recurrent GBM with planned re-resection. Details of the inclusion criteria for the Surgical cohort will be provided in a separate protocol amendment if futility is rejected in Stage 1 of the Simon's two-stage study portion.
3. **Phase 1 dose escalation portion**

   Patients with advanced solid tumors must have measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) documented within 35 days prior to starting study drug, or non-measurable prostate or ovarian cancer that can

be followed by prostate specific antigen (PSA) or cancer antigen-125 (CA-125), documented within 15 days prior to starting study drug.

Patients with glioblastoma or high-grade glioma must have measurable disease, defined by contrast-enhancing MRI, within 15 days prior to starting study drug. Patients with previous low-grade glioma that progressed after prior radiotherapy (with or without chemotherapy) and are found to have high-grade glioma/GBM by biopsy or imaging are also eligible.

Phase 2a dose expansion portion (Simon's two-stage design):
Patients with recurrent glioblastoma must be evaluable per RANO, defined by contrast-enhancing MRI, within 15 days prior to starting study drug.

4. Life expectancy ≥ 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).

   *All listed laboratory parameters, and cardiac troponin (see Exclusion criterion 13), must be included in the study-specific pharmacy prescription chart. During the study, all parameters applicable for any study visit must be reviewed by the investigator and the pharmacy prior to dispensing of any study medication.
6. Patients with advanced solid tumors must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and patients with recurrent or progressive glioblastoma must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
7. Female patients who are not pregnant or breast-feeding and meet one of the following conditions:
   - Postmenopausal defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient.
   - Post-hysterectomy and/or post-bilateral salpingectomy or ovariectomy.
   - Congenital or acquired condition that prevents childbearing.

- 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)
  - intrauterine hormone-releasing system (IUS)
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
  - total heterosexual abstinence

    * The hormonal contraception method must be supplemented with a barrier method (preferably male condom).

8. Male patients must agree not to donate sperm from the first dose of study drug until 90 days after the end of treatment. Male patients, without a vasectomy or other conditions resulting in azoospermia and with a partner of childbearing potential, must agree to use condoms during the study and for at least 90 days after the end of treatment. 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), 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, prior to study-specific screening procedures.
10. Patients must be able and willing to comply with the required food intake restrictions.

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 who have received chemotherapy, radiotherapy, immunotherapy, or investigational agents within 4 weeks (2 weeks for single fraction of palliative radiotherapy, 6 weeks for nitrosoureas or mitomycin C) prior to starting study drug, or who 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 recurrent or progressive GBM or high-grade glioma who have: received radiotherapy within 6 weeks (Phase 1) or 12 weeks (Phase 2a), unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field, or there is histological confirmation of unequivocal tumor progression; received administration of prior anti-tumor chemotherapy within 4 weeks, or within 6 weeks for nitrosoureas; undergone surgical resection within 4 weeks (Phase 2a: 2 weeks) or a stereotactic biopsy/core biopsy within 1 week prior to starting study drug.

2. Patients who have had prior exposure to BAL101553.
3. Inability to swallow oral medication.
4. Increase in steroid dose in GBM or high-grade glioma patients within 5 days prior to first study-drug administration or requirement for > 6 mg/day dexamethasone or equivalent for symptom control.
5. 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).
6. Symptomatic brain metastases or leptomeningeal disease, indicative of active disease, in patients with advanced or recurrent solid tumors.
7. Peripheral neuropathy ≥ CTCAE grade 2.
8. Known human immunodeficiency virus (HIV) infection.
9. Known acute or chronic hepatitis B or hepatitis C infection.
10. Systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg at the screening visit.
11. Blood pressure (BP) combination treatment with more than two antihypertensive medications.
12. Any history of cerebral hemorrhage, cerebral aneurysm, or ischemic stroke; or a history of transient ischemic attack within 24 months prior to screening in patients with advanced or recurrent solid tumors.

    Acute intratumoral hemorrhage in patients with recurrent or progressive GBM or high-grade glioma, considered by the study Investigator to be clinically significant.
    - Patients with MRI or CT demonstrating old hemorrhage or subacute bleed after a neurosurgical procedure (biopsy or resection) will be eligible for treatment.
13. 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 institutional ULN.
- Congestive heart failure of New York Heart Association class III or IV.

14. 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.
15. 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.
16. 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 30 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 or unacceptable toxicity occurs.

In the Phase 2a portion of the study, patients with a mixed response, e.g. a reduction in target lesion area but an increase in non-target disease or occurrence of new lesions, may continue on study treatment if their clinical condition is stable or improving.

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 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 for example:

- Adverse event.
- Abnormal laboratory value.
- Abnormal test procedure result.
- Missing greater than five (Phase 1) or seven (Phase 2a) doses in a cycle, or causing a delay in the start of a cycle by more than 14 days (Phase 1) due to toxicity.
- Intercurrent illness that prevents further administration of treatment.
- Death.
- Withdrawal of consent.

- Withdrawn from the study at Investigator discretion.
- Protocol violation/non-compliance.
- Lost to follow-up.
- New cancer treatment/therapy.
- Administrative reasons.

A patient must be discontinued from the study treatment if any of the following events occur:

- Disease progression.
  (In the Phase 2a portion of the study, patients with a mixed response, e.g., a reduction in target lesion area but an increase in non-target disease or occurrence of new lesions, may continue on study treatment if their clinical condition is stable or improving)
- Drug-related AE(s) in Phase 1 which lead(s) to missing greater than five doses within any 28-day cycle, or lead(s) to a delay of more than 14 days in the commencement of the subsequent cycle.
- Requirement for more than two dose level reductions in a patient.
- Recurrence of the same toxicity, with the same or worse severity, in a patient who had a dose reduction due to toxicity.
- Requirement for other anticancer therapy.
- Grade 4 hypertension.
- Recurrent QTcF > 500 ms or QTcF increase from baseline > 60 ms.
- Pregnancy

For all patients who discontinue the study treatment, AE monitoring must be continued for at least 28 days after the last dose of study drug. Patients will also be contacted to record antineoplastic therapies received within 28 days after discontinuation of study drug (see Sections 7.2.5 and 7.2.6) or thereafter as part of their survival follow-up in Phase 2a (see Section 5.3.5).

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 Replacement of patients

Patients in the dose escalation portion of the study (Section 3.1.2) must meet the following minimum safety evaluation requirements in Cycle 1:

- Received at least one dose of BAL101553 and experienced a DLT.
- Received at least 24 of the scheduled 28 doses of BAL101553 for q24h administration, or at least 48 of the scheduled 56 doses of BAL101553 for q12h administration, 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.

The correct dose must be given as described in Section 6.5.

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

In the Phase 2a dose expansion portion of the study (Simon's two-stage design, see Section 3.1.3), patients with measurable disease at baseline who discontinue the study treatment will be replaced if they did not have at least one postbaseline RANO assessment after having received at least 6 weeks of study treatment.

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Summary of schedule of assessments

Table 8 presents a summary of the schedule of assessments to be performed from Screening through to the End of Study visit for the Phase 1 portion of the study, while Table 9 presents the summary of the Schedule of assessments for the Phase 2a portion of the study.

AEs must be monitored on an ongoing basis and at each study visit and AE monitoring must be continued for at least 28 days following the last dose of study treatment (see Section 5.3.4 and Section 7).

5.2 Changes in response to the COVID-19 pandemic

In response to the COVID-19 pandemic, the treating Investigator, in collaboration with the Sponsor, may perform a safety review and risk assessment for patients who have been treated for at least 6 weeks, to determine, in the patient's best interest, a risk-adapted safety monitoring approach to be implemented any time after the completion of Cycle 2. This will necessarily comprise defined and temporary changes which differ from the provisions of the study protocol in regard to patient-related study procedures.

These temporary changes take precedence over existing protocol provisions, and where any conflict occurs, these changes prevail.

They may include, but are not restricted to, measures such as the following:

- Patients to be seen at the study sites every 8 weeks instead of every 2 weeks
- Scheduled study visits within the 8 weeks will be replaced by telephone follow-up with the patients every 2 weeks by the Principal Investigator or Sub-investigator, with further investigations (such as laboratory assessments, vital signs, physical examinations, or other examinations) being performed as clinically indicated (using local facilities close to the patient's home if required)
- 12-lead ECGs will be assessed every 8 weeks (at site visits) instead of every 4 weeks
- BAL101553 supply for 8 weeks will be provided by the study site to the patient

Principal Investigators must inform the patients about the changes to planned procedures, and document that patient consent has been obtained to these changes.

All changes to study procedures related to the COVID-19 pandemic must be specifically documented in the local source data / study site files.

Table 8 Phase 1 - Schedule of assessments

	Screening	Cycle 1					Cycle 2					Cycle 3 and subsequent cycles					End of Study
Day (D) of cycle[1, 24]	**−15 to −1**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D15**	**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/height	X																
Physical examination/body weight/ECOG performance status[3]	X	X					X					X					X
Vital signs[4]	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
12-lead ECG[6]	X	X	X	X			X	X	X			X					X
Chest X-ray[7]	X																
Hematology[8]	X	X	X	X	X		X	X	X	X		X	X				X
Biochemistry[9]	X	X	X	X	X		X	X	X	X		X	X				X
Coagulation[10]	X	X					X					X					X
Urinalysis[10]	X	X					X					X					X
Cardiac troponin[11]	X	X	X	X	X		X	X	X	X							X
Pregnancy test[12]	X	X					X					X					X
Echocardiography	X																X
Radiological assessment of tumor (RECIST/RANO criteria)[7,13]	X										X			X (ENC)			X
CA-125 or PSA in non-measurable ovarian or prostate tumors[14]	X					X					X			X			X
BAL101553 administration (in clinic)[15]		X	X	X	X		X	X	X	X		X	X				
Drug dispensing and accountability		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Adverse events[16]		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Serious adverse events[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Concomitant therapies		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Blood for pharmacokinetics[17]		X	X	X	X		X	X	X	X							X
24 h urine for pharmacokinetics[18]		X					X										
Dried-blood-spot analysis (Centogene cards)[19]		X															
Blood for CTC analysis[20]	X	X	X	X	X					X							
Blood for CEC/CEP analysis[21]	X	X	X		X												
Blood for OCBs[22]		X	X		X					X							
Tumor biopsy[23]	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).

1. D28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on D1 of the subsequent cycle.
2. Informed consent must be obtained within 28 days of D1/Cycle 1. Screening assessments must be performed and completed within 15 days of D1/Cycle 1 or D1.
3. For D1 of all cycles, the physical exam, ECOG status and weight must be performed within the 72 h prior to dosing; if the Screening exam was performed ≤ 72 h prior to D1, it does not need to be repeated on D1/Cycle1.
4. Complete vital signs will be obtained at Screening and at the End of Study visit. During PK sampling on D1 of Cycles 1, 2 , vital signs will be obtained pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after [first] intake of study medication (see Section 5.5.4); for cohorts using a q12h dosing regimen, vital signs will be also be obtained at 12 h (i.e., prior to the second daily dose) and 14 h (i.e., after the second daily dose) after first dosing on D1 of Cycles 1 and 2. On D8, D15, and D22 of Cycle 1 and Cycle 2, vital signs will be obtained prior to dosing and 0.5 h, 1 h, 2 h and 4 h after [first] intake of the study medication. From Cycle 3 onwards complete vital signs will be obtained prior to dosing and 1 h after [the first] intake of BAL101553 study drug on D1 and D15.
5. On all assessment days during Cycle 1, and Cycle 2, blood pressure (BP) measurements will be obtained every 30 min until at least 4 h after the intake of study drug medication; for cohorts using a q12h dosing regimen, BPs will be also be obtained at 12 h (i.e., prior to the second daily dose) and 14 h (i.e., after the second daily dose) after first dosing on D1 of Cycles 1 and 2. If SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored 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. From Cycle 3 onwards, BP measurements will be obtained (in the context of complete vital signs) prior to dosing and 1 h after [the first] intake of BAl101553 study drug, on D1 and D15 (see Section 5.5.4).
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, as follows (see Section 5.5.5):
   - At Screening to determine study eligibility of patients and at the End of Study visit.
   - On D1 of Cycles 1 and 2: pre-dose; and 1 h, 2 h, 4 h and 8 h after intake of BAL101553 study medication (within 5 min prior to PK blood sampling; see Section 5.7); for cohorts using a q12h dosing regimen, triplicate ECG will be obtained 14 h (i.e., after the second daily dose) after first dosing on D1 of Cycles 1 and 2 (Phase 1).
   - On D8 and D15 of Cycles 1 and 2: prior to, and at 2 h and 4 h after, intake of study medication.
   - On D1 of Cycle 3 and all subsequent cycles: prior to [first] BAL101553 administration.
   - In patients undergoing intra-patient dose escalation or dose reduction on D1, D8 and D15 of Cycles 1 and 2 after intra-patient escalation to a new dose level: prior to, and at 2 h and 4 h after, [first] intake of BAL101553 study medication. From the third cycle onwards, ECGs will only be obtained pre-dose on Day 1.
   - Triplicate 12-lead ECG should also be obtained when patients experience SBP ≥ 180 mmHg or DBP ≥ 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

   ECG from Screening; D1 of Cycles 1, 2; and any abnormal ECG; must be transmitted to a central ECG laboratory for evaluation (including QTc assessment).
7. Chest X-ray: to establish a baseline for safety assessments; to be repeated as clinically indicated. For tumor assessments a chest CT scan should be performed. If a chest CT is performed, then a chest X-ray is not required. Radiology assessments conducted within 35 days prior to D1 of Cycle 1 do not need to be repeated during Screening (see Section 5.6).
8. Hematology must be performed and reviewed (see Section 5.5.7.1):
   - within 72 hours of first administration of BAL101553 on D1 of Cycle 1
   - within 24 hours prior to D1 of any subsequent Cycle
   - within 24 hours prior to administration of BAL101553 on D8, D15 and D22 of Cycle 1 and Cycle 2
   - within 24 hours prior to administration of BAL101553 on D15 of all Cycles from Cycle 3 onwards.
9. Biochemistry must be performed according to the same schedule as Hematology (see Section 5.5.7.2).
10. Coagulation and urinalysis must be performed and reviewed within 72 hours of first administration of BAL101553 on D1 of Cycle 1. Coagulation and urinalysis must also be performed and reviewed within 24 hours prior to [first] administration of BAL101553 on D1 of all subsequent Cycles (see Sections 5.5.7.4 and 5.5.7.5).
11. Cardiac troponin must be performed and reviewed within 72 hours of first administration of BAL101553 on D1 of Cycle 1. Cardiac troponin must also be performed and reviewed within 24 hours prior to administration of BAL101553 on D8, D15 and D22 of Cycle 1, and Cycle 2. The same test (cardiac troponin-I or troponin-T) must be used consistently for a given patient at Screening and throughout the study (see Section 5.5.7.3).
12. Women of child-bearing potential must have a negative serum pregnancy test (hCG) at Screening, and negative serum or urine pregnancy test (hCG) prior to BAL101553 dosing on D1 of every cycle. Screening labs performed ≤ 72 h prior to first dosing, and labs performed within the 24 h prior to all other in-clinic dosing days, do not need to be repeated (see Sections 5.5.7.6 and 7.3).
13. Tumor assessment by radiological exam (CT/MRI scans) will be performed at Screening, or within the 35 days prior to D1 for patients with advanced or recurrent solid tumors and within the 15 days prior to D1 for patients with recurrent or progressive GBM or high-grade glioma; 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. End of Study assessment does not need to be repeated if an assessment was done within the 35 days prior.

14. CA-125 or PSA in patients with non-measurable ovarian or prostate tumors will be assessed at Screening and must be repeated within the 7 days prior to completion of every cycle, before administration of the next cycle of BAL101553. End of Study assessment does not need to be repeated if an assessment was done within the 14 days prior.
15. Patients must fast ≥ 4 h prior to and ≥ 1 h after each BAL101553 administration.
16. AE (including SAE) monitoring must be continued for at least 28 days following the last dose of study treatment. SAEs need to be reported from the time of informed consent to allow for an assessment of serious procedure related events, i.e., serious events/complications related to the screening study procedures. Non-serious AEs will be collected from the time of first study drug administration. Non-serious AEs that occur between informed consent and first study drug administration will be collected as pre-dose medical history.
17. Blood PK samples will be collected from all patients as follows (see Section 5.7.1):

    Dose escalation portion (Phase 1) of the study (see Sections 3.1.2):

    - D1 of Cycles 1 and 2: pre-dose, and at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after intake of BAL101553 study medication; for cohorts using a q12h dosing regimen, a sample will be also be obtained at 12 h (i.e., prior to the second daily dose) after first dosing. Depending on the observed PK during the dose escalation portion of the study, a sample at 72 h may also be obtained.
    - D8, D15 and D22 of Cycles 1 and 2: pre-dose.
    - At the End of Study visit and when a patient reports a DLT, if possible. The sampling schedule may be amended based on observed PK in humans.

    Intra-patient dose escalation or dose reduction

    - In patients undergoing intra-patient dose escalation or dose reduction, additional blood PK samples must be collected on one dosing day at each new dose level for a given patient. These PK samples must be collected pre-dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after dosing. For cohorts using a q12h dosing regimen, a sample will be also be obtained at 12 h (i.e., prior to the second daily dose) and after first dosing.
18. Urine PK samples will be collected from patients with advanced or recurrent solid tumors over two 24-h periods each starting on D1 of Cycles 1 and 2. Patients should be instructed to void prior to dosing on these two days (see Section 5.7.2). Urine samples will not be collected from GBM/glioma pateints.
19. One blood sample (approximately 4 mL) will be obtained pre-dose at D1 of Cycle 1 in an EDTA-tube and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphism and/or genes involved in drug transport or drug metabolism (see Section 5.8.1.1).
20. Samples for CTCs will be obtained from patients with advanced or recurrent solid tumors at Screening; and pre-dose on: D1, D15 and D22 of Cycle 1; and on D22 of Cycle 2 (see Section 5.8.1.1). Samples for CTCs will be obtained from patients with recurrent or progressive GBM or high-grade glioma at Screening; pre-dose and at 2 h and 24 h after [first] intake of BAL101553 study medication on D1 of Cycle 1; and pre-dose on D8 and D22 of Cycle 1 and on D22 of Cycle 2. Samples for CTCs will also be obtained using the same schedules in patients undergoing intra-patient dose escalation, at each new dose level.
21. Samples for analysis of CECs and CEPs will be obtained from patients with advanced or recurrent solid tumors at Screening and on D1 of Cycle 1 pre-dose and at 4 h, 6 h, 10 h, and 24 h after [first] intake of BAL101553 study medication (see Section 5.8.1.1). Up to four additional blood samples will be obtained for analysis of CECs and CEPs at ~72 h (D4), 120 h (D6) and/or 7 days (D8) and 21 days (D22) after [first] study drug administration on Cycle 1 D1, if feasible for the patient and clinical staff. If a tumor biopsy is taken on the same day, blood for biomarker analysis is to be obtained prior to the tumor biopsy. Samples of blood biomarkers (i.e., CECs and CEPs) will also be obtained using the same schedule in patients undergoing intra-patient dose escalation, during the first treatment cycle at each new dose level.
22. Blood samples for analysis of other circulating biomarkers (OCBs; e.g., extracellular vesicles, circulating tumor DNA, circulating tumor RNA or proteins) will be obtained from patients with recurrent or progressive GBM or high-grade glioma pre-dose and 8 h and 24 h after [first] intake of BAL101553 study medication on D1 of Cycle 1; pre-dose on D8 of Cycle 1; and pre-dose on D22 of Cycle 1 and Cycle 2 (see Section 5.8.1.1). Samples for OCBs will also be obtained using the same schedule in patients undergoing intra-patient dose escalation, at each new dose level.
23. Where possible, a tumor biopsy (see Section 5.8.1.2) will be obtained during Screening from patients with advanced or recurrent solid tumors, 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.

    Tumor biopsies will not be obtained from GBM/high-grade glioma patients.
24. Deviations from the visit schedule by ± 3 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. After treatment for more than 12 cycles, D15 visits may be skipped in patients with an adequate and stable condition as per Investigator's clinical judgement.

Table 9 Phase 2a - Schedule of assessments

	Screening	Cycle 1					Cycle 2					Cycle 3 and subsequent cycles			End of Study	OS FUP[18]
Day (D) of cycle[1]	**−15 to −1**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D15**	**D28**		
Informed consent[2]	X															
Inclusion/exclusion criteria	X															
Demographics/medical history/height	X															
Physical examination/body weight/ECOG performance status[3]	X	X					X					X			X	
Vital signs[4], blood pressure[5]	X	X	X	X	X		X	X	X	X		X	X		X	
12-lead ECG[6]	X	X	X	X			X		X			X			X	
Hematology[7], biochemistry[8]	X	X	X	X	X		X	X	X	X		X	X		X	
Coagulation[9]	X	X					X					X			X	
Urinalysis[9]	X	X					X					X			X	
Cardiac troponin[10]	X	X	X	X	X		X		X						X	
Pregnancy test[11]	X	X					X					X			X	
Echocardiography	X														X	
Radiological assessment of tumor (RANO criteria) [12]	X										X			X (ENC)	X	
BAL101553 administration (in clinic)[13]		X	X	X	X		X	X	X	X		X	X			
Drug dispensing and accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for pharmacokinetics[15]		X	X	X	X		X								X	
Dried-blood-spot analysis (Centogene cards)[16]		X														
Liquid biopsy (for biomarker research)[17]	X											X			X	
Survival contact[18]																X

ENC = even-numbered cycles (Note that from Cycle 6 onwards, the interval between MRI scans may be extended from 8 weeks to 12 weeks).

1. D28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on D1 of the subsequent cycle. Deviations from the visit schedule by ± 3 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. After treatment for more than 12 cycles, D15 visits may be skipped in patients with an adequate and stable condition as per Investigator's clinical judgement.
2. Informed consent must be obtained within 28 days of D1/Cycle 1. Screening assessments other than chest X-ray must be performed and completed within 15 days of D1/Cycle 1 or D1.
3. For D1 of all cycles, the physical exam, ECOG status and weight must be performed within the 72 h prior to dosing; if the Screening exam was performed ≤ 72 h prior to D1, it does not need to be repeated on D1/Cycle1.
4. Complete vital signs will be obtained at Screening and at the End of Study visit. During PK sampling on D1 of Cycle 1, vital signs will be obtained pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after intake of study medication (see Section 5.5.4). On other assessment days of Cycles 1 and 2, vital signs will be obtained prior to dosing and 0.5 h, 1 h, and 2 h after intake of the study medication. From Cycle 3 onwards complete vital signs will be obtained prior to dosing and 1 h after intake of BAL101553 study drug on D1 and D15.
5. On all assessment days during Cycles 1 and 2, blood pressure (BP) measurements will be obtained prior to dosing and 0.5 h, 1 h, and 2 h after intake of the study medication. From Cycle 3 onwards BP measurements will be obtained prior to dosing and 1 h after intake of the study medication. If SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored 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 5.5.4).
6. Single 12-lead ECGs are to be obtained as follows (see Section 5.5.5):
   - At Screening to determine study eligibility of patients and at the End of Study visit.
   - On D1 of Cycle 1: pre-dose; and 1 h, 2 h, 4 h and 8 h after intake of BAL101553 study medication (within 5 min prior to PK blood sampling; see Section 5.7.
   - On D8 and D15 of Cycle 1, and D1 and D15 of Cycle 2: pre-dose and 2 h after intake of study medication.
   - On D1 of Cycle 3 and all subsequent cycles: prior to BAL101553 administration.
   - Single 12-lead ECGs should also be obtained when patients experience SBP ≥ 180 mmHg or DBP ≥ 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
7. Hematology must be performed and reviewed (see Section 5.5.7.1):
   - within 72 hours of first administration of BAL101553 on D1 of Cycle 1
   - within 24 hours prior to D1 of any subsequent Cycle
   - within 24 hours prior to administration of BAL101553 on D8, D15 and D22 of Cycle 1 and Cycle 2
   - within 24 hours prior to administration of BAL101553 on D15 of all Cycles from Cycle 3 onwards.
8. Biochemistry must be performed according to the same schedule as Hematology (see Section 5.5.7.2).
9. Coagulation and urinalysis must be performed and reviewed within 72 hours of first administration of BAL101553 on D1 of Cycle 1. Coagulation and urinalysis must also be performed and reviewed within 24 hours prior to administration of BAL101553 on D1 of all subsequent Cycles (see Sections 5.5.7.4 and 5.5.7.5).

10. Cardiac troponin must be performed and reviewed within 72 hours of first administration of BAL101553 on D1 of Cycle 1. Cardiac troponin must also be performed and reviewed within 24 hours prior to administration of BAL101553 on D8, D15 and D22 of Cycle 1, and on D1 and D15 of Cycle 2. The same test (cardiac troponin-I or troponin-T) must be used consistently for a given patient at Screening and throughout the study (see Section 5.5.7.3).
11. Women of child-bearing potential must have a negative serum pregnancy test (hCG) at Screening, and negative serum or urine pregnancy test (hCG) prior to BAL101553 dosing on D1 of every cycle. Screening labs performed ≤ 72 h prior to first dosing, and labs performed within the 24 h prior to all other in-clinic dosing days, do not need to be repeated (see Sections 5.5.7.6 and 7.3).
12. Tumor assessment by radiological exam (MRI scans) will be performed at Screening, or within the 15 days prior to D1; and within two weeks prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553. From Cycle 6 onwards, the interval between MRI scans may be extended from 8 weeks to 12 weeks. End of Study assessment does not need to be repeated if an assessment was done within the 35 days prior.
13. Patients must fast ≥ 4 h prior to and ≥ 1 h after each BAL101553 administration.
14. AE (including SAE) monitoring must be continued for at least 28 days following the last dose of study treatment. SAEs need to be reported from the time of informed consent to allow for an assessment of serious procedure related events, i.e., serious events/complications related to the screening study procedures. Non-serious AEs will be collected from the time of first study drug administration. Non-serious AEs that occur between informed consent and first study drug administration will be collected as pre-dose medical history.
15. Blood PK samples will be collected from all patients as follows (see Section 5.7.1):
    - D1 of Cycle 1: pre-dose and at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after intake of BAL101553 study medication.
    - D8, D15 and D22 of Cycle 1, and D1 of Cycle 2: pre-dose
    - At the End of Study visit and when a patient reports a DLT, if possible.
16. One blood sample (approximately 4 mL) will be obtained pre-dose at D1 of Cycle 1 in an EDTA-tube and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphism and/or genes involved in drug transport or drug metabolism (see Section 5.8.1.2).
17. A liquid biopsy for biomarker research should be obtained at Screening and at the End of Study visit, and on D1 after the confirmatory MRI scan for complete response/partial response (see Section 5.8.1.2).
18. Overall survival follow-up (OS FUP) at 3-month intervals (±14 days) from day of the last dose of study drug; survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries (see Section 5.3.4).

5.3 Summary of study visits

5.3.1 Screening visit

Informed consent must be obtained within the 28 days prior to administration of the first dose of study drug.

Patients must provide written informed consent before any screening-specific assessments are performed. Study centers must maintain a log of all consenting patients, which must include date and time of consent.

Screening assessments must be performed in accordance with Table 8 or Table 9. Screening must be initiated and completed within the 15 days prior to Day 1 of Phase 1 Cycle 1 (except for certain radiology assessments, which may be obtained within the 35 days prior to Day 1).

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.

Abnormal findings from the physical examination must be recorded (see Section 5.5.3). Body weight and height must also be recorded.

Vital signs and ECG must be performed as described in Sections 5.5.4 and 5.5.5.

BP measurements should be obtained as described in Section 5.5.4.3 and Table 10.

Transthoracic echocardiography must be performed as described in Section 5.5.6.

Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis) must be assessed as described in Section 5.5.7.

Women of child-bearing potential must have a negative serum pregnancy test (hCG) conducted at screening, as described in Section 5.5.7.6 (see also Section 7.3).

Procedures for obtaining and handling blood samples and archival tumor specimens are described in Sections 5.8.1 and 5.8.3, respectively. If a tumor biopsy is taken in Phase 1 (if easily accessible and deemed safe for the patient by the Investigator and if patients are willing to undergo biopsy, see Section 5.8.1.1), the blood samples for biomarker analysis should be obtained prior to tumor biopsy.

The assessment of cancer and the selection and reporting of radiological marker lesions or other assessment endpoints (CA-125 or PSA) are described in Section 5.6.

A chest X-ray (or chest CT scan) must be performed in patients in the Phase 1 portion of the study to establish a baseline for safety assessments and will be repeated as clinically indicated. For tumor assessments, a chest CT scan should be performed. When a chest-CT scan is performed, a chest X-ray is not required (see Section 5.6).

Available radiology assessments conducted for solid-tumor patients within the 35 days prior to Day 1 of Phase 1 Cycle 1, or for GBM/high-grade glioma patients within the 15 days prior to Day 1 of Cycle 1, do not need to be repeated during Screening.

5.3.2 Day 1 to Day 28 of the Phase 1 and Phase 2a

BAL101553 capsules will be given to fasted patients daily (q24h or q12h, see Sections 3.2.1 and 3.2.4) , continuously, until disease progression, unacceptable toxicity or another reason for withdrawal from study drug occurs (see Section 4.4). Each patient will be scheduled to receive at least two 28-day treatment cycles; there will be no treatment-free interval between treatment cycles.

Prior to first drug administration, patients will be counselled on how to take BAL101553 and how to fill in information in their drug diary, which will be provided (see Section 6.5). BAL101553 capsules in bottles will be dispensed to patients at each study visit. Patients will be instructed to return all bottles, including any unused drug, at the next visit. Drug accountability will be performed and assessed according to the drug diary entries and the number of capsules returned at each study visit (see Sections 6.5 and 6.6); patients will be counselled on compliance as is appropriate.

5.3.2.1 Day 1 of Cycle 1 and Cycle 2

Eligible patients enrolled in the study will return to clinic on study Day 1. Assessments on Day 1 of Cycle 1 and Cycle 2 will be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study.

On the day of drug administration, all patients must have fasted for at least 4 h (see Section 3.1.4 for more details).

Abnormal findings and clinically significant changes from screening apparent from the physical examination will be recorded. The findings from the physical examination on Day 1 of Cycle 1, before the first administration of BAL101553, will be regarded as baseline result.

Complete vital signs, and ECG will be performed at intervals corresponding to selected PK blood sampling time points, as described in Sections 5.5.4 and 5.5.5.

BP measurements should be obtained pre-dose and post-dose, as described in Section 5.5.4 and Table 10.

On Day 1 of Cycle 1, safety laboratory tests for hematology, biochemistry, cardiac troponin, coagulation and urinalysis (see Section 5.5.7.1) do not need to be repeated if conducted during screening within the 72 h prior to BAL101553 dosing.

Pregnancy testing (hCG) must be conducted for women of child-bearing potential, as described in Section 5.5.7.6.

Blood samples for PK analysis will be collected at serial time-points, as described in Section 5.7.1. 24-h urine sampling will be performed in solid-tumor patients during the Phase 1 portion of the trial for analysis of drug and drug metabolite excretion (see Section 5.7.2). Urine PK samples will not be taken from GBM/high-grade glioma patients.

Blood samples for biomarker analysis will be obtained on Day 1 of Cycle 1 as described in Section 5.8.1.

5.3.2.2 Day 8, Day 15, Day 22 and Day 28 of Cycle 1 and Cycle 2

Patients will return to the clinic and assessments will be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study. 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.

On the day of drug administration, all patients must have fasted for at least 4 h (see Section 3.1.4 for more details).

Vital signs will be performed pre-dose and post-dose as described in Section 5.5.4; ECG will be performed pre-dose and post-dose as described in Section 5.5.5.

BP measurements should be obtained pre-dose and post-dose, as described in Section 5.5.4 and Table 10.

Laboratory safety tests (hematology, biochemistry and cardiac troponin) will be assessed as described in Section 5.5.7.

Blood samples for pharmacokinetic (PK) analysis will be collected pre-dose on Day 8, Day 15 and Day 22 of Cycles 1 (both Phases) and 2 (Phase 1), as described in Section 5.7.1.

Blood samples for biomarker analysis in Phase 1 will be obtained pre-dose on Day 8, Day 15 and Day 22 of Cycle 1; and Day 22 Cycle 2; as described in Section 5.8.1.1.

In Phase 1, tumor biopsies will be obtained on Day 22 of Cycle 1 and/ Cycle 2, if easily accessible and deemed safe for the patient by the Investigator, and if the patient is willing to undergo biopsy (see Section 5.8.1.2).

Patients with measurable tumors will undergo radiological assessment of the tumor between Days 15 and 28 of Cycle 2. Efficacy assessments for patients with non-measurable ovarian or prostate cancer will be performed between Days 22 and 28 of all cycles. The assessment of cancer and the selection and reporting of radiological marker lesions or other assessment endpoints (CA-125 or PSA) are described in Section 5.6.

If efficacy evaluations on Day 28 of Cycle 2 demonstrate absence of disease progression, patients may be eligible to continue treatment with BAL101553.

5.3.2.3 Day 1 of subsequent treatment cycles

Patients eligible to continue treatment will return to clinic, and assessments on Day 1 of subsequent cycles will be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study.

On the day of drug administration, all patients must have fasted for at least 4 h (see Section 3.1.4 for more details).

Abnormal findings and clinically significant changes from baseline (Day 1 of Cycle 1) apparent from the physical examination will be recorded.

Vital signs will be performed pre-dose and and post-dose as described in Section 5.5.4. ECG will be performed pre-dose as described in Section 5.5.5.

BP measurements should be obtained pre-dose and post-dose, as described in Section 5.5.4 and Table 10.

Laboratory safety tests (hematology, biochemistry, coagulation and urinalysis) will be assessed as described in Section 5.5.7.

In Phase 2a, a liquid biopsy for biomarker research should be obtained after the confirmatory MRI scan for complete response/partial response (see Section 5.8.1

Pregnancy testing must be conducted for women of child-bearing potential, as described in Section 5.5.7.6.

5.3.2.4 Day 15 and Day 28 of subsequent treatment cycles

Patient will return to clinic and assessments will be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study.

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.

On the day of drug administration, all patients must have fasted for at least 4 h (see Section 3.1.4 for more details).

Vital signs will be performed pre-dose and post-dose as described in Section 5.5.4.

BP measurements should be obtained pre-dose and post-dose, as described in Section 5.5.4 and Table 10.

Laboratory safety tests (hematology and biochemistry) will be assessed on Day 15 as described in Section 5.5.7.

Where possible in Phase 1, post-treatment tumor biopsies (see Section 5.8.1.2) may be obtained on Day 22 of one subsequent cycle after Cycle 2, or at progressive disease.

Patients with measurable tumors will undergo radiological assessment of the tumor during the last two weeks (Day 15 to Day 28) of all even numbered cycles. From Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks. Efficacy assessments for patients with non-measurable ovarian or prostate cancer will be performed during the last week (Day 22 to Day 28) of all cycles. The assessment of cancer and the selection and reporting of radiological marker lesions or other assessment endpoints (CA-125 or PSA) are described in Section 5.6.

After treatment for more than 12 cycles, D15 visits may be skipped in patients with an adequate and stable condition as per Investigator's clinical judgement.

5.3.3 End of Study visit

End of Study assessments are to be performed in patients who no longer receive BAL101553 treatment, and must take place within 7 days after the decision to discontinue treatment. Assessment will be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study.

Abnormal findings and clinically significant changes from baseline (Day 1 of Cycle 1) apparent from the physical examination will be recorded.

Vital signs (including BP) will be performed as described in Section 5.5.4. An ECG will be performed, as described in Section 5.5.5.

Transthoracal echocardiography will be performed as described in Section 5.5.6.

Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis) will be assessed as described in Section 5.5.7.

Pregnancy testing must be conducted for women of child-bearing potential (see Section 5.5.7.6).

A blood sample for PK analysis will be collected, as described in Section 5.7.1.

In Phase 2a, a liquid biopsy for biomarker research should be obtained (see Section 5.8.1.2).

Radiology efficacy assessments must be repeated, if these have not been performed within the 35 days prior to the End of Study visit. Assessment of CA-125 or PSA in patients with non-measurable ovarian or prostate cancer must be repeated if these have not been performed within the 14 days prior to the End of Study visit. The assessment of cancer and the selection and reporting of radiological marker lesions or other assessment endpoints (CA-125 or PSA) are described in Section 5.6.

5.3.4 Follow-up contact

Assessment of vital status and AE monitoring must be continued for at least 28 days following the last dose of study treatment. Patients must also be contacted to record antineoplastic therapies received after discontinuation of study drug. All cancer medications/therapies given to the patient ≤ 28 days after the last dose of study drug must be recorded in the CRF.

Follow-up information can be obtained during an in-clinic visit, or by telephone if no physical assessments are required. Patients exhibiting abnormalities or reporting AEs at the time of follow-up contact must be followed (see Sections 7.2.5 and 7.2.6).

5.3.5 Overall survival follow-up

Survival follow-up in the Phase 2a portion will start the day of the last dose of study drug. All patients and/or family will be contacted at 3-month intervals (±14 days), with the patient status to be recorded as *Alive* (date); *Dead* (date); *Alive, but withdrew consent for further follow up* (last date under consent); or *Lost to Follow Up* (date of last contact). Survival updates may be made more often than every 3 months if the patient is seen at the investigational site for other reasons, and for overall study status assessments. The survival follow-up period will continue until the study has been completed (see Section 9.5), or other discontinuation criteria are met (see Section 4.4).

Note: Survival follow-up can be done either over the telephone, or by collection of public records in accordance with local laws.

5.4 Medical history, prior and concomitant medications

A full medical history must be obtained at Screening.

All prior medications taken within 30 days of 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, dose regimen, 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.

All non-antineoplastic medications which were received by the patient within 4 weeks prior to screening must also be recorded in the CRF.

5.4.1 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 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. The concurrent use of Optune™ is not permitted.
- 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.

5.4.2 Precautions for concomitant medications metabolized by CYP450 2C9

In vitro studies suggested a potential for interactions in drug metabolism between BAL27862, the active component of BAL101553, and concomitant use of drugs interfering with 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.

A list of known medications that are metabolized substrates, inhibitors, and inducers of CYP450 2C9 can be accessed at:
https://drug-interactions.medicine.iu.edu/MainTable.aspx.

5.4.3 Permitted use of prophylactic/supportive concomitant treatments

5.4.3.1 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.

5.4.3.2 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.

5.4.3.3 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 at the discretion of the Investigator, in accordance with applicable guidelines and the respective prescribing information. The Sponsor must be notified by the Investigator if a patient requires the use of hematopoietic growth factors.

5.4.3.4 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.

5.4.3.5 Blood pressure elevations

Prophylactic antihypertensive treatment is not primarily recommended. If transient blood pressure elevations are observed following administration of oral BAL101553, the administration of short-acting antihypertensive drugs (such as nifedipine retard 10–20 mg or captopril 12.5–25 mg) should be considered. See Table 10 for details.

Patients may also receive chronic antihypertensive treatment (e.g., long-acting calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, thiazide diuretics or beta blockers). Additional short-acting antihypertensive medication may be given as add-on therapy (on an “as needed” basis).

Patients who experience symptomatic BP elevations (e.g., symptoms consistent with hypertensive encephalopathy, suspected intracerebral hemorrhage, stroke or transient ischemic attack, acute myocardial infarction, acute left ventricular or dissecting aortic aneurysm) should be managed and treated according to institutional standards of care.

Table 10 Blood pressure requirement for initiation and continuation of BAL101553 dosing

Systolic BP	**Diastolic BP**	
< 140 mmHg (Phase 1) < 160 mmHg (Phase 2a)	< 90 mmHg (Phase 1) < 100 mmHg (Phase 2a)	Required for patient eligibility at screening
< 160 mmHg	< 100 mmHg	Required on study to continue long-term study treatment
< 180 mmHg	< 110 mmHg	Required to continue dosing

Recommended interventions related to blood pressure

Blood pressure	**Timepoint**	**Recommended intervention**
SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	Screening (Phase 1)	Patient ineligible unless repeat BP measurements are SBP < 140 mmHg AND DBP < 90 mmHg.
SBP ≥ 160 mmHg or DBP ≥ 100 mmHg (confirmed upon repeated measurements)	Any post-Screening study visit day	Initiate antihypertensive treatment or modify existing treatment to achieve SBP < 160 mmHg AND DBP < 100 mmHg within 6 weeks.
SBP ≥ 180 mmHg or DBP ≥ 110 mmHg (confirmed upon repeated measurements)	Any post-Screening study visit day	Withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg.
Any recording of SBP > 220 mmHg or DBP > 110 mmHg	Any post-Screening study visit day	DLT: withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg; then reduce dose by one level.
SBP ≥ 160 mmHg or DBP ≥ 100 mmHg that persists for > 6 weeks despite antihypertensive treatment	Any post-Screening study visit day	DLT: withhold dose until SBP < 160 mmHg AND DBP < 100 mmHg; then reduce dose by one level.
Grade 4 hypertension	Any post-Screening study visit day	DLT: discontinue patient from study.

5.5 Safety assessments

The Investigator will evaluate patient safety by monitoring and recording all AEs and serious adverse events (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, chest X-ray/CT; and by evaluation of concomitant medications (see schedule of assessments; Table 8 and Table 9).

Safety assessments must be performed at intervals indicated in the schedule of assessments (see Table 8 and Table 9). More frequent assessments may be performed at the Investigator's discretion, if medically indicated.

5.5.1 Eastern Cooperative Oncology Group performance status

All patients must be evaluated for ECOG performance status at Screening; prior to BAL101553 administration on Day 1 of each continuous doing treatment cycle (or within the 72 h prior to these days); and at the End of Study visit. Table 11 provides the scale to be used for these assessments.

Table 11 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

5.5.2 Adverse event monitoring

All AEs occurring from the first intake of study medication to the final assessment at follow-up must be documented on the AE CRF page, regardless of whether the event is considered to be related to the study drug or not; see Section 7.1). If possible, a diagnosis should be documented rather than signs and symptoms. All AEs must be recorded in English language.

Patients who withdraw because of a drug-related AE must be followed-up until recovery. Beyond 28 days after last study drug administration, only those procedures relevant to any remaining toxicities or AEs will be performed.

Reporting of SAEs is described in Section 7.2.3.

5.5.3 Physical examination

A complete physical examination must be performed in accordance with Table 8, or Table 9 for patients in the Phase 2a portion of the study.

Physical examination will include examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system and measurement of body weight.

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

An AE form must be completed for changes in physical examination which are identified as clinically significant.

5.5.4 Vital signs

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

5.5.4.1 Phase 1

Vital signs must be performed in accordance with Table 8.

Vital signs must be obtained at Screening; on Days 1, 8, 15 and 22 of Cycles 1 and 2; on Days 1 and 15 of Cycle 3 and all subsequent cycles; and at the End of Study visit.

On Day 1 of Cycles 1 and 2, vital signs (excluding BP measurements) must be obtained pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after intake of BAL101553 study drug; for cohorts using a q12h dosing regimen, vital signs will be also be obtained at 12 h (i.e., prior to the second daily dose) and 14 h (i.e., after the second daily dose) after first dosing on Day 1 of Cycles 1 and 2. Measurements must be obtained within the 5 min prior to PK blood sampling.

On Days 8, 15 and 22 of Cycles 1 and 2, vital signs (excluding BP measurements) must be obtained pre-dose and 0.5 h, 1 h, 2 h and 4 h after intake of BAL101553 study drug.

On Days 1 and 15 of Cycle 3 and all subsequent cycles, vital signs (excluding BP measurements) must be obtained pre-dose and 1 h after intake of BAL101553 study drug.

5.5.4.2 Phase 2a Simon's two-stage design

Vital signs must be performed in accordance with Table 9.

Vital signs must be obtained at Screening; on Days 1, 8, 15 and 22 of Cycles 1 and 2; on Days 1 and 15 of Cycle 3 and all subsequent cycles; and at the End of Study visit.

On Day 1 of Cycle 1, vital signs (excluding BP measurements) must be obtained pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after intake of BAL101553 study drug. Measurements must be obtained within the 5 min prior to PK blood sampling.

On Day 1 of Cycle 2 and Days 8, 15 and 22 of Cycles 1 and 2, vital signs (excluding BP measurements) must be obtained pre-dose and 0.5 h, 1 h and 2 h after intake of BAL101553 study drug.

On Days 1 and 15 of Cycle 3 and all subsequent cycles, vital signs (excluding BP measurements) must be obtained pre-dose and 1 h after intake of BAL101553 study drug.

5.5.4.3 Blood pressure measurements

At Screening and at the End of Study visit, (sitting) 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. Details on appropriate BP measurements are outlined in Table 10.

5.5.4.3.1 Phase 1

On Days 1, 8, 15, 22 of Cycles 1 and 2, triple BP measurements (i.e., the average of three BP measurements taken at 1–2-min intervals) should be obtained for both arms pre-dose. BP measurements may be repeated if the initial SBP is ≥ 140 mmHg or DBP ≥ 90 mmHg. Single BP measurements should be obtained every 30 min after [first] dosing, until at least 4 h post-dose (see Section 5.5.4 and Table 10 for BP requirements for initiation and continuation of BAL101553 dosing); for cohorts using a q12h dosing regimen, single BPs will be also be obtained at 12 h and 14 h (i.e., after the second daily dose) after first dosing on Day 1 of Cycles 1 and 2. The post-dose BPs should be obtained for the arm that gave the highest pre-dose measurement. If SBP ≥ 160 mmHg or DBP ≥ 100 mmHg occur, triple BP should be monitored every 10–15 min until return to SBP < 160 and DBP < 100 mmHg. Patients should only be discharged home once blood pressure levels have stabilized at SBP levels < 160 mmHg and DBP levels < 100 mmHg.

On Days 1 and 15 of Cycle 3 and all subsequent cycles, triple BP measurements (i.e., the average of three BP measurements taken at 1 to 2-min intervals) should be obtained for both arms pre-dose. A single BP measurement should be obtained 1 h after [first] dosing (see Section 5.5.4 and Table 10 for BP requirements for initiation and continuation of BAL101553 dosing). The post-dose BP should be obtained for the arm that gave the highest pre-dose measurement. If SBP ≥ 160 mmHg or DBP ≥ 100 mmHg occurs, triple BP should be monitored every 10–15 min until return to SBP <160 mmHg and DBP < 100 mmHg. Patients should only be discharged home once blood pressure levels have stabilized at SBP levels < 160 mmHg and DBP levels < 100 mmHg.

5.5.4.3.2 Phase 2a Simon's two-stage design

Single BP measurements will be performed in the context of complete vital signs. In Cycles 1 and 2, BP should be obtained pre-dose and 0.5 h, 1 h, and 2 h after dosing, in Cycle 3 and all subsequent cycles BP should be obtained pre-dose and 1 h after dosing. BP measurements may be repeated if the initial pre-dose SBP is ≥ 160 mmHg or DBP ≥ 100 mmHg. If post-dose SBP ≥ 160 mmHg or DBP ≥ 100 mmHg occur, BP should be monitored every 10–15 min until return to SBP < 160 and DBP < 100 mmHg. Patients should only be discharged home once blood pressure levels have stabilized at SBP levels < 160 mmHg and DBP levels < 100 mmHg.

5.5.5 Electrocardiograms

5.5.5.1 Phase 1

ECGs must be performed in accordance with Table 8.

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 the 5 min prior to PK blood sampling. ECG measurements will be made at the following time points:

- Screening: to determine eligibility of patients.
- Day 1 of Cycles 1 and 2: pre-dose; 1 h, 2 h, 4 h, and 8 h after [first] BAL101553 dosing
  - For cohorts using a q12h dosing regimen, triplicate ECG will be also be obtained at 14 h (i.e., after the second daily dose) after first dosing on Day 1 of Cycles 1 and 2 (Phase 1).
- Days 8 and 15 of Cycles 1 and 2: pre-dose; 2 h and 4 h after [first] BAL101553 dosing.
- Day 1 of Cycle 3 and all subsequent cycles: pre-dose.
- End of Study visit.
- Triplicate 12-lead ECG should also be obtained when patients experience SBP ≥ 180 mmHg or DBP ≥ 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

In patients undergoing intra-patient dose escalation or dose reduction during, triplicate 12-lead ECGs must be obtained on Days 1, 8 and 15 of Cycles 1 and 2, pre-dose and 2 h and 4 h after BAL101553 dosing, at each new dose level. From the third cycle onwards, triplicate 12-lead ECGs will only be obtained pre-dose on Day 1.

ECGs performed at Screening, on Day 1 of Cycles 1 and 2, and any abnormal ECGs, will be transmitted to a central ECG laboratory for evaluation, including QTc assessment.

ECGs must always be recorded after at least 5 min rest and while the patient is in a supine or semi-supine position. ECGs must be assessed by the Investigator or his/her designee. The ECG printouts are to be signed and dated by the Investigator or his/her designee. Further instruction and training on handling the device provided and transmitting data will be provided to the study centers prior to study initiation.

The designated physician at the site must review the ECG to assess any abnormalities including prolongation of QTcF. 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.

5.5.5.2 Phase 2a Simon's two-stage design

ECGs must be performed in accordance with Table 9.

Standard, single, 12-lead ECG will be performed using local devices. During PK assessments, ECG recordings must be obtained within the 5 min prior to PK blood sampling. ECG measurements will be made at the following time points:

- Screening: to determine eligibility of patients.
- Day 1 of Cycle 1: pre-dose; 1 h, 2 h, 4 h, and 8 h after BAL101553 dosing
- Days 8 and 15 of Cycle 1, and Days 1 and 15 of Cycle 2: pre-dose, and 2 h after BAL101553 dosing.
- Day 1 of Cycle 3 and all subsequent cycles: pre-dose.
- End of Study visit.
- Single 12-lead ECG should also be obtained when patients experience SBP ≥ 180 mmHg or DBP ≥ 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

ECG must always be recorded after at least 5 min rest and while the patient is in a supine or semi-supine position. ECG must be assessed by the Investigator or his/her designee. The ECG printouts are to be signed and dated by the Investigator or his/her designee.

The designated physician at the site must review the ECG to assess any abnormalities including prolongation of QTcF.

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.

5.5.5.3 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.

In Phase 1, all significant QTc prolongations or other relevant ECG abnormalities, must be transmitted to the central ECG reading laboratory for evaluation and confirmation.

5.5.6 Transthoracic echocardiography

A transthoracic echocardiograph (2D or 3D) 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 at screening and at end of study and must be performed by the same person whenever feasible.

5.5.7 Laboratory parameters

The laboratory safety tests include hematology, biochemistry, cardiac troponin, coagulation and urinalysis as per schedule of assessments (see Table 8 or Table 9). 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.

5.5.7.1 Hematology

The schedule for hematology blood samples is described in Table 8 or Table 9. Hematology must be performed and reviewed:

- Within 72 h of the first administration of BAL101553 on Day 1 of Cycle 1.
- Within the 24 h prior to Day 1 of any subsequent cycle.
- Within the 24 h prior to administration of BAL101553 on Days 8, 15 and 22 of Cycles 1 and 2.
- Within the 24 h prior to administration of BAL101553 on Day 15 of all cycles from Cycle 3 onwards.

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).

General guidance regarding dose modifications for toxicities related to hematological laboratory assessments is provided in Table 6.

5.5.7.2 Biochemistry

The schedule for biochemistry blood samples is described in Table 8 or Table 9. Biochemistry must be performed according to the same schedule as Hematology (see Section 5.5.7.1).

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

General guidance regarding dose modifications for toxicities related to biochemical laboratory assessments is provided in Table 6.

5.5.7.3 Cardiac troponin

The schedule for cardiac troponin blood samples is described in Table 8 or Table 9. Cardiac troponin must be performed and reviewed within 72 h of the first administration of BAL101553 on Day 1 of Cycle 1. Cardiac troponin must also be performed and reviewed within the 24 h prior to administration of BAL101553 on Days 8, 15 and 22 of Cycle 1, on Days 1 and 15 of Cycle 2, and in Phase 1 also on Days 8 and 22 of Cycle 2.

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.

5.5.7.4 Coagulation

The schedule for coagulation blood samples is described in Table 8 or Table 9. Coagulation and urinalysis must be performed and reviewed within 72 h of first administration of BAL101553 on Day 1 of Cycle 1. Coagulation and urinalysis must also be performed and reviewed within the 24 h prior to administration of BAL101553 on Day 1 of all subsequent cycles.

Coagulation analyses include International Normalized Ratio for reporting prothrombin time and Activated Partial Thromboplastin Time.

5.5.7.5 Urinalysis

The schedule for urinalyses is described in Table 8 and Table 9. Urine samples must be obtained prior to BAL101553 dosing on Day 1 of all cycles. Results and must be reviewed prior to BAL101553 administration. Screening labs performed ≤ 72 h prior to first dosing do not need to be repeated on Day 1 of Cycle 1. Labs performed within the 24 h prior to Day 1 of all other cycles, do not need to be repeated on those days.

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).

5.5.7.6 Pregnancy testing

Women of child-bearing potential must have a negative serum pregnancy (hCG) test during Screening, and negative serum or urine pregnancy (hCG) test prior to BAL101553 dosing on Day 1 of every cycle. Screening labs performed ≤ 72 h prior to first dosing, and labs performed within the 24 h prior to all other in-clinic dosing days, do not need to be repeated.

5.5.7.7 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, for biomarker assessments, and for tumor markers (CA-125 or PSA), where indicated.

The anticipated blood volumes are:

5.5.7.7.1 Phase 1

Screening: ~40 mL for solid-tumor patients (20 mL for biomarker assessments and 20 mL for the safety laboratory); ~30 mL for patients with GBM or high-grade glioma (10 mL for biomarker assessments and 20 mL for the safety laboratory). An additional 5 mL of blood may be required when tumor marker assessments (CA-125 or PSA) are indicated.

End-of-Study visit: ~22 mL (20 mL for safety laboratory and 2 mL for PK assessment). An additional 5 mL of blood may be required when tumor marker assessments (CA-125 or PSA) are indicated.

Patients with advanced or recurrent solid tumors

Cycle 1: ~204 mL for the 28-day treatment cycle (56 mL for safety laboratory, 24 mL for PK assessments and 124 mL for biomarker assessments). For dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken for PK analysis.

Cycle 2: ~90 mL for the 28-day treatment cycle (56 mL for safety laboratory, 24 mL for PK assessments and 10 mL for biomarker assessments). An additional 5 mL of blood may be required when tumor marker assessments (CA-125 or PSA) are indicated. For dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken for PK analysis.

All subsequent cycles: ~30 mL (safety laboratory). An additional 5 mL of blood may be required when tumor marker assessments (CA-125 or PSA) are indicated.

For patients undergoing intra-patient dose escalation or dose reduction, the anticipated additional volume of blood for PK assessments at each new dose level is ~24 mL (for dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken). For patients undergoing intra-patient dose escalation only, the additional volume of blood for biomarker assessments at each new dose level is and 130 mL.

Patients with recurrent or progressive glioblastoma or high-grade glioma

Cycle 1: ~247 mL for the 28-day treatment cycle (56 mL for safety laboratory, 24 mL for PK assessments and 167 mL for biomarker assessments). For dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken for PK analysis.

Cycle 2: ~113 mL for the 28-day treatment cycle (56 mL for safety laboratory, 24 mL for PK assessments and 33 mL for biomarker assessments). For dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken for PK analysis.

All subsequent 28-day cycles - ~30 mL (safety laboratory).

For patients undergoing intra-patient dose escalation or dose reduction, the anticipated additional volume of blood for PK assessments at each new dose level is ~24 mL (for dose cohorts using a q12h dosing regimen, an additional 2 mL will be taken). For patients undergoing intra-patient dose escalation only, the additional volume of blood for biomarker assessments at each new dose level is and 160 mL.

5.5.7.7.2 Phase 2a Simon's two-stage design

Screening: ~25 mL (20 mL for safety laboratory, 5 mL for liquid biopsy).

End-of-Study visit: ~22 mL (20 mL for safety laboratory and 2 mL for PK assessment). An additional 10 mL of blood may be required in case of liquid biopsies.

Patients with recurrent glioblastoma in Phase 2a

Cycle 1: ~80 mL for the 28-day treatment cycle (56 mL for safety laboratory, 24 mL for PK assessments).

Cycle 2: ~58 mL for the 28-day treatment cycle (56 mL for safety laboratory, 2 mL for PK assessments).

All subsequent cycles: ~30 mL (safety laboratory). An additional 10 mL of blood may be required in case of liquid biopsies.

5.6 Efficacy assessments

At Screening, patients with advanced or recurrent solid tumors must have measurable disease (according to RECIST criteria v1.1), or non-measurable disease that can be followed by an acceptable tumor marker (CA-125 or PSA), prior to initiation of study treatment.

Patients with recurrent or progressive glioblastoma or high-grade glioma must be evaluated according to RANO criteria.

All radiological tests that demonstrated tumor at baseline (i.e., at Screening, or within 35 days prior to starting study drug for patients with advanced or recurrent solid tumors or within 15 days prior to starting study drug in patients with recurrent or progressive glioblastoma or high-grade glioma) must be repeated within 1 (Phase 1) or 2 (Phase 2a) weeks of completion of every even numbered cycle prior to the next administration of BAL101553. 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 unequivocal progression is observed, concerning mixed response see Section 4.4.

At study treatment completion (End of Study visit), radiology efficacy assessments must be repeated if these have not been performed within 35 days prior to this day. Assessment of CA-125 or PSA in patients with non-measurable ovarian or prostate cancer must be repeated if these have not been performed within 14 days prior to this day.

5.6.1 Measurable tumors

5.6.1.1 Assessment of solid tumors

Patients with measurable tumors will be evaluated using the methods and criteria in the RECIST guidelines, version 1.1 (see Appendix 5). Efficacy assessments must be performed to determine whether treatment should be continued.

5.6.1.2 Assessment of glioblastoma or high-grade glioma

Patients with recurrent or progressive glioblastoma or high-grade glioma, including those with non-measurable disease at baseline, will be evaluated using the methods and criteria in the RANO guidelines (see Appendix 6). Efficacy assessments must be performed to determine whether treatment should be continued.

5.6.2 Non-measurable solid tumors

5.6.2.1 Assessment of ovarian cancer

Patients with non-measurable ovarian cancer will be evaluated by the CA-125 Rustin criteria (Rustin 2004). Efficacy assessments must be performed in the last week of each continuous dosing cycle in order to determine whether treatment should be continued.

5.6.2.2 Assessment of prostate cancer

Patients with non-measurable prostate cancer will be evaluated by the PSA Working Group 2 criteria (Scher 2008). Efficacy assessments must be performed in the last week of each continuous dosing cycle in order to determine whether treatment should be continued.

5.6.3 Clinical progression

Patients who do not meet the criteria for progressive disease as described in Sections 5.6.1 and 5.6.2, but who exhibit signs and symptoms of clinical progression, will be considered for study purposes to have progressive disease.

5.7 Pharmacokinetic assessments

All samples for PK analysis will be analyzed by a central laboratory. The collection, storage, and shipping of plasma and urine samples must be performed as described in the 'BAL101553 Pharmacokinetics Manual' provided to the study centers prior to study initiation.

5.7.1 Blood samples for pharmacokinetic assessments

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.

Detailed instructions and procedures for collecting and handling samples for PK analysis are provided in the 'BAL101553 Pharmacokinetics Manual' at the site.

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

Unless otherwise stipulated in the 'BAL101553 Pharmacokinetics Manual' at the site, the PK of BAL101553 and BAL27862 will be evaluated by analysis of blood samples collected.

5.7.1.1 Phase 1

Unless otherwise stipulated in the 'BAL101553 Pharmacokinetics Manual' at the site, the PK of BAL101553 and BAL27862 will be evaluated by analysis of blood samples collected:

- Day 1 of Cycles 1 and 2 at the following time points:
  - Pre-dose
  - 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after dosing.
    - Depending on the observed PK during the dose escalation portion of the study, a sample at 72 h (Day 4) may also be obtained.
  - For cohorts using a q12h dosing regimen, a PK sample will be also be obtained at 12 h (i.e., prior to the second daily dose) after first dosing.
- Days 8, 15 and 22 of Cycles 1 and 2:
  - Pre-dose
- When a patient reports a DLT, a single blood sample for PK analysis should be obtained, if possible (date and time of blood sampling must be recorded in the CRF).
- At the End of Study visit, blood must be taken for determination of trough PK levels.
- In patients undergoing intra-patient dose escalation or dose reduction, additional blood PK samples must be collected on one dosing day at each new dose level for a given patient. These PK samples must be collected pre-dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after dosing. For cohorts using a q12h dosing regimen, a sample will be also be obtained at 12 h (i.e., prior to the second daily dose) after first dosing.

5.7.1.2 Phase 2a Simon's two-stage design

Unless otherwise stipulated in the 'BAL101553 Pharmacokinetics Manual' at the site, the PK of BAL101553 and BAL27862 will be evaluated by analysis of blood samples collected:

- Day 1 of Cycle 1 at the following time points:
  - Pre-dose
  - 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after dosing (Cycle 1 only).
- Days 8, 15 and 22 of Cycle 1 and Day 1 of Cycle 2:
  - Pre-dose
- When a patient reports a DLT or DLT equivalent, a single blood sample for PK analysis should be obtained, if possible (date and time of blood sampling must be recorded in the CRF).
- At the End of Study visit, blood must be taken for determination of trough PK levels.

5.7.2 24-hour urine sampling for pharmacokinetic assessments

For solid-tumor patients in the Phase 1 portion of the study only, urine must be collected over two 24-h periods, starting on Day 1 of Cycles 1 and 2. The total volume of urine and the concentration of BAL101553 and BAL27862 will be measured to determine the total amounts excreted in urine.

Detailed instructions and procedures for collecting and handling samples for PK analysis are provided in the 'BAL101553 Pharmacokinetics Manual' at the site.

5.8 Biomarker assessments

Samples for biomarker assessments will be analyzed by the sponsor or in specialized laboratories. The collection, storage, and shipping of CTCs, CECs, CEPs, other circulating biomarkers (OCBs; e.g., extracellular vesicles, circulating tumor DNA, circulating tumor RNA, or proteins), and of other biomarker blood or tumor samples, will be performed as described in the 'BAL101553 Biomarker Laboratory 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.

5.8.1 Collection of blood for the assessment of circulating cells, other circulating biomarkers and dried-blood-spot analysis

5.8.1.1 Phase 1

For the isolation and enumeration of CTCs, blood samples will be collected from patients with advanced or recurrent solid tumors: at Screening; and prior to BAL101553 dosing on Day 1, Day 15 and Day 22 of Cycle 1; and Day 22 of Cycle 2. Samples will be collected from patients with recurrent or progressive GBM or high-grade glioma: at Screening; pre-dose and 2 h and 24 h after [first] BAL101553 administration on Day 1 of Cycle 1; and pre-dose on Day 8 and Day 22 of Cycle 1 and Day 22 of Cycle 2. Samples for CTCs will also be obtained using the same schedule in patients undergoing intra-patient dose escalation, at each new dose level. CTCs may be stained for biomarkers if feasible.

Circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs) will be collected in patients with advanced or recurrent solid tumors: at Screening, prior to BAL101553 dosing on Day 1 of Cycle 1; and at 4 h, 6 h, 10 h, and 24 h after intake of the BAL101553 on Day 1 of Cycle 1. Up to four additional blood samples can be obtained for analysis of CECs and CEPs at approximately 72 h (Day 4), 120 h (Day 6), 7 days (Day 8) and/or 21 days (Day 22) after start of study drug administration on Cycle 1 Day 1, if feasible for the patient and clinical staff. Samples for CECs and CEPs will also be obtained using the same Day 1 schedule in patients undergoing intra-patient dose escalation, during the first treatment cycle at each new dose level.

For the isolation of OCBs, blood samples will be collected in patients with recurrent or progressive GBM or high-grade glioma: pre-dose, and 8 h and 24 h after [first] BAL101553 administration on Day 1 of Cycle 1; pre-dose on Day 8 of Cycle 1; and pre-dose on Day 22 of Cycle 1 and Cycle 2. Samples for OCBs will also be obtained using the same schedule in patients undergoing intra-patient dose escalation, at each new dose level.

For each CTC analysis timepoint one 10 mL blood sample should be obtained in EDTA tubes. For each CEC and CEP analysis timepoint, one 10 mL blood sample should be obtained in EDTA tubes. For each OCB analysis timepoint, 22.5 mL of blood will be collected in EDTA tubes.

In addition, on Day 1, prior to first study drug administration, 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 polymorphism and/or genes involved in drug transport or drug metabolism.

The assessment of CTCs, CECs, CEPs and OCBs will be mandatory in Phase 1 of this study; however, the decision to reduce sample numbers or forego collection completely made be made at the discretion of the Sponsor. 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.

The total blood volume obtained for biomarker assessment in the study will be ~154–174 mL for solid-tumor patients and ~209 mL for GBM/high-grade glioma patients in Phase 1. Patients who dose escalate will have an additional 130 mL (solid-tumor patients) or 160 mL (GBM/high-grade glioma) of blood taken for each dose-level change.

If a tumor biopsy is done on the same day, blood collection for blood biomarkers should be obtained prior to the tumor biopsy.

5.8.1.2 Phase 2a Simon's two-stage design

In Phase 2a, a liquid biopsy for biomarker research should be obtained at Screening and at the End of Study visit, and on Day 1 of the next Cycle after the confirmatory MRI scan for complete response/partial response.

In addition, on Day 1, prior to first study drug administration, 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 polymorphism and/or genes involved in drug transport or drug metabolism.

The total blood volume obtained for biomarker assessment will be 34 mL.

5.8.2 Collection of tumor biopsies

Tumor biopsies will be obtained from patients if easily accessible and deemed safe for the patient by the Investigator, and if patients are willing to undergo biopsy. Tumor biopsies will be performed during Screening (Day −15 to Day −1). 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 pharmacodynamic biomarkers and biomarkers potentially predictive of tumor response (e.g., proliferation and cell death rates, vascularization and the expression of potential stratification biomarkers).

5.8.3 Archival tumor blocks

In the Phase 1 portion of the study, 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).

In the Phase 2a portion of the study (Simon`s two-stage design), all patients will be required to have GBM tumor samples available for central laboratory testing of EB1 using immunohistochemistry.

6 STUDY DRUG

6.1 Blinding and randomization

The Phase 1 and Phase 2a portions 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 analysis are available before the start of the study and at all times during the study.

6.3 Shipping and storage conditions

All study drug must be shipped to the study centers and stored at temperatures between 2–25 °C, and kept under secure conditions, e.g., in the hospital pharmacy. Patients should store the study drug between 2–25 °C. 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

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

The patient's supply of study drug will be packaged in bottles with child-resistant caps. Patients will be dispensed a supply of study drug sufficient for no more than one month and six days of therapy. Any unused study drug, as well as empty bottles, should be returned to the study center for performance of drug accountability and for assessment of compliance (see Section 6.6).

6.5 Administration of study drug

Prior to first drug administration, patients will be counselled on how to take BAL101553. A drug diary will be provided to the patient to record their daily drug intake and will include:

- The cycle number and week number.
- The number, frequency and dosing-strength of capsules to be taken each day.
- The contact information of the Principal Investigator.
- The date of study drug intake (to be filled in by the patient each day).
- Confirmation that study drug was taken as instructed (to be filled in by the patient each day).
- An area for comments.

Patients must have observed the fasting period described in Section 3.1.4. Capsules must be taken with (at least) 250 mL of still water. No other intake of food is permitted for 1 h after taking the dose. Instructions on what to do in the case of a missed dose are presented in Section 3.2.7.

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.

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

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

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.

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

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 dispensed to the patient
- Identification of the patient to whom the drug was dispensed
- Date(s), quantity and batch number of the drug returned to the site
- Principal Investigator name
- Quantity of the drug remaining

The inventory must be available for inspection by the Sponsor's CRA(s). All supplies, including partially filled or empty bottles and the dispensing logs, must be kept at the pharmacy to be checked by the Sponsor's CRA(s) either after each dose cohort or at the end of the study.

6.6.3 Drug disposal

After performance of drug accountability and review by the CRA, partially used or empty bottles of study drug may be destroyed at the study center according to standard institutional procedures. The Investigator (or designee) must maintain records of any such destruction. These records must show the identification and quantity of each unit disposed of, 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.

7 PATIENT SAFETY

7.1 Adverse events

7.1.1 Definition of adverse events

An AE is any adverse change from the patient's baseline (pre-therapy) medical condition which occurs during the course of a clinical study, from the start of first study medication, whether considered related to treatment or not.

An event involving the exacerbation or worsening of a pre-existing illnesses must be recorded as an AE. However, lack of efficacy or insufficient clinical response should not be recorded as an AE.

In this study, a treatment-emergent AE is defined as any AE occurring between first administration of study drug and last scheduled follow-up contact (28 days after last study administration).

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. These test results must be recorded on the AEs page of the CRF, under the signs, symptoms or diagnosis associated with them.

7.1.2 Evaluation of adverse events

The severity of AEs will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) (Phase 1) and v5.0 (Phase 2a).

Details of the CTCAE can be found here:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

For AEs that can be described by the CTCAE 5.0 guidelines, the CTCAE Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

The relationship of AEs to the study treatment will be assessed as:

- Not related
- Unlikely
- Possible
- Probable

Appendix 7 provides criteria for relationship assessments.

7.1.3 Documentation of adverse events

All AEs occurring after the start of first study drug administration must be reported on the AE CRF pages.

Serious adverse events (SAEs) must be reported from the time of informed consent to allow for an assessment of serious procedure related events, i.e., serious events/complications related to the screening study procedures (see Section 7.2).

Non-serious AEs that occur between informed consent and first study drug administration will be collected as pre-dose medical history.

If possible, a diagnosis should be documented rather than signs and symptoms. All AEs must be recorded in English language. Each AE should be described by:

1. Its duration (start and end dates).
2. The severity grade (CTCAE grade 1–4, or 3-point scale, see Section 7.1.2).
3. Its relationship to the study treatment (assessment of causality, see Section 7.1.2 and Appendix 7).
4. The action(s) taken with regards to the study treatment or additional treatments given for the event.
5. Whether it is an SAE (see Section 7.2).
6. The outcome.

7.1.4 Progression of the disease under study

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or SAE, unless its outcome is death. However, symptoms of disease progression should be recorded as AEs. If the symptoms of disease progression meet the seriousness criteria, the AE will be reportable to the Sponsor as an SAE (see Section 7.2).

7.2 Serious adverse events

Any SAE occurring from informed consent signature until last scheduled follow-up contact, irrespective of the treatment received by the patient, must be reported to the Sponsor or designated safety representative within one working day of awareness of the event (see below).

7.2.1 Definition of serious adverse events

An SAE is any AE that at any dose that:

- 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 in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

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

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

A life-threatening AE is any adverse experience that places the patient at risk of death from the reaction at the time it occurred, 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 less than 24 h).

Preplanned hospitalizations and elective surgery, which are not due to a worsening or exacerbation of an underlying disease, would not constitute an SAE.

7.2.2 Unexpected adverse event or serious adverse event

An unexpected AE or SAE is one for which the nature or severity of the event is not consistent with the applicable Reference Safety Information (Section 6 of the Investigator's Brochure) .

7.2.3 Reporting of serious adverse events

Any SAEs occurring from informed consent form signature until the last follow-up contact, whether considered treatment-related or not, must be reported immediately to the Sponsor's safety representative listed hereunder within 24 h of awareness of the event. SAEs regardless of relationship to treatment will be collected until the last scheduled follow-up contact (28 days after last study drug administration).

AE reporting will not be solicited after the last scheduled follow-up contact, however any SAEs (including deaths) that occur after this time must be reported, if considered related to study drug.

Safety contact

[redacted]

The Sponsor's safety representative must submit expeditable SAEs to health care authorities and the central Independent Ethics Committee/Institutional Review Boards (IEC/IRB), as required by national law. Expectedness of serious adverse drug reactions related to BAL101553 will be assessed against the applicable Investigator's Brochure.

The Investigator must notify the local IEC/IRB of an SAE in writing, in accordance with local laws and regulations.

7.2.4 Documentation of serious adverse events

The description of the AE must be as complete as possible and allow for a medical assessment of the case. As a minimum, the SAE report must at least contain:

- A subject identifier.
- An AE description, including severity of the event.
- Action taken with regards to study treatment.
- Outcome information.
- The Investigator's causality assessment.

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

Causality must be rated by the Investigator according to Appendix 7. A causal relationship is suspected for all AEs reported with a relationship of 'possible', 'probable' and those with missing or unknown relationships.

7.2.5 Treatment and follow-up of adverse events

The Investigator or other physician in attendance must administer therapy as clinically indicated. All study-related SAEs and AEs must be followed-up until they have returned to baseline status or stabilized. If a clear explanation is established, it must be recorded on the CRF.

Any AE which remains unresolved after completion of the study 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.

7.2.6 Follow-up of abnormal laboratory test results

In the event of unexplained, abnormal laboratory test values, the tests must be repeated and followed-up until they have returned to the normal range (or baseline level) and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it must be recorded on the CRF.

7.3 Pregnancy

Reproductive and fertility studies in animals have not been performed with BAL101553, therefore, 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 trial patient, nor their partner, becomes pregnant during the trial or within the 3 months 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 and also providing each patient with information about appropriate medically-approved effective contraception.

Women of childbearing potential must have negative serum pregnancy tests as described in Section 7.3, and must agree to use highly effective contraceptive methods for the duration of the study, and for an additional 90 days, as described in Inclusion criterion 7 (see Section 4.2).

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 site 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 3 months following the last study drug administration. A pregnancy must be reported by submitting a Pregnancy Report Form, according to the requirements (timelines and contact details) of an SAE (see Section 7.2.3). The patient must be monitored until conclusion of the pregnancy and infants must be followed-up at least for 8 weeks after delivery.

The Investigator must immediately notify the safety contact (see Section 7.2.3) about any pregnancy. In addition, pregnancies resulting in an adverse outcome must be reported as SAEs. Induced abortion if not for an AE would not constitute an SAE.

The Investigator must notify the local IEC/IRB about any pregnancies resulting in an adverse outcome, according to local regulations and laws.

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

Primary study endpoints:

- Phase 1: Frequency and characteristics of BAL101553-related DLT, or other toxicities which are relevant for determination of the MTD.
- Phase 2a expansion portion (Simon's two-stage design): Best objective response according to RANO criteria.

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 1.1 in patients with solid tumors, based on the change from baseline in tumor measurements as measured in patients with measurable disease, and according to RANO criteria in patients with progressive or recurrent GBM or high-grade glioma (Phase 1 only).
  - Change from baseline in tumor markers (CA-125, PSA) in patients whose disease is characterized by these tumor markers utilizing Rustin criteria for ovarian cancer or PSA Working Group 2 criteria for prostate cancer.
  - Progression-free survival and OS.
- Pharmacokinetic assessments (BAL101553 and BAL27862):
  - C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\tau}$, AUC_{0-last}, $AUC_{0-\infty}$, $t_{½}$, systemic clearance and volume of distribution.
  - Total 24 h urinary excretion of BAL101553 and BAL27862.
- Exploratory endpoints:
  - Change from baseline in biomarkers (including but not limited to numbers of CTCs, CECs, CEPs).

8.2 End of study

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

8.3 Statistical and analytical methods

8.3.1 Analysis populations

Separate analyses will be provided for patients with advanced or recurrent solid tumors and for patients with recurrent or progressive GBM or high-grade glioma in the Phase 1 dose escalation portion of the study, and for patients with recurrent GBM in the Phase 2a expansion portion (Simon's two-stage design) of the study. Separate analyses will also be performed for the Surgical cohort in the Phase 2a expansion portion of the study; this separate cohort will be performed as a single-arm study if futility is rejected in Stage 1 of the Simon's two-stage study portion, and will include patients with planned re-resection of recurrent GBM to determine brain tumor tissue levels of BAL27862. Details of analyses in this Surgical cohort will be provided in a separate protocol amendment.

8.3.1.1 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 the primary population for analyzing efficacy in Phase 1.

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

8.3.1.3 Maximum tolerated dose-determining population (Phase 1 dose escalation portion)

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

- Received at least one dose of BAL101553 and has experienced a DLT.
- Received at least 24 of the scheduled 28 doses for q24h BAL101553 administration, or at least 48 of the scheduled 56 doses for q12h BAL101553 administration, 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 85% of the scheduled doses (i.e., less than 24 of the scheduled 28 doses using a once-daily regimen, or less than 48 out of the scheduled 56 doses using a twice-daily regimen) during Cycle 1, 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 receive more than 125% of the assigned dose during Cycle 1 (total dose for the 28-day cycle), 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.

8.3.1.4 Pharmacokinetic analysis population

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

8.3.1.5 Efficacy-evaluable population (Phase 2a expansion portion of the study, Simon's two-stage design)

The efficacy evaluable population (EEP) is the subset of the FAP who had at least one postbaseline RANO assessment after having received at least 6 weeks of study treatment.

8.3.2 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.

An interim analysis for stage transition in the Phase 2a dose expansion portion will be performed when the specified number of patients required for Stage 1 had at least one post-baseline RANO assessment after having received at least 6 weeks of study treatment, but no later than after the completion of Cycle 12.

If the required number of responses has not been observed at the time of enrollment of the last patient in Stage 1, enrollment may be suspended, or the cohort may be terminated due to apparent futility. If the required number of responses is reached earlier, the interim analysis may be performed earlier, and stage transition may occur based on a joint decision taken by the Investigators and the Sponsor (see Section 3.1.3).

8.3.2.1 Patient demographics and other baseline characteristics

Background and demographic characteristics of the full analysis population including age, gender, height, weight, body surface area, tumor type, previous anticancer treatments, medical conditions, performance status etc. will be listed individually by patient, and summarized by dose cohort using descriptive statistics or contingency tables.

8.3.2.2 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 group and treatment cycle in the safety population.

8.3.2.3 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 group.

8.3.2.4 Dose-limiting toxicity, MAD determination and MTD recommendation

The dose-limiting toxicities will be listed by patient for each dose cohort.

The MAD is defined as the dose level at which DLT are observed during treatment Cycle 1 in ≥ two of (up to) three patients with DLT in the first three patients of a dose cohort, or ≥ two of (up to) six patients with DLT in a dose cohort that was expanded to six patients 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.

The MTD may be different for patients with advanced or recurrent solid tumors and for patients with recurrent or progressive GBM/high-grade glioma.

8.3.2.5 Objective response rate

The objective response rate will be calculated within the FAP (Phase 1 portion of the study), as the proportion of patients responding (i.e., with a best observed objective response of complete or partial response, based on RECIST criteria v1.1 for patients with advanced or recurrent solid tumors, CA-125 Rustin criteria for ovarian cancer, or PSA Working Group 2 criteria for prostate cancer); and based on RANO critieria for patients with recurrent or progressive GBM/high-grade glioma.

In the Phase 2a portion of the study (Simon's two-stage design), the patients with measurable disease at baseline in the EEP will be the primary population for the calculation of the objective response rate.

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

8.3.2.6 Disease control rate

The disease control rate will be calculated within the FAP (Phase 1 portion of the study), 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 cohort and by disease subgroup if appropriate.

In the Phase 2a portion of the study (Simon's two-stage design), the EEP will be the primary population for the calculation of the disease control rate.

8.3.2.7 Progression-free and overall survival

Progression-free survival is defined as the interval between the date of first study drug administration and the earliest date of objective disease progression according to RECIST criteria v1.1 for patients with advanced or recurrent solid tumors, CA-125 Rustin criteria for ovarian cancer, PSA Working Group 2 criteria for prostate cancer; and based on RANO criteria for patients with recurrent or progressive GBM/high-grade glioma; or Investigator-confirmed clinical progression (see Section 5.6.3); or death due to any cause in the absence of progression. Patients who have not progressed or died at EOS will be censored at the time of their latest objective tumor assessment.

Overall survival is the time from first study drug administration to the date of death / or censored at the time the patient was last known to have been alive.

Progression-free survival will be listed for the FAP (Phase 1 portion of the study) by patient and dose group and by disease subgroup if appropriate.

In the Phase 2a portion of the study (Simon's two-stage design), OS and PFS will be calculated for the FAP and EEP. Median OS and PFS and the proportion of patients with PFS at 6 months after start of study drug treatment (PFS6) will be assessed in the Phase 2a portion of the study (Simon's two-stage design).

8.3.2.8 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., electrocardiogram, 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 will be presented in individual listings and summary tables.

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.

Laboratory evaluations

Laboratory values will be converted into SI units and the severity grade determined based on CTCAE v5.0 whenever applicable.

The frequency of laboratory abnormalities will be displayed by worst CTCAE v5.0 grade and by dose level and cycle as appropriate. Newly occurring CTCAE v5.0 laboratory abnormalities will be displayed in a separate listing. Shift tables will be provided for laboratory parameters classified according to CTCAE v5.0.

Other safety data

Data from other tests (e.g., electrocardiogram) 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.

8.3.2.9 Pharmacokinetic analysis

All PK parameters will be presented as listings and descriptive summary statistics including arithmetic and geometric means, coefficient of variations, standard deviation, minimum, median and maximum.

A detailed description of the PK analysis will be provided in the 'BAL101553 Pharmacokinetics Manual'.

8.3.2.10 Biomarker analysis

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

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

8.3.3 Sample size calculation

8.3.3.1 Phase 1 dose escalation portion

The accelerated 3+3 design applied in Phase 1 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.

8.3.3.2 Phase 2 dose expansion portion (Simon's two-stage design)

Simon's two-stage design will be used in Phase 2a. The null hypothesis that the true response rate is 14% will be tested against a one-sided alternative. In the first stage, 9 evaluable patients will be accrued. If there are 1 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 10 additional evaluable patients will be accrued for a total of 19. The null hypothesis will be rejected if 6 or more responses are observed in 19 patients. This design yields a type I error rate of 3.7% and power of 81% when the true response rate is 40%.

For actual patient numbers see Section 3.3.

8.3.4 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 date 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 date. 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.

Prior to study-specific screening procedures in the Phase 2a portion of the study (Simon's two-stage design), a tissue-screening program adhering to local standards in selected countries will be established to support the identification of potential patients whose GBM tissue is EB1-positive based on IHC. The GBM tissue-testing algorithm is outlined in Appendix 4.

In the context of this tissue screening program, a coded list with GBM tissue samples available for testing will be populated by each study site or the associated pathology laboratory, including confirmation of available patient consent for tissue testing. Each tissue sample provided to the central pathology laboratory for EB1-testing will be tracked with a patient-sample number and confirmation that patient consent for tissue testing is available. The EB1-IHC staining result will be provided by the central pathology laboratory to the study site for each sample, and patients with EB1-positive GBM tissue samples will be approached by the study investigator for potential participation in the study.

In the Phase 2a portion of the study (Simon's two-stage design), patients whose GBM tissue was identified as EB1-positive by IHC as determined by central laboratory testing will be approached by the study investigator to discuss potential study participation, and to initiate the patient information and informed consent process if applicable.

9.1.1 Investigator's study file

The Investigator's Study File must contain all essential documents as required by ICH E6 (R2), e.g., the protocol/amendments, Investigator's Brochure, CRFs and Query Forms, IEC/IRB and governmental approval with correspondence, informed consent forms, patient enrollment and identification logs, drug accountability records, staff curriculum vitae, authorization forms and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient who signs an informed consent for participation in the study, a CRF must be completed and signed by the Investigator or authorized Sub-investigator. This also applies to records for those patients who fail to complete the study (even during a pre-treatment screening period if a CRF was initiated). If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts must be made to clearly document the outcome of the AE.

The Investigator must 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 for example, patient hospital/clinic records, physician's and nurse's 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 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 local regulations.

These files must be made available for inspection, upon reasonable request, to authorized representatives of Sponsor or 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 documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

9.1.5 Sample retention

Blood and tissue samples may be stored for future medical and/or scientific research projects related to BAL101553. All patients will be asked to provide informed consent for this purpose, authorizing the Sponsor to use their study information and samples for future research projects.

9.2 Monitoring

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

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

The Investigator shall 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 agrees to cooperate with the CRA to ensure that any deviations or issues detected in the course of monitoring visits are resolved.

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, Good Clinical Practice, and regulatory requirements. These audits may also be conducted for quality assurance to ensure that complete and accurate data are submitted and that adverse events, complications and/or adverse reactions are being identified and reported. The study may also be inspected by health 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 the Sponsor, and be reviewed and approved by the Head of Development, the Clinical Pharmacologist, the Project Physician and the Qualified Person for Pharmacovigilance.

Protocol amendments must be submitted to the appropriate IEC/IRB for information and approval, in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients, or when the change(s) involves only logistical or administrative aspects of the study, e.g., change in CRA(s), change of telephone number(s).

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 this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator must ensure that adequate consideration is given to the protection of the patients' interests.

9.6 Publication policy

The Sponsor is committed to register all therapeutic studies in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that results of these studies are made available to the medical community in agreement with national and international regulations.

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 have to 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 the Investigator. 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 will be determined by mutual agreement.

10 ETHICS AND GOOD CLINICAL PRACTICE

The study must be conducted in compliance with the protocol and in accordance with the ICH Tripartite Guideline E6 (R2), current "Guideline for Good Clinical Practice" and applicable regulatory requirements.

10.1 Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IEC or IRB-approved informed consent.

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. Written informed consent must be obtained from each patient prior to initiation of any study procedures. It must also be explained to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for obtaining written informed consent must be provided by the Investigator or 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 should comply with applicable regulatory requirements and adhere to ICH GCPs and the ethical principles that have their origin in the Declaration of Helsinki. Copies of signed consent forms must be given to the patient and originals filed at the study center.

In the case where the patient is unable to read, an impartial witness must be present during the entire informed consent discussion. After the patient has orally consented to participation in the study, the witness' signature on the form will 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 risk/benefit assessment, the consent form must be reviewed and updated. All patients, including those already being treated, must be informed of the new information, given a copy of the revised form, and asked to give their consent to continuing on in the study.

Prior to study-specific screening procedures in the Phase 2a portion of the study (Simon's two-stage design), a tissue-screening program adhering to local standards in selected countries will be established to support the identification of potential patients whose GBM tissue is EB1-positive by IHC as determined by central laboratory testing.

In the context of this tissue-screening program, each study site or the associated pathology laboratory will confirm availability of appropriately-documented consent for each potential patient on IEC- or IRB-approved informed consent forms for tissue testing prior to submitting tissue for testing. Depending on the country and/or study site, patient consent for tissue testing may already be available, or may have to be newly obtained.

Potential patients whose GBM tissue was identified as EB1-positive based on IHC will be approached by the study investigator to discuss potential study participation, and to initiate the patient information and informed consent process if applicable.

10.2 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 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 Guideline E6 (R2). The Investigator must ensure that all local data protection laws are respected. The Sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.3 Independent Ethics Committees/Institutional Review Boards

This protocol and any accompanying material provided to the patient, such as 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 with ICH Guideline E6 (R2) and any relevant supplementary guidance on GCP, and with applicable laws and regulations. Approval from the IEC/IRB must be obtained before starting the study, and must be documented, specifying the date on which the committee met and granted the approval.

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.

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12 APPENDICES

Appendix 1 Starting dose rationale details for study CDI-CS-002

The starting dose of daily oral BAL101553 for patients with advanced or recurrent solid tumors is based on consideration of the following elements:

- Two repeat-dose GLP toxicity studies in one rodent (4-week oral rat study [CDI-TOX-024]) and one non-rodent (4-week oral dog study [CDI-TOX-025]).
- Human pharmacokinetic data from study CDI-CS-001 with IV BAL101553 administered over 2 hours on Days 1, 8 and 15 of every 28-day treatment cycles.
- Toxicokinetic and bioavailability data from studies in rats and dogs.
- *In vitro* data in Caco-2 cells and human liver microsomes.
- An assessment of expected human BAL27862 PK exposures with daily oral dosing of BAL101553 in the context of known PK, safety and efficacy data from study CDI-CS-001 (IV BAL101553).

A stepwise approach was taken to determine the appropriate starting dose. This approach is summarized in Table 12 and described in more detail below.

Step 1: Pivotal GLP repeat toxicity studies in rats and dogs

Two pivotal 4-week toxicological studies with daily oral administrations of BAL101553 were conducted in rat and dogs (CDI-TOX-024 and CDI-TOX-025). The highest non-severely toxic dose (HNSTD) in each study is shown in Table 13.

In accordance with ICH guideline S9 on the nonclinical evaluation for anticancer pharmaceuticals, the recommended approach for defining the starting dose for first in human studies is a calculation based on the most appropriate, i.e., usually the most sensitive, species using 1/10 (10%) of the HNSTD in the rat or 1/6 (16.7%) of the HNSTD in the dog.

When applying commonly accepted factors for converting the animal dose (in mg/kg) to the human dose (in mg/m^2) (i.e., a factor of 6 for the rat and a factor of 20 for the dog) the lowest and therefore most conservative human starting dose is based on the HNSTD in female rats (see Table 14).

Table 12 Overview of starting dose rationale for daily oral BAL101553 dosing of patients with advanced or recurrent solid tumors

Step	Description	Proposed *per diem* dose for oral BAL101553
Step 1	Calculation of starting dose based on HNSTD obtained from GLP repeat-dose toxicity studies in rats (CDI-TOX-024) and dogs (CDI-TOX-025).	3 mg/m^2
Step 2	Consideration of accumulation factor of 1.5 based human PK data from clinical study CDI-CS-001 (IV BAL101553 administered at Days 1, 8 and 15 of 28-day treatment cycles) suggesting an average half-life of 15 h for the active BAL27862.	2 mg/m^2
Step 3	Consideration of expected absorption (presumed 100%) and first-pass hepatic effect (presumed as being low) based on *in vitro* permeability studies in Caco-2 cells and incubation of BAL27862 in human liver microsomes.	2 mg/m^2
Step 4	Consideration of toxicokinetic data in rats and dogs suggesting that for a given exposure level (AUC), daily oral dosing with BAL101553 results in less toxicity than IV weekly BAL101553 at corresponding exposure levels (studies CDI-TOX-024/025).	2 mg/m^2
Step 5	Assessment of expected human PK exposures with daily oral dosing in the context of known PK, safety and efficacy data from study CDI-CS-001 (IV BAL101553), suggesting that daily oral dosing of BAL101553 at a dose level of 1 mg/m^2 may result in similar weekly exposure (AUC) as IV weekly dosing at 30 mg/m^2, a dose level that has been shown as safe and potentially efficacious in study CDI-CS-001.	1 mg/m^2
Step 6	Conversion from a mg/m^2 per day dosing approach to fixed flat dosing (mg/day), assuming a BSA range of 1.6 to 2.4 mg mg/m^2 and using a midpoint BSA of 2.0 mg/m^2.	**2 mg**

BSA: body surface area; HNSTD: highest non-severely toxic dose; IV: intravenous

Table 13 HNSTD in rodent (rat) and non-rodent (dog) species

Study number (duration)	Species	N	HNSTD (mg/kg/day)	Fraction of HNSTD (mg/kg/day)	Main toxicities observed at HNSTD	Main toxicities observed above HNSTD
CDI-TOX-024 (4 weeks)	rat	n=10 per sex/dose	Male: 10	(1/10) Male: **1**	• degenerative changes in reproductive organs • bone marrow depression • reduced IgM 1st immune response • atrophic changes in lymphatic system • GI tract mucosal degeneration	• HNSTD was the highest tested dose
			Female: 5	(1/10) Female: **0.5**	• reduced IgM 1st immune response • atrophic changes in lymphatic system	• liquid feces • impaired conditions • mortalities • bone marrow depression • reduced IgM 1st immune response • atrophic changes in lymphatic system • GI tract mucosal degeneration • liver increased mitosis
CDI-TOX-025 (4 weeks)	dog	n=3 per sex/dose	2	(1/6) **0.33**	• slight body weight loss • bone marrow depression • sperm cell depletion/ degeneration • borderline prolongation of QTc	HNSTD was the highest tested dose

HNSTD (highest non-severely toxic dose) is defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings.

Table 14 Calculation of the human starting dose based on the HNSTD in rodent (rat) and non-rodent (dog) species

Animal species	10% of HNSTD (mg/kg/day)	Conversion factor[1] of animal doses (mg/kg) to human doses (mg/m^2)	Calculated human starting dose (mg/m^2)
Male rat	1	6	6
Female rat	**0.5**	**6**	**3**
Male or female dog	0.33	20	6.6

[1]Based on "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers Guidance for Industry and Reviewers U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), July 2005 Pharmacology and Toxicology"

Step 2: Human pharmacokinetic data from intravenous BAL101553

As shown in Table 15, the average half-life of BAL27862 (active drug) was dose-independent and the overall half-life ($t_{1/2}$) across doses was approximately 15 h, which corresponds to a calculated accumulation factor of 1.5 for a daily administration.

In animals after daily oral dosing of BAL101553 no accumulation of BAL27862 was observed. However, this is explained by the much shorter half-life of BAL27862 in animals (i.e., $t_{1/2}$ of 4 to 5 h in dogs for the highest dose group in the 4-week oral pivotal study, CDI-TOX-025).

Therefore, rather than a starting dose of 3 mg/m^2, which would be suggested based on the HNSTD in female rats (see Table 14), a daily oral dose of 2 mg/m^2 is suggested when considering the accumulation factor.

Table 15 Mean (SD) pharmacokinetic parameters of BAL27862 in study CDI-CS-001

BAL101553 dose (mg/m^2) (number of patients treated at the respective dose level)	BAL27862		
	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (hours)
15 (n=1)	154	1830 (7.07)	**17.1 (1.67)**
30 (n=4)	224 (68.7)	2500 (652)	**15.9 (3.18)**
45 (n=3)	413 (12.5)	5970 (1360)	**16.8 (8.48)**
60 (n=10)	479 (139)	6940 (4340)	**15.8 (5.58)**
80 (n=7)	615 (104)	7790 (3220)	**12.8 (3.77)**

Step 3: Expected bioavailability and first-pass hepatic effect of oral BAL101553

Studies in rats and dogs (CDI-TOX-011/012/024/025 and S49377) demonstrated a bioavailability of BAL27862 between 30 to 50% (rats) and 50 to 100% (dogs) when administered as either an oral solution or as powder filled capsule. After oral administration of BAL101553, only the active drug BAL27862 but not the pro-drug BAL101553 was present in the systemic circulation suggesting complete cleavage of the pro-drug BAL101553 in the gastrointestinal tract/intestinal brush border cells.

Caco-2 permeability studies demonstrated an excellent permeability of BAL27862 after incubation with either BAL101553 or BAL27862. BAL101553 was cleaved in the incubation medium and intracellularly. These data further support an anticipated high or complete absorption of BAL27862 in the gastrointestinal tract. In these experiments it was also demonstrated that BAL27862 is not a Pgp substrate.

In addition, the liver first pass-effect is expected to be low based on results from BAL27862 incubations with human liver microsomes and the long half-life of BAL27862 observed in the clinical study CDI-CS-001 using IV administration.

In summary, the available data suggest a complete conversion of the pro-drug BAL101553 to the active drug BAL27862 in the gut, a high/complete absorption of BAL27862 and a low liver first-pass effect. Therefore no modification of the oral BAL101553 starting dose is required as the bioavailbility is expected to be 100%.

Step 4: Toxicokinetic data in rats and dogs (IV versus oral administration)

The AUC was demonstrated to be the PK/PD driver for efficacy in the non-clinical efficacy studies with BAL101553/BAL27862. In the clinical study CDI-CS-001 (IV BAL101553), vascular side effects of BAL101553 such as blood pressure elevations were shown to be related to C_{max}. Therefore both AUC and C_{max} are considered important PK parameters to assess the efficacy and safety profile of BAL101553/BAL27862 with AUC being most important for antitumor efficacy and C_{max} potentially most important for side effects.

In efficacy animal models (xenografted mouse models) and in toxicological studies, daily oral doses of BAL101553 were generally better tolerated than weekly IV administrations at corresponding (weekly) AUCs. As shown in Table 16, in male dogs a (weekly) AUC of 1890 ng·h/mL BAL27862 was achieved by a (weekly) dose of IV 4.6 mg/kg BAL101553 and was associated with moderate toxicity, whereas at a similar (weekly) AUC of 1990 ng·h/mL BAL27862 achieved with a daily oral dose of BAL101553 of 0.5 mg/kg no signs of toxicity were observed.

The achievement of comparable AUCs of BAL27862 at lower C_{max} levels due to daily oral vs weekly intravenous BAL101553 dosing may have contributed to the better tolerability of daily oral dosing in the animal studies.

Another important observation in the animal studies was that with daily oral dosing with BAL101553, toxicity was dose related and the PK of BAL27862 were dose-proportional with respect to AUC and C_{max} (CDI-TOX-024/025).

Table 16 Overview of toxicokinetic data in animal studies for weekly IV vs daily oral BAL101553

	BAL101553 IV, once weekly				BAL101553 oral once daily			
Species	**Dose** (mg/kg)	**Weekly AUC_{last}** (ng·h/mL) **BAL27862**	**C_{max}** (ng/mL) **BAL27862**	**Toxicity**	**Dose** (mg/kg)	**Weekly AUC_{last}** (ng·h/mL) **BAL27862**	**C_{max}** (ng/mL) **BAL27862**	**Toxicity**
Female rats[1]	6.1	1170	1450	(+)	2.5	3290	179	(+)
	15.2	3570	3630	+	5.0	5100	255	+
	38	10500	8960	+++	10	8890	497	+++
Male rats[1]	6.1	1010	1440	(+)	2.5	1630	69	(+)
	15.2	2680	3850	+	5.0	3200	122	(+)
	38	8710	8430	++	10	5610	226	++
Female dogs[2]	1.5	619	266	-	0.5	1730	83	-
	3	1010	574	(+)	1	2730	125	(+)
	4.6	1750	852	++	2	9450	349	+
Male dogs[2]	1.5	650	284	-	0.5	1990	81	-
	3	1340	617	(+)	1	4930	177	+
	4.6	1890	875	++	2	7770	312	++

[1]study CDI-TOX-011/024: bolus IV administration once weekly for 3 weeks or daily oral administration for 4 weeks as a solution

[2]study CDI-TOX012/025 1-hour IV administration once weekly for 3 weeks or daily oral administration for 4 weeks as a solution

Step 5: Assessment of expected human PK exposures with daily oral dosing in the context of known PK, safety and efficacy data from study CDI-CS-001 (IV BAL101553)

Table 17 shows the expected PK parameters in patients with daily oral dosing based on PK modeling using Phoenix WinNonLin 6.3 and assuming 100% bioavailability and a rate of absorption as observed in dogs. The predicted AUC and C_{max} after daily oral administration of BAL101553 shows that a daily oral BAL101553 dose of 1 mg/m^2 is expected to result in a weekly AUC of 2630 ng·h/mL, which is comparable to the weekly AUC using a weekly IV BAL101553 (2-h infusion) dose regimen at a dose level of 30 mg/m^2.

Importantly, in study CDI-CS-001 weekly IV BAL101553 given as 2-h infusion on days 1, 8 and 15 of every 28-day treatment cycles was well tolerated at the dose level of 30 mg/m^2 with observation of a partial objective response in a patient with an ampullary (pancreaticobiliary) cancer.

Considering the PK modeling result a starting dose level of 1 mg/m^2 seems therefore appropriate.

Predicted C_{max} levels with daily oral dosing of BAL101553 that correspond to C_{max} levels observed with weekly IV dosing at dose levels ≥ 30 mg/m^2 (i.e., C_{max} levels of BAL27862 above 200 ng/mL) are not expected until a daily oral dose level of 6 mg/m^2 (corresponding to a fixed-flat dose of 12 mg/day) is reached.

Considering the conservative starting dose determination (1 mg/m^2, or 2 mg/day fixed-flat dosing), the dose related toxicity observed in animal studies with daily oral dosing of BAL101553 and the expected linear pharmacokinetics of BAL27862 with daily oral BAL101553 dosing, an accelerated dose escalation scheme with increases of dose levels by 100% until occurrence of grade 2 toxicity is justified.

Table 17 Predicted PK exposure of BAL27862 in humans with BAL101553 daily oral dosing

BAL101553 weekly IV dose in mg/m^2	Observed mean weekly AUC_{last} (ng·h/mL)	Observed mean C_{max} (ng/mL)	BAL101553 oral daily dose in mg/m^2 and [mg flat dose]	Predicted weekly AUC_{last} (ng·h/mL)	Predicted upper range of C_{max} (ng/mL)
15	1830	158	0.5 [1 mg/d]	1310	19
30	2410	213	1 [2 mg/d]	2630	38
45	6270	402	2 [4 mg/d]	5250	75
60	6340	479	4 [8 mg/d]	10500	150
80	7790	615	6 [12 mg/d]	15750	225

Step 6: Conversion of BSA-based to fixed-flat daily dosing

Conversion from a mg/m^2 per day dosing approach to fixed-flat dosing (mg/day) was selected for practical reasons, considering that two oral dosage strengths are available for study CDI-CS-002, i.e., a 1 mg capsule and a 5 mg capsule. The conversion from mg/m^2 to mg was based on the assumption of a BSA range of 1.6 to 2.4 mg mg/m^2 in the patients included in the study, using a midpoint of 2.0 mg/m^2. This results in a human starting dose of 2 mg/day, corresponding to approximately 1 mg/m^2.

Food effect

In vitro studies with Caco-2 cell lines suggested a reduced permeability of BAL27862 when comparing incubations in presence of fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) media.

This effect was confirmed in a dedicated pharmacokinetic study in dogs. The study compared the pharmacokinetics of BAL27862 after oral administration of 10 mg BAL101553 as capsule (clinical formulation) in the fasted and fed state (Table 18). The exposure (AUC_{last}) was reduced by approximately 26% in the fed compared to the fasted state. However, the concomitant administration of food introduced a large variability in the absorption rate with T_{max} ranging from 2-6 h compared to 1.5-3 h in the fasted state.

Therefore, for the Phase 1 portion of study CDI-CS-002 (dose escalation with MTD determination) it is recommended oral administration of the capsules in the fasted state. For practical reasons patients will be asked to take BAL101553 capsules in the morning before breakfast after a fasting period of at least 4 h and patients should refrain from intake of food for at least 1 h after oral BAL101553 administration.

Table 18 BAL27862 derived pharmacokinetic parameters in dogs (n=3) after single oral administration (fasted or fed) of BAL101553

Dose and formulation	Status	C_{max} (ng/mL); Mean (%CV) [min-max]	T_{max} (h) [min-max]	AUC_{last} (ng·h/mL); Mean (%CV) [min-max]	F (%) [min-max]
10 mg capsule	Fasted	171; 57.5	2.0	1160; 47.8	90
		[67.5-263]	[1.5 to 3.0]	[577 to 1680]	[46 to >100]
	Fed	76.8; 19.1	3.0	860; 38.%	70
		[60.4 to 88.6]	[2.0 to 6.0]	[541 to 1200]	[43 to 96]

CV: coefficient of variation; F: Bioavailability
Bioavailability is based on the comparison of the exposure after oral administration of a 10 mg capsule of BAl101553 to the mean AUC_{last} observed in female dogs after IV administration of 2 mg/kg BAL27862 assuming a body weight of 10 kg (CDI-TOX-012).

Appendix 2 Dose escalation scheme in the case of a DLT at the starting dose

Table 19 Dose escalation scheme in the event of a DLT at the starting dose for patients with solid tumors

Cohort 1	**Dose level (mg/day)**		**2**					
	Cohort 1 toxicity		DLT ≥ 2 of [up to] 6 pts					
Cohort 2	% change in dose		(-50%)					
	Dose (mg/m²/day):		**0.5**					
	Approx. dose/day[b] (mg); dose/month[a] (mg) at BSA (m²) of:	**1.7**	**0.9 24**					
		2	**1.0 28**					
		2.3	**1.2 32**					
	Cohort 2 toxicity		NRT				G2	DLT
Cohort 3	% change in dose		+40%				expand to 6 pts at current dose level	stop treatment
	Approx. dose/day[2] (mg); dose/month[c] (mg) at BSA (m²) of:	**1.7**	**1.2 33**					
		2	**1.4 39**					
		2.3	**1.6 45**					
	Cohort 3 toxicity		NRT			G2	DLT	
Cohort 4	% change in dose		+40%			expand to 6 pts at current dose level	expand to 6 pts at previous dose level	
	Approx. dose/day[b] (mg); dose/month[c] (mg) at BSA (m²) of:	**1.7**	**1.7 47**					
		2	**2.0 55**					
		2.3	**2.3 63**					
	Cohort 4 toxicity		NRT	G2	DLT			
Cohort 5	% change in dose		+40%	expand to 6 pts at current dose level	expand to 6 pts at previous dose level			
	Approx. dose/dayb[2] (mg); dose/month[c] (mg) at BSA (m²) of:	**1.7**	**2.3 65**					
		2	**2.7 77**					
		2.3	**3.2 88**					

No relevant toxicity (NRT); ≥ Grade 2 toxicity in ≥ 2 of 3 pts (G2); dose-limiting toxicity (DLT)

Example monthly and daily dose calculations

a) [dose per day (mg/m²)] × [BSA (m²)] × [28 days] = dose per month at that BSA
b) [dose per month at a given BSA] / [28 days] = approximate dose per day at that BSA
c) [dose per month at a given BSA] × [% increase] = dose per month at that BSA at next dosing level

Table 20 Example of a flexible daily dose regimen (mg/day) for three example body surface areas, to be followed in the event of a DLT in Cohort 1 (solid-tumor patients; 40% increases between cohorts)

Cycle Day			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Monthly dose (mg)
Cohort																															
Cohort 2	BSA (m^2)	1.7	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	24
		2.0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	28
		2.3	1	1	1	1	1	1	2	1	1	1	1	1	1	2	1	1	1	1	1	1	2	1	1	1	1	1	1	2	32
Cohort 3	BSA (m^2)	1.7	1	1	1	1	1	1	2	1	1	1	1	1	1	2	1	1	1	1	1	1	2	1	1	1	1	1	2	2	33
		2.0	1	1	1	1	1	2	2	1	1	1	1	2	2	2	1	1	1	1	2	2	2	1	1	1	1	2	2	2	39
		2.3	1	1	1	2	2	2	2	1	1	1	2	2	2	2	1	1	1	2	2	2	2	1	1	2	2	2	2	2	45
Cohort 4	BSA (m^2)	1.7	1	1	1	2	2	2	2	1	1	2	2	2	2	2	1	1	2	2	2	2	2	1	1	2	2	2	2	2	47
		2.0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	55
		2.3	2	2	2	2	2	2	3	2	2	2	2	2	3	3	2	2	2	2	2	3	3	2	2	2	2	2	3	3	63
Cohort 5	BSA (m^2)	1.7	2	2	2	2	2	3	3	2	2	2	2	2	3	3	2	2	2	2	2	3	3	2	2	2	2	3	3	3	65
		2.0	2	2	3	3	3	3	3	2	2	3	3	3	3	3	2	2	3	3	3	3	3	2	3	3	3	3	3	3	77
		2.3	3	3	3	3	3	3	4	3	3	3	3	3	3	4	3	3	3	3	3	3	4	3	3	3	3	3	3	4	88

Table 21 Summary of the rules governing dose escalation decisions in the event of a DLT at the starting dose

Number of patients with treatment-related toxicities in the first 3 patients of a dose cohort[1]	Escalation decision
No relevant toxicity (NRT)	Enroll 3 patients at the next dose level[2].
≥ Grade 2 CTCAE toxicity (G2) in ≥ 2 of 3 pts	• Enter 3 additional patients at this dose level. o If 0 of these 6 patients experiences DLT, enter 3 patients at the next higher dose level[2].
≥ 1 of 3 patients with dose-limiting toxicity (DLT)	• If this occurs in the first cohort after the starting dose reduction the escalation must be stopped. • For any other dose cohort, enter 3 additional patients at the previous dose level. o If ≥ 2 of these 3 patients (total of ≥ 2 of the 6 patients) experience DLT, then dose escalation is stopped. o If 0 of these 3 patients (total of 0 of the 6 patients) experience DLT, enter 3 patients at the next higher dose level[2]. – If 0 of these 3 patients (total of 1 of the 6 patients) experience DLT, enter 3 patients at the next higher dose level[2]. – If ≥ 1 of these 3 patients (total of ≥ 2 of the 6 patients) experience DLT, then dose escalation is stopped.

The number of patients refers to patients evaluable for DLT assessment.
[1]Treatment related means causal relationship of the event to BAL101553 is considered to be at least "possible".
[2]Refer to Appendix 2, Table 19 for descriptions of provisional dose levels.
CTCAE= Common Terminology Criteria for Adverse Events version 4.03.

Appendix 3 Recommended Phase 2 Dose (RP2D) rationale for patient with GBM

The objective of the Phase 1 portion of the study was to determine the MTD and to characterize DLTs of daily oral BAL101553 in adult patients with advanced solid tumors and patients with recurrent or progressive GBM or high-grade glioma. The protocol defined separate MTD assessments for both groups and Table 22 summarizes the respective results; Table 24 and Table 25 provide an overview of drug-related AEs by toxicity grade.

Table 22 Primary results in Phase 1

Cohort	Dose (mg/d)	N	Dose level declaration	DLTs with CTCAE grade (G) by patient
Solid tumors	2	3		
	4	3		
	8	3		
	16	7	MTD	
	20	7		• Hyponatremia G4 • Hyponatremia G4
	30	3	MAD	• Hyponatremia G2, hypokalemia G2, hallucinations G2 • Hyponatremia G3
GBM/high grade glioma	8	4		
	15	3		
	20	7		• Fatigue and depression G2
	25	3		
	30	8	MTD	
	35	3	MAD	• Hallucinations G3, confusion G3, gait disturbance G2 • Confusion G2, gait disturbance G3

Of note, eight patients experienced drug-related hallucinations of any grade and/or hyponatremia of grade ≥ 3. These adverse effects of special interest (AESIs) often had an early onset and further analysis revealed a potential relationship with exposure.

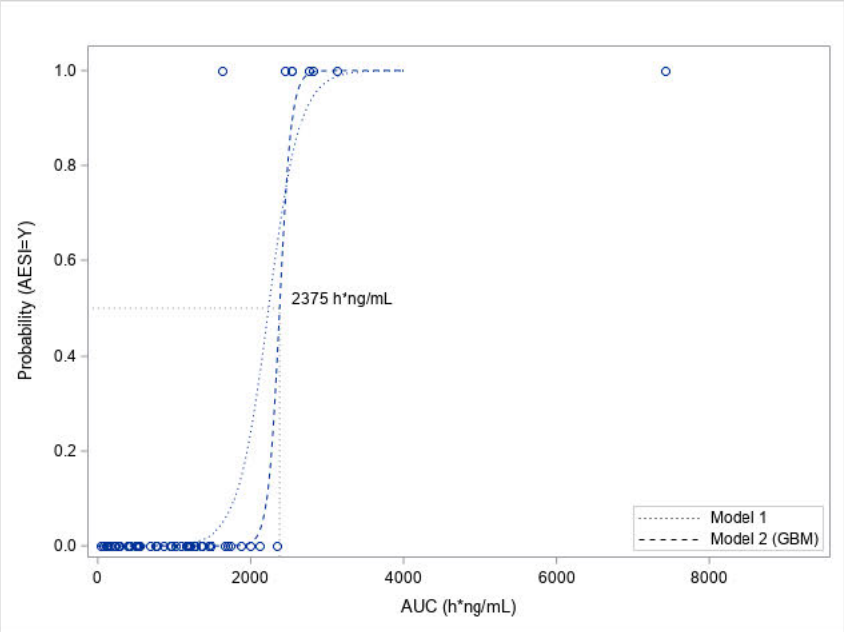
Table 23 summarizes the results of the logistic regression predicting AESIs based on AUC_{inf} (model 1) or AUC_{inf} and cohort (model 2).

Table 23 Logistic regression

Model	Covariates	Regression parameters			AIC	Cohort	AUC (P=0.5)
		Intercept	Beta 1 (AUC_{inf})	Beta 2 (cohort)			
1	AUC_{inf}	−11.090	0.00497	–	16.323	–	2233
2	AUC_{inf}, cohort	−23.506	0.01326	−7.97953	14.196	ST	1773
						GBM	2375

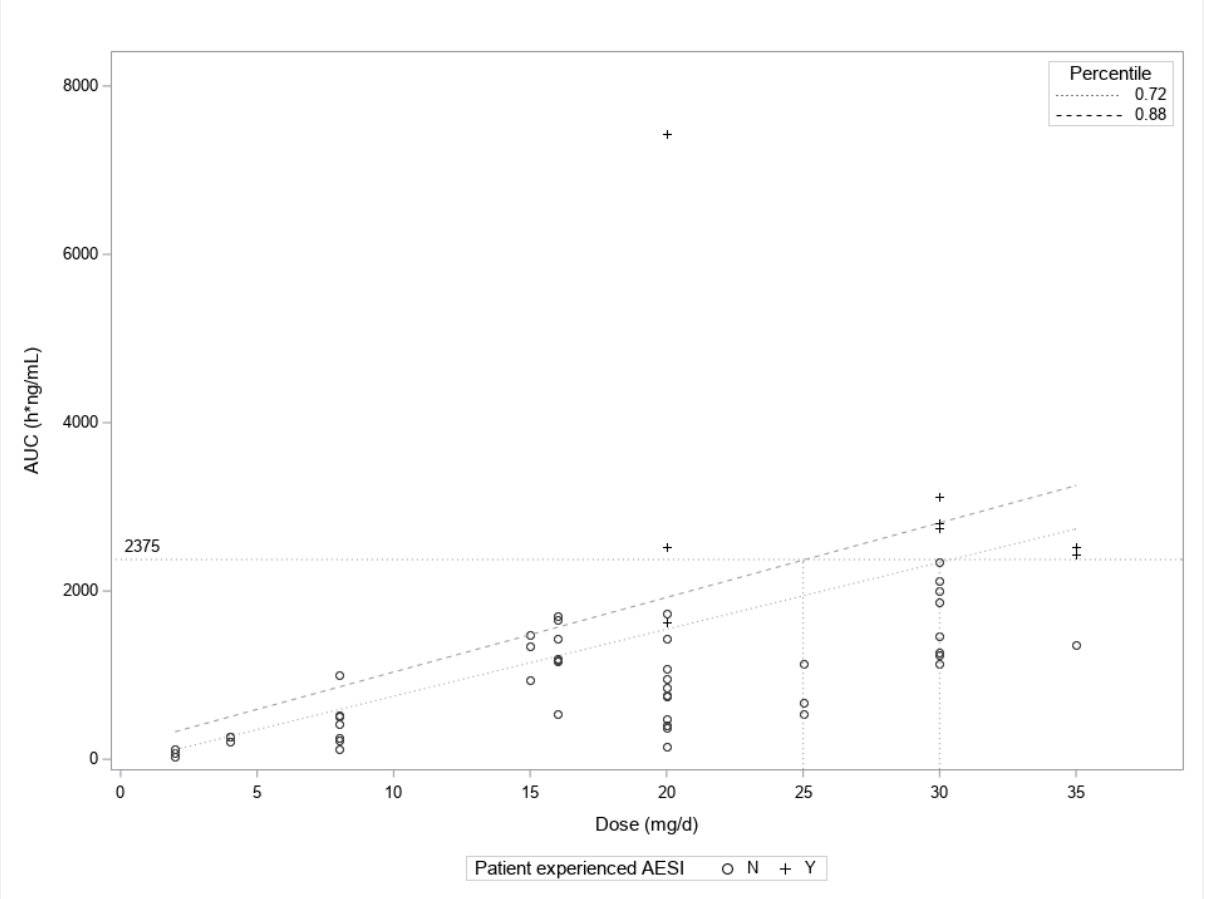
The Akaike Information Criterion (AIC) favors selection of model 2. Figure 5 presents the AESI probability in response to AUC_{inf} for model 1 and model 2 when patients belong to the GBM cohort. In the latter case the risk threshold is 2375 h*ng/mL.

Figure 5 Logistic regression between AUC and adverse events of special interest (AESI; hallucinations of any grade or hyponatremia of grade ≥ 3)



Quantile regression allows then to predict for each dose level the proportion of patients whose exposure will exceed this threshold. This model provides robust predictions as it utilizes all data not only those from patients at a certain dose level. Figure 6 shows for each dose level the AUC_{inf} of all patients treated in Phase 1 and it highlights those, which experienced AESIs. The horizontal line representing the risk threshold intersects the 88% and 72% percentile lines at dose levels of 25 mg/d and 30 mg/d, respectively. This means that 12% at 25 mg/d and 28% at 30 mg/d are at a risk of 50% or more to experience AESIs.

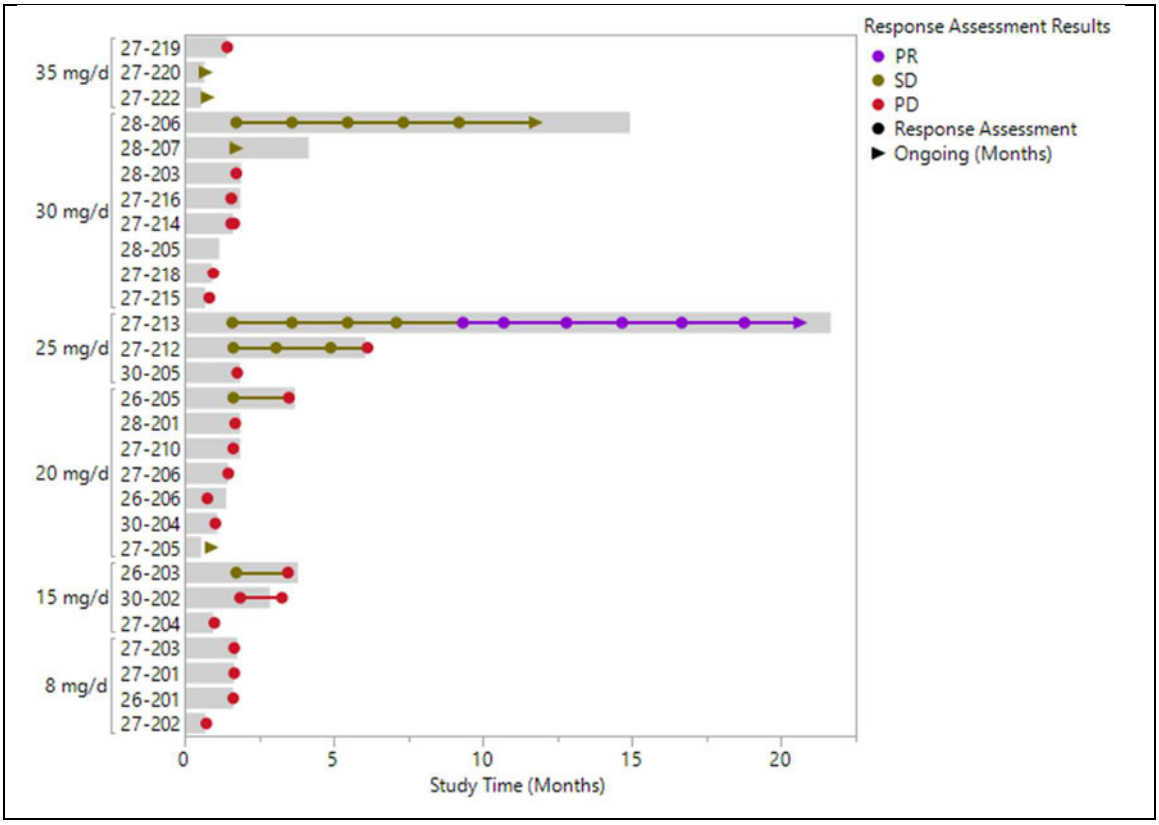
Figure 6 Quantile regression of AUC_{inf} versus dose



The model above suggests that the proportion of patients being at risk is more than twofold at 30 mg/d compared to 25 mg/d. In addition, Table 24 presents the frequency of AEs by toxicity grade in GBM/high-grade glioma patients of Phase 1. In this patient group, which is most relevant for the planned Phase 2a, there were grade 3 toxicities only seen at 30 and 35 mg/d but not at the dose levels up to 25 mg/d.

Figure 7 shows that long-term disease stabilizations and objective response occurred in Phase 1 only at 25 and 30 mg/d.

Figure 7 Swimmer plot of Glioblastoma / high-grade glioma patients in Phase 1



Summary

- Phase 1 data suggest an increased probability to experience certain DLTs when exposure in GBM patients exceeds 2375 h*ng/mL; at the MTD declared in GBM/ high-grade glioma patients, 28% of patients are expected to exceed this threshold. This doubles the proportion predicted at 25 mg/d which is estimated at 12%.
- In Phase 1, no toxicities ≥ grade 3 were seen at 25 mg/day in GBM/ high-grade glioma patients
- Long-term disease stabilizations and objective response were only seen at 25 mg/d and 30 mg/d

Conclusion

The daily dose of 25 mg seems to offer the best potential benefit-risk ratio in GBM patients.

Table 24 GBM patients with treatment-emergent adverse events probably or possibly related to oral BAL101553, by System Organ Class, Preferred Term and worst severity

Drug-related AEs, n(%)	8 mg/d (N=4)		15 mg/d (N=3)		20 mg/d (N=7)		25 mg/d (N=3)		30 mg/d (N=8)		35 mg/d (N=3)	
Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
SOC / PT (occurred in >1 patient)												
ALL	**4 (100)**		**3 (100)**		**4 (57)**		**3 (100)**		**4 (50)**	**1 (13)**	**1 (33)**	**2 (67)**
Blood and lymphatic system disorders			**1 (33)**				**1 (33)**		**1 (13)**			
Anaemia			1 (33)				1 (33)		1 (13)			
Cardiac disorders										**1 (13)**		
Ear and labyrinth disorders							**1 (33)**		**1 (13)**			
Gastrointestinal disorders	**1 (25)**				**2 (29)**		**2 (67)**		**1 (13)**		**1 (33)**	
Diarrhoea	1 (25)				2 (29)							
Nausea					1 (14)		2 (67)		1 (13)		1 (33)	
General disorders and administration site conditions			**2 (67)**		**1 (14)**		**2 (67)**				**1 (33)**	**1 (33)**
Fatigue			2 (67)		1 (14)		2 (67)					
Gait disturbance											1 (33)	1 (33)
Investigations	**1 (25)**		**2 (67)**						**1 (13)**			
Alanine aminotransferase increased			1 (33)						1 (13)			
Aspartate aminotransferase increased			1 (33)						1 (13)			
Metabolism and nutrition disorders	**1 (25)**				**1 (14)**		**2 (67)**		**1 (13)**			
Hypokalaemia							1 (33)		1 (13)			
Hyponatremia					1 (14)				1 (13)			
Musculoskeletal and connective tissue disorders					**1 (14)**							
Nervous system disorders	**1 (25)**		**2 (67)**		**1 (14)**				**1 (13)**		**1 (33)**	
Lethargy			1 (33)		1 (14)							
Seizure	1 (25)		1 (33)									
Psychiatric disorders					**1 (14)**						**1 (33)**	**1 (33)**
Confusional state											1 (33)	1 (33)
Hallucination											1 (33)	1 (33)
Skin and subcutaneous tissue disorders			**1 (33)**				**2 (67)**					
Alopecia							2 (67)					
Vascular disorders									**1 (13)**			

Table 25 Solid tumor patients with treatment-emergent adverse events probably or possibly related to oral BAL101553, by System Organ Class, Preferred Term and worst severity

Drug-related AEs, n(%)	2 mg/d (N=3)		4 mg/d (N=3)		8 mg/d (N=3)		16 mg/d (N=7)		20 mg/d (N=7)		30 mg/d (N=3)	
Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
SOC / PT (occurred in >1 patient)												
ALL	1 (33)		3 (100)		1 (33)	1 (33)	2 (29)	2 (29)	2 (29)	5 (71)	1 (33)	2 (67)
Blood and lymphatic system disorders			1 (33)									
Cardiac disorders									1 (14)			
Gastrointestinal disorders	1 (33)		1 (33)		1 (33)		2 (29)		3 (43)	1 (14)	1 (33)	
Constipation					1 (33)		1 (14)			1 (14)	1 (33)	
Diarrhoea	1 (33)				1 (33)				3 (43)			
Nausea			1 (33)		1 (33)				2 (29)			
General disorders and administration site conditions	1 (33)		1 (33)		1 (33)		2 (29)		2 (29)	1 (14)		
Fatigue	1 (33)		1 (33)		1 (33)		2 (29)		2 (29)	1 (14)		
Infections and infestations			1 (33)				1 (14)					
Investigations								1 (14)	3 (43)	1 (14)		
Alanine aminotransferase increased							1 (14)		1 (14)			
Aspartate aminotransferase increased							1 (14)		1 (14)			
Blood alkaline phosphatase increased								1 (14)	1 (14)			
Troponin increased									1 (14)	1 (14)		
Metabolism and nutrition disorders			1 (33)				1 (14)		3 (43)	2 (29)		2 (67)
Decreased appetite			1 (33)				1 (14)		1 (14)			
Hyponatremia									1 (14)	2 (29)		2 (67)
Musculoskeletal and connective tissue disorders			1 (33)						3 (43)			
Arthralgia			1 (33)						1 (14)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					1 (33)							
Nervous system disorders			2 (67)				1 (14)		3 (43)		1 (33)	
Lethargy			2 (67)				1 (14)		1 (14)			
Psychiatric disorders									1 (14)	2 (29)	2 (67)	
Hallucination, visual										1 (14)	2 (67)	
Skin and subcutaneous tissue disorders					1 (33)				3 (43)			
Hair colour changes									2 (29)			
Vascular disorders						1 (33)		1 (14)		1 (14)		
Hypertension						1 (33)		1 (14)		1 (14)		

Appendix 4 EB1 Clinical Trial Assay

In the Phase 2a portion of this study (Simon's two-stage design), a tissue screening program adhering to local standards in selected countries will be established to support the identification of potential patients using EB1 immunohistochemistry (IHC) testing.

EB1 tissue staining methodology based on immunohistochemistry in GBM tissue

EB1-tissue staining performed to date was conducted at the University of Basel [redacted] using a Ventana discovery Ultra platform.

For the Phase 2a portion of this study (Simon's two-stage design), a dedicated Clinical Trial Assay is being developed, and is expected to be available in June 2020 (CE marked version in Sepetmber 2020). Patient selection will occur via central EB1 immunohistochemistry (IHC) testing in a CAP/CLIA laboratory under Good Laboratory Practice (GLP) conditions, in the context of a biomarker stratified design. Technical/analytical validation of the assay will be performed according to CAP/CLIA regulations, ICH Q2(R1) guidelines, and according to applicable regulatory requirements including consideration of applicable CLSI/LA28-A2 guidelines and associated normative regulations. An experienced CRO will develop the Clinical trial Assay, and will serve as a Central Pathology Laboratory for EB1-testing and evaluation.

EB1 GBM tissue testing process

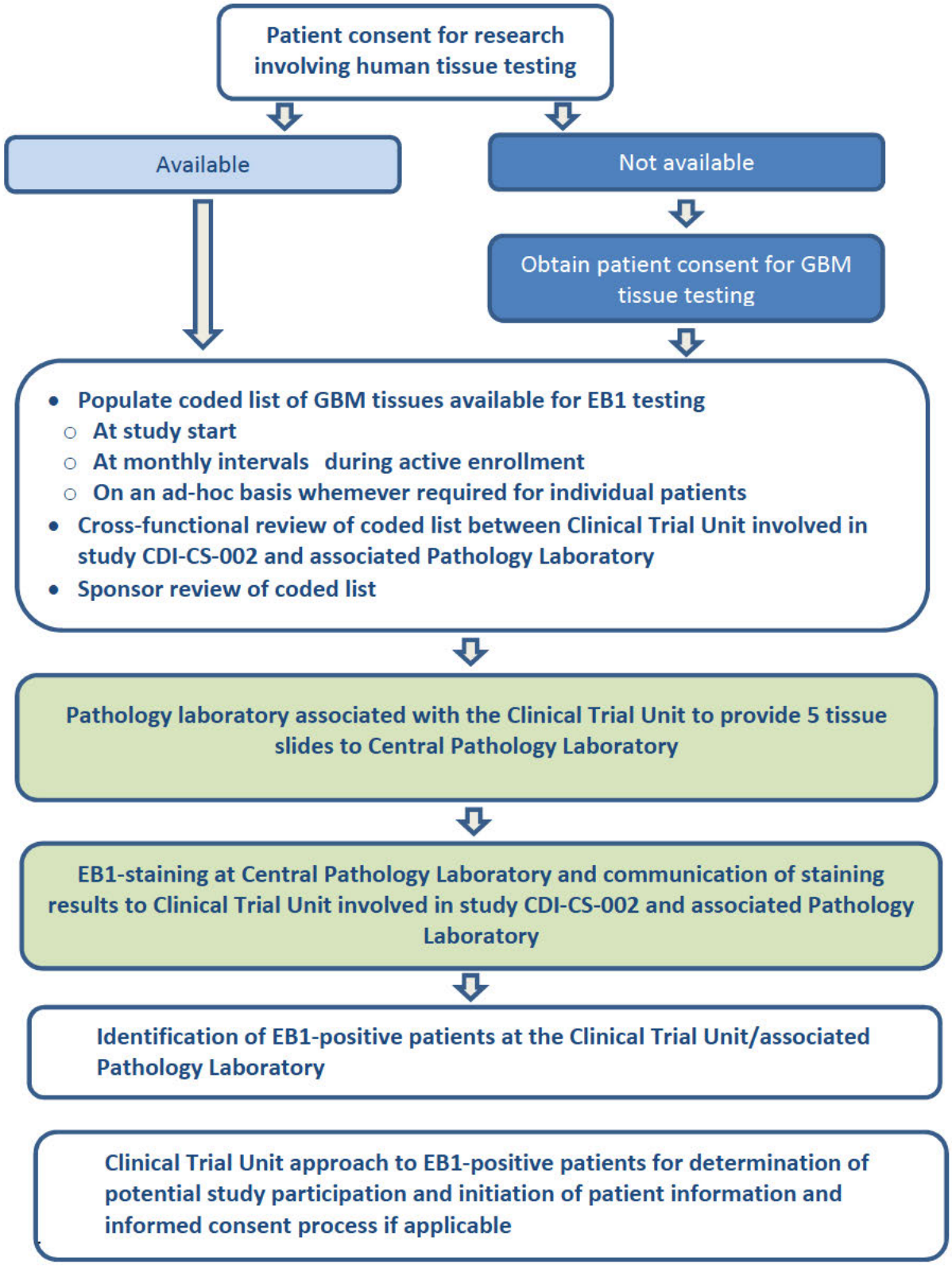
The GBM tissue testing algorithm is outlined in Figure 8. In brief, following clarification that patient consent for tissue testing is available, the Clinical Trial Unit at a respective study site and the associated pathology laboratory will populate a coded patient list of available GBM tissues for EB1 staining.

Such list will be populated at the beginning of the study and then updated approximately at monthly intervals or ad-hoc for individual patients whenever needed.

Tissue slides will be sent for EB1-staining to the Central Pathology Laboratory.

EB1-positivity requires moderate to strong EB1-staining intensity. EB1 staining diagnostic criteria will be provided in a separate Laboratory manual. EB1 staining results will be provided by the Central Pathology Laboratory to the Clinical Trial Unit and the associated pathology laboratory. The Clinical Trial unit and the associated pathology laboratory will follow-up on all GBM tissue samples determined as EB1-positive in the central pathology assessment and will identify EB1-positive patients and approach these EB1-positive patients to discuss a potential study participation and initiate the patient information and informed consent process if applicable.

Figure 8 Schematic overview GBM tissue testing process for EB1



Appendix 5 Response evaluation and criteria in solid tumors (RECIST) guidelines, version 1.1

Source

Eisenhauer EA, Therasse P, Bogaerts J, et al. 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 6 RANO criteria for glioblastoma and high-grade gliomas

Source

Wen PY, Macdonald DR, Reardon DA, et al. 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.

Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Appendix 7 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.

Appendix 8 Investigator's protocol signature page

BASILEA
INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	CDI-CS-002 / Version 11.0	Basilea Product No:	BAL101553
Protocol Title:	An open-label Phase 1/2a study of oral BAL101553 in adult patients with advanced solid tumors and in adult patients with recurrent or progressive glioblastoma or high-grade glioma		
Basilea Pharmaceutica International Ltd			
Approval Date:	1 July 2021	By (Project Physician):	Thomas Kaindl, MD
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 Independent Ethics Committee / Institutional Review Board 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	