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SAP - Final Analysis

Sponsor:	Basilea Pharmaceutica International Ltd
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
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Version History

Date	Version #	Description of Revision(s)	Author
23Nov2017	Final 1.0	This is the first approved version of the SAP	[redacted]
18May2022	Final 2.0	Updated as per protocol version 11.0	

Table of Content

1 LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine amino transferase
AP	Alkaline phosphatase
AST	Aspartate amino transferase
APTT	Activated partial thromboplastin time
$AUC_{0-\infty}$	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
ATC	Anatomical Therapeutic Chemical (Classification System)
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
BSA	Body surface area
CA-125	Cancer antigen-125
CDI	Cell death inducer
CI	Confidence interval
CLs	Systemic clearance
C_{max}	Maximum observed plasma concentration
CK	Creatine phosphokinase
CR	Complete Response
CRF	Case report form
CT	Computed tomography
CTC(s)	Circulating tumor cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
D	Day (of a treatment cycle)
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

FAP	Full analysis population
H	hour
hCG	Human chorionic gonadotropin
HR	Heart rate
INR	International normalized ratio (for reporting prothrombin time)
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
MAD	Maximum administered dose
MRI	Magnetic resonance imaging
msec	milliseconds
MTD	Maximum tolerated dose
N	Number
OS	Overall Survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic(s)
PR	Partial response
PSA	Prostate specific antigen
PT	Preferred term
QTcF	QT interval corrected for heart rate (Fridericia correction)
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	Red blood cell
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SD	Stable disease
SOC	System organ class
$t_{½}$	Terminal elimination half-life
t_{max}	Time to maximum plasma concentration
WBC	White blood cell

2 INTRODUCTION

This statistical analysis plan covers the detailed procedures for performing the statistical analyses and producing tables, listings and figures in the study described in Basilea Pharmaceutica International Ltd. (Basilea) Protocol CDI-CS-002, version 11.0 dated July 1st, 2021.

Considering that no patient was evaluated using Prostate specific antigen (PSA) or Cancer antigen-125 (CA-125), none of the analyses specified in the protocol based on these criteria will be detailed in this SAP.

The design and analysis of data for the surgical cohort mentioned in the protocol is also not included in this SAP, as a separate protocol amendment would be created when applicable.

3 STUDY OBJECTIVES, ENDPOINTS AND DESIGN

3.1 Study Objectives

3.1.1 Phase 1 dose escalation portion

3.1.1.1 Primary objectives

The primary objectives of the Phase I 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.

3.1.1.2 Secondary objectives

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

- 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.

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

3.1.2.1 Primary objectives

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 Response Assessment in Neuro-Oncology (RANO) criteria. A tissue screening program adhering to local standards in selected countries will be established to support the identification of potential patients.

3.1.2.2 Secondary objectives

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

- 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).

3.1.3 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
- To explore the potential utility of biomarkers in blood and/or tumor tissue as predictive biomarkers.

3.2 Study Endpoints

3.2.1 Primary endpoints

The primary study endpoints are:

- 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.

3.2.2 Secondary endpoints

Secondary endpoints are:

- Overall safety endpoints:
  - Type and frequency of AE, SAEs, laboratory, echocardiogram and Electrocardiogram (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 Response Evaluation Criteria in Solid Tumors (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).
  - PFS 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 (CL/F), volume of distribution (Vz/F), accumulation ratio.
  - Total 24-h urinary excretion of BAL101553 and BAL27862.

3.2.3 Exploratory endpoints

Exploratory endpoints are:

- Change from baseline in biomarkers (including but not limited to numbers of CTCs, CECs, CEPs).

3.3 Study Design

3.3.1 Study design

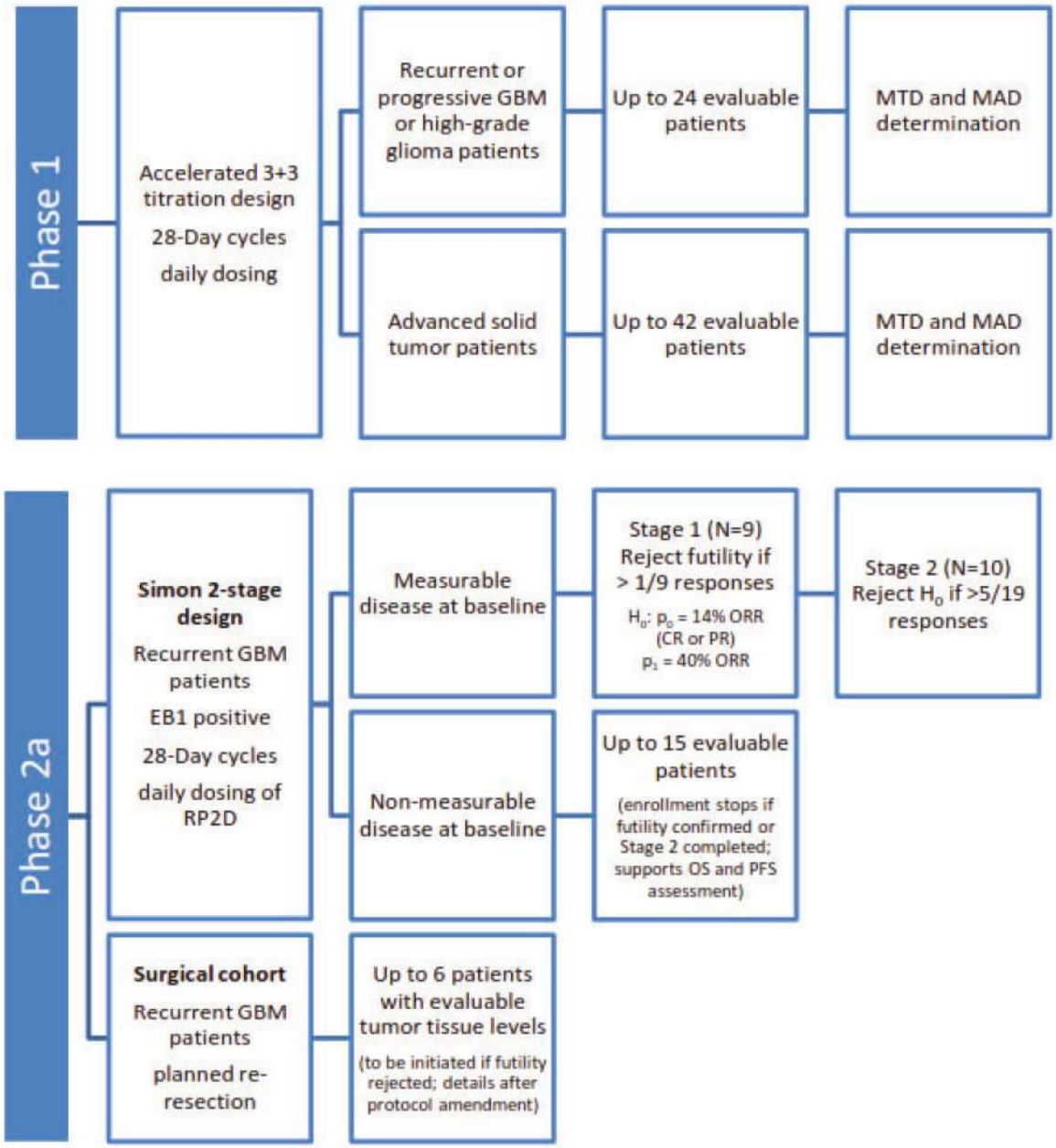
This is a first-in-human, single-agent, open-label, multicenter, Phase 1/2a study for daily oral BAL101553 comprised of two parts:

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 nonclinical 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 1.

Figure 1: Schematic overview of study design



Each treatment cycle will comprise 28 days of continuous, daily oral BAL101553 administration to patients in a fasted state.

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.

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.

3.3.1.1 Dose Escalation (Phase I)

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 Cmax 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 (PD), or unacceptable toxicity. For each dose cohort, new patients will be recruited and evaluated for safety, pharmacokinetics, pharmacodynamic effects, and for antitumor activity.

Planned dose escalation levels

Cohort size is variable, and will be expanded if patients experience specific Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 -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 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 1 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 $\geqslant$ 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 $\geqslant$ 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

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.

Table 1 Cohorts 1–4: Planned 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.

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.

3.3.1.2 Expansion Portion (Phase IIa)

Additional patients will be enrolled and treated at the RP2D dose of 25 mg/day (see protocol section 1.5.4). Enrolled patients will be evaluated for safety, pharmacokinetics, pharmacodynamic effects, and for antitumor activity.

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.

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. Efficacy assessments to assess objective response to treatment must be scheduled at the end of at least each even-numbered treatment cycle (e.g., end of Cycle 2, 4, 6, etc.) and subsequent treatment cycles may not be initiated if disease progression is observed. 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 Computed tomography (CT)/ Magnetic resonance imaging (MRI) scans may be extended from 8 weeks to 12 weeks.

3.3.2 Assessments and study duration

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. 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 will be replaced if they could not complete at least one 28-day treatment cycle. Patients in the Phase 2a expansion portion of the study (Simon's two-stage design) 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.

Table 2 and 3 presents a summary of the schedule of assessments to be performed from Screening through to the End of Study.

Table 2 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 of protocol); 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 of protocol).
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 of protocol):
   - 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 5.5.7 of protocol); 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 of protocol).
8. Hematology must be performed and reviewed (see Section 5.5.7.1 of protocol):
   - 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 of protocol).
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 of protocol).
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 Sections 5.5.4 of protocol).
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 of protocol).
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 of protocol):

    Dose escalation portion (Phase 1) of the study (see Section 3.1.2 of protocol):
    - 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 of protocol). 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 of protocol).
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 of protocol). 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 of protocol). 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 feas ble 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 of protocol). 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 of protocol) 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 3 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 of protocol). 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 of protocol).
6. Single 12-lead ECGs are to be obtained as follows (see Section 5.5.5 of protocol):
   - 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 of protocol.
   - 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 of protocol):
   - 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 of protocol).
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 Section 5.5.7.4 and 5.5.7.5 of protocol Sections).
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 of protocol).
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 Section 5.5.7.6 and 7.3 of protocol).

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 of protocol):
    - 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 of protocol).
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 of protocol).
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 of protocol).

3.3.3 Planned sample size

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.

The dose escalation portion of the study is completed. 26 patients with advanced or recurrent solid tumors and 28 patients with recurrent or progressive GBM or high-grade glioma were dosed. In each of the groups, 24 patients were evaluable for MTD assessment.

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%.

3.4 Interim analyses

No interim analyses are planned for the phase 1 portion of the study. Upon completion of the phase 1 portion of the study, the Phase 1 data will be cleaned and data will be locked. Advanced or recurrent solid tumors and recurrent or progressive GBM or high-grade glioma will be analyzed separately.

The phase 2a parts will also be analyzed separately once data are cleaned and data locked.

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.

4 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.

4.1 All enrolled population

The All Enrolled population includes all patients who enrolled into the study after signing an informed consent form and satisfying inclusion/exclusion criteria.

4.2 Full analysis population (FAP)

The FAP includes all patients who received at least one partial or complete dose of study drug, based on the intent-to-treat (ITT) principle. The FAP will be the primary population for analyzing efficacy in Phase 1.

4.3 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 will 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.

4.4 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.

4.5 Pharmacokinetic analysis population(PK)

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

4.6 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 post baseline RANO assessment after having received at least 6 weeks of study treatment.

For objective response rate and stage transition, the analysis will be based on patients with measurable disease at baseline in the EEP.

5 STATISTICAL CONSIDERATIONS AND ANALYSIS

5.1 Derived variables

The following derived variables will be applied throughout the study:

- Baseline is defined as the last available assessment prior to first dose intake (including unscheduled assessments), e.g. Cycle 1 Day 1 pre-dose.

- Last/Final for safety is the first available value after treatment or, if not available, then immediately before last treatment.

- Adverse event (AE) duration (in days) will be calculated as (the times will not be considered): Event end date - Event onset date + 1.

- The following algorithm will be used for the study day determination:

    - Day 1 = Day of first study drug administration (i.e. at Cycle 1 Day 1). The day before day 1 is day-1.
    - Prior to Day 1 the algorithm is (<visit/examination date> minus <date of first study drug administration >)
    - Day 1 and subsequent days = (<visit/examination date> minus <date of first study drug administration >) + 1.

- Duration of exposure (in days) will be calculated as: Date of last study drug administration – Date of first study drug administration + 1.

- The response according to RECIST or RANO criteria will be as reported in the Case report form (CRF).

5.2 Handling of missing data and/or invalid data and outliers

5.2.1 Handling of missing response

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

5.2.2 Handling of missing or incomplete dates

Incomplete/partial dates will be replaced by derived variables and imputed using the following rules:

- if the day of the month is missing it is imputed to be the 15th if not in the month of treatment
- if both the day and month are missing, they are imputed to be June 30 if not in year of treatment
- missing years will be left as missing

In case this leads to inconsistencies with other available patient's data, the imputation values will be handled case-by-case.

6 STATISTICAL PLAN AND METHODS

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 (phase 1 dose escalation), and for patients with recurrent GBM (phase 2a). Data will be listed by study phase and disease subgroup.

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 may be prepared once these patients have completed treatment, or have been discontinued.

The statistical analysis will be performed using the software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual data as well as results of statistical analyses will be presented in individual patient data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: mean, standard deviation, median, minimum, maximum and number of observations. Categorical data will be described using frequency and percentage. Shift tables will be provided, where appropriate. One additional decimal point for mean, median, Q1 and Q3 and 2 additional decimal points for SD will be used. Percentages will be rounded to one decimal place. Unscheduled assessments will only be listed and will not be included in the tables, unless otherwise specified. Any changes in the planned statistical methods will be documented in the clinical study report.

The following international dictionaries will be used for medical coding:

- Medical History events: MedDRA (version 19.1 or later version)
- Medications: WHO Drug Dictionary (March 1st, 2016 – Format B2 or later version)
- AEs: MedDRA (version 19.1 or later version)

6.1 Background characteristics

6.1.1 Patient disposition

Enrollment and disposition data will be presented for each patient in data listings and summarized by frequency tables for all enrolled patients.

Inclusion and exclusion criteria violations and patient enrollment eligibility will be listed.

6.1.2 Protocol deviations

All important protocol deviations reported by the clinical team will be presented in a data listing. Protocol deviations will be reviewed prior to database.

6.1.3 Demographic and baseline characteristics

Background and demographic characteristics of the FAP and EEP for phase 2a including age, sex, race, patient status at selection, female of child-bearing potential, reason not of childbearing potential, height, weight, body surface area (BSA), tumor type, previous anticancer treatments, medical conditions, performance status etc. will be summarized by dose cohort using descriptive statistics or frequency tables. Percentages will be based on the number of patients with available observations in the FAP and EEP for phase 2a.

Demographic information will be presented in data listings.

6.1.4 Medical history

Previous or current diseases as well as previous cancer treatments will be presented in data listings.

Medical history data will be summarized by dose cohort, system organ class (SOC) and preferred term (PT) using the FAP for and EEP for phase 2a.

6.2 Efficacy analysis

6.2.1 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 response (CR) or partial response (PR), based on RECIST criteria v1.1 for patients with advanced or recurrent solid tumors); and based on RANO criteria 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.

A patient who has a response unknown or not reported will be treated as non-responder.

The proportion and its exact 95% confidence interval (CI) will be presented by disease subgroup and by dose cohort.

Waterfall plots, spider plots and swimmer plot summarizing tumor size, best response and treatment duration will also be provided.

6.2.2 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., best response of CR, PR, or stable disease (SD)).

A patient who has a response unknown or not reported will be treated as non-responder.

The proportion and its exact 95% CI will be presented by disease subgroup and dose cohort.

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.

6.2.3 Progression-free survival

Progression-free survival is defined as the interval between the date of first infusion and the earliest date of objective disease progression according to RECIST criteria v1.1 for patients with advanced or recurrent solid tumors, and based on RANO criteria for patients with recurrent or progressive GBM/high-grade glioma; or Investigator-confirmed clinical progression; 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.

If a patient has no post-baseline objective tumor assessment then the PFS will be censored to 0 day.

Progression-free survival will be summarized for the FAP (Phase 1 portion of the study) by disease subgroup and dose cohort.

In the Phase 2a portion of the study (Simon's two-stage design), PFS will be summarized for the FAP and EEP. Median PFS and 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), using KM method. The 95% CI will be calculated with Brookmeyer-Crowley method. The associated survival curve will be displayed.

6.2.4 Overall Survival

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.

Overall survival will be summarized using KM method for the FAP (Phase 1 portion of the study) and the FAP and EEP for the Phase 2a portion of the study (Simon's two-stage design).

6.3 Safety analysis

Safety assessments will be conducted throughout the entire study period. Analyses will be performed using safety population, unless otherwise specified.

The safety evaluations will include analyses of AEs, laboratory assessments (hematology, biochemistry, cardiac troponin, coagulation, urinalysis), pregnancy testing in women of childbearing potential, ECG, transthoracal echocardiography, chest X-ray / CT / MRI, vital signs, ECOG performance status, physical examination, and evaluation of concomitant medications.

6.3.1 Treatment exposure and compliance

The duration (in days) of BAL101553 exposure will be listed and summarized using descriptive statistics.

The actual dose of BAL101553 received and study drug dose interruptions and reductions will be listed and summarized using descriptive statistics.

Study drug compliance will be calculated as: 100 × [(total dose received)]/(sum of total planned dose for each dosing period, excluding period of interruption due to AE).

Study drug compliance will be summarized using standard summary statistics by disease subgroup and dose cohort. Study drug compliance will also be summarized in categories "<80%", "≥80%-≤125%" and ">125%" using frequency tables.

6.3.2 Dose-limiting toxicity

The dose limiting toxicities will be listed and will be summarized for each disease subgroup and dose cohort from part I using the MTD determining population.

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.

6.3.3 Adverse events (AEs)

AE tables and listings will display only treatment-emergent AEs. Any non-treatment-emergent AE will be displayed on a separate listing.

Treatment-emergent events are defined as all events occurring after BAL101553 treatment begins, up to 28 days after last study drug administration. Any AE starting prior to first treatment on Cycle 1 Day 1, or more than 28 days after last study drug administration will be considered as non-treatment emergent. The relationship of an AE to treatment is recorded as unrelated, unlikely, possible and probable. For analysis purposes, 'related' AEs will be those reported as possibly related or probably related, or those for which the relationship is unknown.

AEs will be presented in data listings including dose cohort, disease subgroup, patient, dates/times of event, MedDRA SOC, PT, duration of the event, seriousness, CTCAE grade, intensity, drug adjustment, treatment taken, relationship to study drug and outcome.

An overview table (including only treatment-emergent AEs) will be also presented with the number (and percentage) of patients with:

- At least one AE
- At least one related AE
- CTCAE grade 3/4 or severe AEs
- CTCAE grade 3/4 or severe related AEs
- At least one SAE
- At least one related SAE
- AEs leading to dose modifications (i.e. dose reduced or dose interruption)

- Related AEs leading to dose modifications (i.e. dose reduced or dose interruption)
- AEs leading to study drug discontinuation
- Related AEs leading to study drug discontinuation
- AEs leading to death.
- Related AEs leading to death.

The number of events will be also included in this overview table. This table will be displayed by disease subgroup and dose cohort for all the study period.

All treatment-emergent AEs and treatment-emergent AEs related to treatment will be summarized by incidence rate tables broken down by:

- SOC and PT.
- SOC, PT and worst CTCAE grade/intensity.
- SOC, PT and worst CTCAE grade/intensity.
- SOC, PT and drug relationship.

The incidence rate table for treatment-emergent AEs and treatment-emergent AEs related to treatment by SOC, PT and worst CTCAE grade/intensity will be repeated by treatment cycle using the actual dose received within each cycle.

In addition, all treatment-emergent AEs and treatment-emergent AEs related to treatment will be summarized by SOC, PT and

- Worst CTCAE grade and cycle of occurrence of first event.
- Worst CTCAE grade during cycle 1 and during study.

Treatment-emergent AEs leading to dose modifications and leading to study drug discontinuation will be also summarized by SOC and PT.

6.3.4 Laboratory evaluation

Laboratory safety assessments include hematology, biochemistry, cardiac troponin, coagulation and urinalysis.

The laboratory tests for safety analyses consist of the following:

- Hematology: Hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, platelet count and total and differential white blood cell (WBC) count (neutrophil including bands, lymphocyte, monocyte, eosinophil and basophil counts).
- Biochemistry: Serum creatinine, blood urea nitrogen (BUN), uric acid, sodium, potassium, chloride, bicarbonate, magnesium, calcium, inorganic phosphorus, glucose, albumin, total protein, Aspartate amino transferase (AST), Alanine amino transferase (ALT), total bilirubin, alkaline phosphatase (AP), lipase, lactate dehydrogenase(LDH) and creatine phosphokinase (CK).
- Cardiac troponin: Either troponin T or troponin I.
- Coagulation: International normalized ratio (INR) for reporting prothrombin time and activated partial thromboplastin time (APTT).

- Urinalysis: Dipstick analysis for specific gravity, glucose, protein, and blood. Microscopic analysis for white blood cells, RBCs and any additional findings (such as casts).
- Pregnancy test (at screening, D1 of every cycle): Serum or urine test for human chorionic gonadotropin (hCG).

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

The laboratory parameters will be presented in data listings sorted by disease subgroup, dose cohort, patient, study day, study time and analyte. Out-of-range values will be flagged with h (high) or l (low). Out-of-marked-range values (defined by Basilea SOP LIS-GLO-000412 Preferred Units and Marked Factors) will be flagged with H (marked high) or L (marked low).

Descriptive statistics for each laboratory analyte at each assessment time will be tabulated. The change from baseline will be also summarized.

An analysis of individual patient changes by disease subgroup dose and cohort will be given using shift tables showing the change from CTCAE grade/intensity at baseline to the worst CTCAE grade/intensity (including unscheduled assessments) during the study.

6.3.5 Vital signs

Summary statistics by disease subgroup, dose cohort and scheduled time point will be presented for each vital sign. The change from baseline will also be presented.

Summary statistics for baseline blood pressure (BP) and change from baseline (pre-dose on each study day to post-dose timepoints) will be presented by dose level for each study day. The mean maximum change from baseline (pre-dose on each study day to post-dose timepoints) will also be presented by dose levels for each study day. In case BP is collected on both arms, the average value will be taken for the analyses.

The number of patients with values outside marked reference ranges (shown below) will also be tabulated by disease subgroup, dose cohort and scheduled time point.

The vital signs marked reference ranges are:

Diastolic Blood Pressure (DBP): < 60 mmHg or > 100 mmHg.

Systolic Blood Pressure (SBP): < 80 mmHg or > 180 mmHg.

Pulse: < 40 beats/min or > 120 beats/min.

Temperature: <36.0 5 degree Celsius or >38.5 degree Celsius.

Vital sign assessments will be presented for each patient in a data listing.

6.3.6 ECG results

A summary of clinically significant findings from the 12-lead ECG (CRF data) will be provided for each disease subgroup, dose cohort and time point using a shift table. For this analysis, if the findings for the three assessments at Cycle 1 Day 1 pre-dose are different, the baseline will be defined as the worst assessment prior to first dose intake (if Cycle 1 Day 1 assessments are not done, screening assessments will be used as baseline). For each post-dose time point, the worst assessment of the three triplicates will be taken for the analysis.

The 12-lead ECG results (RR interval and QT interval corrected for heart rate (Fridericia correction) (QTcF) interval reported in the CRF) and changes from baseline will be summarized using standard descriptive statistics by disease subgroup, dose cohort and scheduled time point. The mean of the three ECGs measurements taken at each time point will be used for the summary. For this analysis, the baseline value will be defined as the mean of the three ECGs measurements taken prior to first dose intake.

The same analysis will be repeated on central ECG data (Heart rate (HR), RR, PR, QRS, QT, QTcB, QTcF)

ECG results will be presented for each patient in a data listing.

Outlier analysis:

The number and percentage of patients with maximum on-treatment value of QT/QTc intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as <5 msec, >5= msec and <10 msec, >=10 msec and <20 msec, >=20 msec and <30 msec, >=30 msec and <60 msec, and >=60 msec will be tabulated based on scheduled and unscheduled 12-lead ECG measurements (CRF and central ECG data).

The following abnormalities will also be tabulated:

- PR abnormality: PR increase from baseline>=25% when PR>200msec
- QRS abnormality: QRS increase from baseline>=25% when QRS>100 msec
- HR abnormality: HR decrease from baseline >=25% when HR<50bpm, or >=25% increase when HR>100bpm.

6.3.7 Physical examination

General physical examination assessments will be listed by dose cohort, patient and study day.

6.3.8 Prior and Concomitant medications

Medications and significant non-drug therapies prior to and after the start of the study drug will be listed by patient.

The concomitant medications taken from the start of the study drug (i.e. medications which start before and stop after first study drug administration or medications which start after first study drug administration) will be summarized by Anatomical Therapeutic Chemical (ATC) term and PT.

6.3.9 Chest X-ray/CT

Chest X-ray or CT scan abnormality results will be presented for each patient in a data listing.

6.3.10 ECOG performance status

Eastern Cooperative Oncology Group (ECOG) will be presented for each patient in a data listing.

6.3.11 Transthoracal echocardiography

Transthoracal echocardiography results will be presented for each patient in a data listing.

6.4 Pharmacokinetic analysis

6.4.1 Pharmacokinetic Parameters

PK parameters for BAL101553 and BAL27862 will be calculated from the concentration-time data using a non-compartmental analysis (NCA) method in Phoenix WinNonlin (Version 8 or higher) using Plasma Model 200 - 202 with extravascular dosing or Urine Model. Actual elapsed sampling times relative to time of study drug administration will be used for all parameter estimations.

The following parameters will be derived, as data permit, for Day 1 of Cycles 1 and 2:

C_{max}	Maximum observed concentration
t_{max}	Time to reach maximum observed concentration
AUC_{0-t}	Area under the concentration-time curve from the time of dose administration to the last quantifiable concentration, calculated by linear-log trapezoidal rule
$AUC_{0-\tau}$	Area under the concentration-time curve over a dosing interval, calculated by linear-log trapezoidal rule
$AUC_{0-\infty}$	Area under the concentration-time curve from the time of dose administration extrapolated to infinity, calculated by linear-log trapezoidal rule
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$, where λ_z is the terminal phase rate constant
CL/F	Apparent total body clearance (BAL101553 only)
V_z/F	Apparent total volume of distribution (BAL101553 only)
AR	Accumulation ratio, calculated as Cycle 2 Day 1 $AUC_{0-\tau}$/Cycle 1 Day 1 $AUC_{0-\tau}$
Ae	Total amount of drug excreted in urine over 24 hr
Fe	Fraction of dose excreted in urine over 24 hr

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of λ_z. C_{max} and any data point in the distribution phase will not be included in the calculation of λ_z. A minimum of 3 points will be used for determination of the terminal elimination phase rate constant. A time interval of at least 1 half-life will be required to calculate λ_z. An adjusted r^2 value > 0.80 will be considered acceptable for the calculation of the terminal elimination phase rate constant. If adjusted r^2 falls below 0.80, or the above conditions are not met, then the terminal elimination phase rate constant and the associated values of $t_{1/2}$, $AUC_{0-\infty}$, CL/F, and V_z/F will be flagged. If the extrapolated $AUC_{0-\infty}$ is more than 20%, then $AUC_{0-\infty}$, V_z/F and CL/F will be flagged. Flagged values will not be included in the calculation of descriptive statistics.

6.4.2 Descriptive Summaries

Concentration-time data and PK parameters will be summarized in listings of the individual values with summary statistics by Part, dose group and day. Descriptive statistics to be reported for concentration-time data and estimated PK parameters include the number of non-missing observations (n), arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, CV% of geometric mean (GeoCV).

The BAL101553 and BAL27862 concentrations will be presented in descriptive summary tables, individual listings, mean profile plots, and individual profile plots.

The PK population will be used for all summaries of the PK concentrations and parameters.

Individual plasma concentrations (BAL101553 and BAL27862) will plotted by disease subgroup, dose cohort and study day in spaghetti plots.

The geometric mean of plasma concentration (BAL101553 and BAL27862) will also be plotted by dose cohort and visit.

6.5 Biomarker analysis

This plan does not address the biomarker analysis or summarization for this study, as Basilea will be responsible for these.

7 CHANGES FROM THE PLANNED ANALYSIS IN STUDY PROTOCOL

Not applicable.

8 REFERENCES

EMEA. CPMP/ICH/363/96: Note for Guidance on Statistical Principles for Clinical Trials - ICH Topic E9. London: EMEA; 1998.

Integrated Addendum to ICH E6(R1), GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 9 November 2016.

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