BAL101553

STATISTICAL ANALYSIS PLAN

CDI-CS-003

NCT02895360

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

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Compound:	BAL101553
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Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
AST	Aspartate amino transferase
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity; calculated as $AUC_{0-last} + C_{last/\lambda z}$
AUC_{0-last}	Area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{0-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
BSA	Body surface area
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 v4.03	Common Terminology Criteria for Adverse Events version 4.03
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEP	Efficacy evaluable population
FAP	Full analysis population
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin

HR	Heart rate
ICH	International Council for Harmonisation
INR	International normalized ratio
ITT	Intention-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred Term
QTcF	QT interval corrected for heart rate (Fridericia correction)
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SD	Standard deviation
SOC	System Organ Class
$t_{½}$	Terminal elimination half-life
t_{max}	Time to maximum plasma concentration
TFL	Table, Figure and Listing
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

This statistical analysis plan (SAP) specifies 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-003. The version of the protocol at the time of preparation of this SAP is Version 6.0 dated 24 May 2018.

At the time of writing this document, the Phase 1 part of the study is completed while the Phase 2a part is ongoing.

Pharmacokinetic analysis for this study are addressed in a separate PK-SAP. Concentration data will be listed.

2 STUDY OBJECTIVES, ENDPOINTS AND DESIGN

2.1 Study Objectives

2.1.1 Primary objective

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

2.1.2 Secondary objectives

The secondary objectives are:

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

2.1.3 Exploratory objectives

The exploratory objectives are:

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

2.2 Study Endpoints

2.2.1 Primary endpoint

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

2.2.2 Secondary endpoints

Secondary endpoints are:

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

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

  Phase 2a
  - Tabulated listing of BAL101553 and BAL27862 plasma concentrations.

2.2.3 Exploratory endpoints

The exploratory endpoints are:

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

2.2.4 Study Design

2.2.5 Study design

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

- The first part is a Phase 1 multiple-ascending-dose-escalation portion using a 3+3 titration design to determine the MTD, to be carried out in up to 42 evaluable patients (completed with 20 patients dosed, of which 16 patients were evaluable).
- The second part is a Phase 2a expansion portion to further characterize safety and tolerability of BAL101553 at the MTD (70 mg/m2) and to obtain efficacy data. The Phase 2a part of the trial will include two target populations, each with up to 20 evaluable patients: the first will comprise platinum-resistant/refractory ovarian,

fallopian tube or primary peritoneal cancer (collectively referred to herein as 'ovarian cancer') patients; and the second will comprise GBM patients in first relapse.

2.2.5.1 Dose escalation Portion (Phase 1)

Patients were enrolled in sequential (escalating) dose levels comprising three to six patients, using a body surface area (BSA)-adjusted dosing approach. BAL101553 was administered over 48 hours beginning on days 1, 8 and 15 of an every 28 day treatment cycle with the exception Cycle 2 where, instead of the Day 15 infusion, each patient was administered a daily oral dose of BAL101553 from Days 15 to 21. For each dose cohort, new patients were recruited and evaluated for safety, pharmacokinetics, and efficacy.

Cohort size was variable, dependent primarily on whether patients experienced DLTs during Cycle 1. Each dose level utilized a 3+3 dose-escalation design and was based upon the occurrence of BAL101553-related dose limiting toxicities (DLTs) during Cycle 1 of treatment. The dose in the first cohort was 30 mg/m^2 (per 48 hour infusion). Dose increments of approximately 50% were planned from 30 mg/m^2 onwards, until DLT was observed. Once a DLT was observed in any patient, the dose increment for all subsequent dose levels would be approximately 33%.

If a DLT was observed in one patient at the starting dose level (30 mg/m^2), this dose level would be expanded [up] to six patients. If two or more of these [up to] six patients experience a DLT, the dose for the subsequent dose level would be decreased to 15 mg/m^2 and all subsequent dose levels would be increased by approximately 33%.

Dose escalation and cohort enrollment will be decided by the Dose-cohort Escalation Committee who will meet at appropriate intervals to review the safety information.

2.2.5.2 Expansion portion (Phase 2a)

Once the MTD has been defined, up to 40 additional evaluable patients will be enrolled and treated at the MTD dose, comprising of up to 20 evaluable patients in two target populations. The first population will include platinum-resistant/refractory ovarian, fallopian tube or primary peritoneal cancer (collectively referred to herein as 'ovarian cancer') patients; while the second will consist of GBM patients in first relapse.

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

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

2.2.5.3 Assessments

Table 1 presents a summary of the schedule of assessments performed from Screening through the End of Study visit in the phase 1 part of the study. Table 2 presents a summary of the Schedule of Assessments in the Phase 2 part. (Cross-references in the footnotes are to protocol sections).

Table 1 Phase 1 - Schedule of assessments

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

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

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

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

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

   Cycle 3 onwards: Pre-dose, 1 h after the start of study-drug infusion and at the end of the 48-hour study-drug infusion, on all dosing days.
   The body weight measurement must be obtained within the 3 days prior to dosing on D1 of all cycles.
5. Triple BP measurements should be taken at Screening, pre-dose on all dosing days, at any D22 in-clinic visit, and at the End-of-Study visit. Single BP measurements will be obtained:

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

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

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

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

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

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

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

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

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

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

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

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

14. Tumor assessment by radiological exam (CT/MRI scans) will be performed at Screening (or within the 28 days prior to D1) and within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553. From Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks. The End-of-Study assessment does not need to be repeated if an assessment was done within the 28 days prior (see Section 5.4.3.1).
15. Patients who do not have an implantable venous access system (PORT) will undergo (ambulatory) surgery and will receive subsequent training by a qualified nursing team on the use and proper handling of the venous access system (see Section 5.4.1.4.6). Implantation of the PORT will be recorded in medical history (see Section 5.4.1.4).
16. On D1 of Cycle 1 and D21 of Cycle 2, patients will be hospitalized up to 3 days after the start of study-drug infusion or first oral-drug administration for serial PK sampling and safety monitoring. The pump should be inspected for functionality 1 h after the start of infusion, after the 30-h PK sample, and 2 h prior to the end of infusion. On all other IV dosing days, patients must stay in the study unit for at least 1 h after the start of the BAL101553 infusion, and must return to the unit at least 2 h before the end of the 48-hour infusion. Seven consecutive days of BAL101553 oral dosing (Cycle 2 D15–21) will replace the Cycle 2 D15 IV administration of the drug.
17. Non-serious changes in, or worsening of, a patient's condition that occur between informed consent and first study-drug administration will be collected as pre-dose medical history (see Section 5.4.1.1). If any such occurence is considered to be serious, it will additionally be reported following the procedures of an serious adverse event (SAE), to allow for an assessment of serious procedure-related events. All AEs occurring from the time of first study-drug administration to 28 days following the last dose of study drug will be collected following the procedures outlined in Section 7.3.2.1. AEs occurring between D1 and D28 of Cycle 1 will be assessed against the DLT definitions outlined in Table 2. DLTs will additionally be recorded on the End-of-Cycle 1 assessment page of the CRF.
18. Blood PK samples will be collected from all patients at the End-of-Study visit, when a patient reports a DLT (if possible) and as follows (see Section 5.4.4):

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

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

    The sampling schedule may be amended based on observed PK in humans. In patients undergoing intra-patient dose escalation or dose reduction, blood PK samples will be collected during one cycle at each new dose level for a given patient, according to the schedule for Cycle 1 above.
19. One blood sample (approximately 4 mL) will be obtained in an EDTA-tube pre-dose on D1 of Cycle 1 and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphisms and/or genes involved in drug transport or drug metabolism or potential biomarkers (see Section 5.4.5.1.2).
20. Samples for CTCs will be taken at at least two study sites, with the goal to obtain samples from at least 50% of patients at each dose level. Samples will be obtained pre-dose on: D1 and D15 of Cycle 1; and D22 of Cycles 1 and 2. Samples for CTCs will also be obtained using the same schedule in patients undergoing intra-patient dose escalation or dose reduction, at each new dose level (see Section).
21. Where possible, a tumor biopsy will be obtained during Screening if it is agreed to by the patient, is easily accessible, and is deemed safe for the patient. Also, if possible, a post-treatment biopsy can be obtained on D22 of Cycle 1 and/or Cycle 2. Additional post-treatment biopsies may be obtained on D22 of one subsequent cycle after Cycle 2, or at progressive disease (see Section 5.4.5.2).

Table 2 Phase 2a - Schedule of assessments

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

ENC = even-numbered cycles.
*Note: D22 visits are optional from Cycle 3 onwards. **Note: For patients in the Phase 2a portion of the study who did not have disease progression at the end of the 28-day safety follow-up period, the patient and/or their treating physicians will also be contacted at 4 months and 6 months after the date of their first study-drug administration for the purpose of assessing progression-free survival.

1. Deviations from the visit schedule by ± 2 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. D28 assessments of a given cycle may be performed on D29 of that cycle, i.e., pre-dose on D1 of the subsequent cycle.
2. Informed consent must be obtained within the 28 days prior to D1 of Cycle 1. Screening assessments must be performed and completed within the 15 days prior to D1/Cycle 1, with the exception of radiology assessments, which if conducted within 21 days (GBM patients) or 28 days (ovarian cancer patients) prior to D1 of Cycle 1, do not need to be repeated during Screening.
3. This includes results available regarding BRCA1/BRCA2 mutation status in patients with ovarian cancer and IDH mutation status in GBM patients.
4. For D1 of all cycles, the physical exam and ECOG status must be performed within the 3 days prior to dosing; if the Screening exam was performed ≤ 3 days prior to D1, these do not need to be repeated on D1/Cycle 1 (see Sections 5.4.2.3 and 5.4.2.1).
5. Complete vital signs (see Section 5.4.2.4) will be obtained at Screening, at any D22 in-clinic visit, at the End-of-Study visit, and:
   Cycle 1: On D1, pre-dose; 0.5 h, 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.
   *Patients treated prior to the first Safety Evaluation only.
   All other dosing days: pre-dose, 1 h after the start of study-drug infusion, and at the end of infusion.
   The body weight measurement must be obtained within the 3 days prior to dosing on D1 of all cycles.
6. Triple BP measurements should be taken at Screening, pre-dose on all dosing days, at any D22 in-clinic visit, and at the End-of-Study visit. Single BP measurements will be obtained:
   Cycle 1: On D1, 0.5 h, 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.
   *Patients treated prior to the first Safety Evaluation only.
   All other dosing days: 1 h after the start of study-drug infusion, and at the end of infusion.

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

   If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, triple BP measurements will be taken every 10–15 min until return to SBP/DBP < 160/90 mmHg. Patients should only be discharged home once BP levels have stabilized to SBP levels < 160 mmHg and DBP levels < 100 mmHg (see Section 5.4.2.5).
7. Three sequential (i.e., triplicate) 12-lead ECG are to be obtained, each separated by ~1 min and all taken within a 10-min time window, at Screening to determine study eligibility of patients, at the End-of-Study visit and as follows (see Section 5.4.2.6):
   Cycle 1: On D1, pre-dose; 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.
   *Patients treated prior to the first Safety Evaluation only.
   All other dosing days in Cycles 1 and 2: pre-dose, 1 h after start of study-drug infusion, and at the end of infusion.
   Cycle 3 onwards: Pre-dose on D1 only.
   Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
   Any abnormal on-study ECG must be transmitted to a central ECG laboratory for evaluation (including QTc assessment).

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

    The same test (cardiac troponin-I or troponin-T) must be used consistently for a given patient at Screening and throughout the study.
14. Women of child-bearing potential must have a negative serum pregnancy test (hCG) at Screening; and a negative serum or urine pregnancy test (hCG) prior to BAL101553 dosing on D1 of every cycle and at the End-of-Study visit. Screening labs performed ≤ 3 days prior to first dosing, and labs performed within 1 day prior to all other in-clinic dosing days, do not need to be repeated (see Section 5.4.2.8.6).
15. Tumor assessment by radiological exam (CT/MRI scans) and CA-125 monitoring (only in ovarian cancer patients) will be performed at Screening, or within the 28 days prior to D1 (within the 21 days prior to D1 for GBM patients); and within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553. The End-of-Study assessment does not need to be repeated if an assessment was done within the 28 days prior (see Section 5.4.3.1).
16. Patients who do not have an implantable venous access system (PORT) will undergo (ambulatory) surgery and will receive subsequent training by a qualified nursing team on the use and proper handling of the venous access system (see Section 5.4.1.4.6). Implantation of the PORT will be recorded in medical history (see Section 5.4.1.4).
17. On D1 of Cycle 1, patients may be hospitalized up to 3 days after the start of study-drug infusion for serial PK sampling and safety monitoring (see Section 6.5). The pump should be inspected for functionality 1 h after the start of infusion, after the 24–30-h PK sample, and 2 h prior to the end of infusion. On all other IV dosing days, patients must stay in the study center for at least 1 h after the start of the BAL101553 infusion, and must return to the unit at least 2 h before the end of the 48-hour infusion.

18. Non-serious changes in, or worsening of, a patient's condition that occur between informed consent and first study-drug administration will be collected as pre-dose medical history (see Section 5.4.1.1). If any such occurence is considered to be serious, it will additionally be reported following the procedures of an serious adverse event (SAE), to allow for an assessment of serious procedure-related events. All AEs occurring from the time of first study-drug administration to 28 days following the last dose of study drug will be collected following the procedures outlined in Section 7.3.2.1.

19. Blood PK samples will be collected from all patients at the End-of-Study visit and as follows (see Section 5.4.4):
    Cycle 1: On D1, pre-dose; 1 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.
    On D8, pre-dose and at the end of infusion.
    *Patients treated prior to the first Safety Evaluation only.
    Cycle 2: on D1 and D8, pre-dose and at the end of infusion.
    In patients undergoing intra-patient dose reduction: at each new dose level, D1 and D8 of the first cycle: pre-dose and at the end of infusion.
    The sampling schedule may be amended based on observed PK in humans.

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

21. Samples for CTCs will be taken at at least two study centers, with the goal to obtain samples from at least 50% of ovarian cancer patients. Samples will be obtained pre-dose on: D1 and D15 of Cycle 1; and D22 of Cycles 1 and 2 (see Section 5.4.5.1). Samples for CTC analysis will not be obtained from GBM patients.

22. Where possible, a tumor biopsy will be obtained from ovarian cancer patients during Screening if it is agreed to by the patient, is easily accessible, and is deemed safe for the patient. Also, if possible, a post-treatment biopsy can be obtained on D22 of Cycle 1 and/or Cycle 2. Additional post-treatment biopsies may be obtained on D22 of one subsequent cycle after Cycle 2, or at progressive disease (see Section 5.4.5.2). Tumor biopsies will not be obtained from GBM patients.

2.2.6 Planned sample size

Of the 20 patients dosed in the dose-escalation portion, 16 were MTD-evaluable.

Up to 20 evaluable ovarian cancer patients and up to 20 evaluable GBM patients will be included in the expansion portion.

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

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

2.2.7 Interim analyses

No interim analyses are planned.

3 ANALYSIS POPULATIONS

3.1 Full analysis population

The full analysis population (FAP) includes all patients who received at least one partial or complete dose of study drug. The FAP will be used for analyzing efficacy.

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

3.2 Efficacy evaluable population

Separate Efficacy evaluable populations (EEPs) will be defined for the Phase 2a ovarian cancer and GBM target populations.

The EEPs include all Phase 2a patients:

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

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

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

3.3 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 must be used for all safety related analyses (AEs, vital signs, laboratory data, etc.).

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

3.4 Maximum tolerated dose-determining population

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

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

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

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

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

3.5 Pharmacokinetic analysis population

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

4 STATISTICAL CONSIDERATIONS AND ANALYSIS

4.1 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 the value immediately before last treatment (but not before first treatment).
- Adverse event duration (in days, hours or fractions of hours) will be calculated as:
  - (<event end date.time> minus <event onset date.time>) in days or hours.

  If only the date is collected:
  - ((<event end date> minus <event onset date>) + 1) in days
- 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.
- Age will not be recalculated rather, that collected by the investigator will be used for all analyses.
- 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 v1.1 guidelines (ovarian cancer patients) or RANO criteria (GBM patients) will be as reported in the CRF.

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

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

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. In the event that this leads to inconsistencies with other available data for the patient or if in the month of treatment, the imputation values will be handled case-by-case.
- If both the day and month are missing, they are imputed to be 30 June if not in the year of treatment. In the event that this leads to inconsistencies with other available data for the patient or if in the year of treatment, the imputation values will be handled case-by-case.
- Missing years will be left as missing.

- Missing time will be replace by '00:00' for start times and '23:59' for end times if time is required.
- Missing minutes will be replace by '00' for start times and '59' for end times if time is required.

5 STATISTICAL PLAN AND METHODS

The statistical analysis will be performed using the software package SAS version 9.3 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual patient data, and results of statistical analyses, will be presented in individual patient data listings and statistical summary tables.

Where necessary, tables, figures and listings (TFLs) will be presented by phase in which case Phase 1 TFLs will be presented by dose level and overall while Phase 2a will be presented by cancer type and overall.

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 will be used for mean, median, Q1, Q3, and two additional decimal points will be used for SD. Percentages will be rounded to one decimal place or more if most results are close to 0 or 100.

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 19.0 or later)
- Medications: WHO Drug Dictionary (WHODrug Enhanced version March 2017 or later)
- Adverse events: MedDRA (version 19.0 or later)
- Prior cancer related surgery (MedDRA Version 19.0 or later)
- Prior and concomitant procedures (MedDRA Version 19.0 or later)
- Prior cancer treatments (WHODrug Enhanced version March 2017)

5.1 Background characteristics

5.1.1 Patient disposition

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

Inclusion and exclusion criteria violations and patient enrollment eligibility will be presented by dose cohort and patient in data listings.

5.1.2 Protocol deviations

Important protocol deviations such as the following will be tabulated by center and category and listed:

- Entered into the study even though they did not satisfy entry criteria
- Development of withdrawal criteria (as per protocol) during the study, but patient not withdrawn
- Wrong study treatment received, or an incorrect dose
- Use of prohibited concomitant medications (as per protocol)
- Other data deviations as observed upon review of the data

Reported protocol deviations will be reviewed prior to database lock.

5.1.3 Demographic and baseline characteristics

Background and demographic characteristics of the full analysis population (FAP) including age at screening, gender, height, weight, race, patient status at selection, child-bearing potential status for female patients, birth control details, tumor type, body surface area (BSA) at baseline, ECOG performance status and medical conditions (including diagnosis and extent of cancer at screening), will be summarized by dose cohort using descriptive statistics or frequency tables, as appropriate. Percentages will be based on the number of patients with available observations in the FAP.

Demographic information will be presented in data listings sorted by dose cohort and patient.

5.1.4 Medical history

Previous or current diseases as well as previous cancer treatments (including surgery and radiotherapy) will be presented in data listings sorted by dose cohort and patient.

Medical history data will be summarized by dose cohort, system organ class and preferred term using the FAP.

5.2 Efficacy analysis

5.2.1 Dose-limiting toxicity

The dose limiting toxicities in Phase 1 will be listed by patient, and will be summarized for each dose cohort from Phase 1 using the MTD-determining population.

5.2.2 Objective response rate

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

Progressive disease may be determined based on clinical or radiological (RECIST v1.1 or RANO criteria) assessments. Clinical progression is considered PD.

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

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

5.2.3 Disease control rate

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

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

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

5.2.4 Progression-free survival

Progression-free survival (PFS) is defined as the interval between the date that the first infusion started, and the earliest date of objective disease progression according to RECIST v1.1 criteria (excluding GBM patients), RANO criteria (GBM patients) or Investigator-confirmed clinical progression; or death due to any cause in the absence of progression.

Patients who have not progressed or died at study closure will be censored at the time of their last objective tumor assessment.

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

Progression-free survival at 6 months defined as the proportion of patients who have not progressed 6 months after first study drug administration will be summarized alongside the overall Progression-free survival.

Progression-free survival at 6 months and overall will be summarized for the EEPs and FAP by dose group. The following statistics will be displayed:

- The proportion of patients progression-free associated with its exact 95% CI.
- The median time to progression or death will be determined by Kaplan-Meier method. Its 95% CI will be performed using the Brookmeyer-Crowley method. The associated survival curve will be displayed.
- PFS at 6 month timepoint to be estimated using the Kaplan-Meier method

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

5.2.5 Exploratory and additional efficacy analysis

5.2.5.1 Tumor measurements

The percentage change from baseline to the smallest tumor size (in the sum of diameters i.e., the sum of the longest diameter for non-nodal target lesions plus the sum of the short axis for nodal lesions based on RECIST criteria or sum of products of perpendicular diameters of all measurable enhancing lesions based on RANO criteria) will be summarized using standard descriptive statistics. These data will also be listed by patient and dose group. The percentage changes in the sum of tumor diameters will be presented in waterfall and spider plots.

5.2.5.2 Biomarker analysis

This SAP does not address biomarker analysis for this study.

5.2.6 Pharmacokinetic analysis

Pharmacokinetic analysis for this study is addressed in a separate SAP (concentrations will however be listed).

5.3 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 adverse events, laboratory assessments (hematology, biochemistry, cardiac troponin, coagulation and urinalysis), pregnancy testing in women of childbearing potential, ECG, transthoracal echocardiography, chest X-ray/CT scan, vital signs, ECOG performance status, physical examination, and evaluation of concomitant medications.

5.3.1 Treatment exposure

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

The actual dose of BAL101553 received and study drug dose (including oral dose) interruptions and reductions will be listed by patient, and summarized using descriptive statistics by dose group and treatment cycle.

Actual dose administered at visit (for infusions) is computed as:

Actual dose = planned dose *(total amount administered [ml] / pump volume [ml])

Treatment compliance per administration will be computed as:

Compliance [%] = actual amount / planned amount = (Total Amount [ml] / nominal pump volume [ml])*100%

Overall treatment compliance will be computed as the average of treatment compliance per administration over all administrations.

5.3.2 Adverse events

Adverse event (AE) tables and listings will display only treatment-emergent adverse events. Any non-treatment-emergent AEs will be displayed in 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 adverse event starting prior to the first treatment on Cycle 1 Day 1 will be considered as medical history, while AEs that start more than 28 days after last study drug administration will be considered as non-treatment-emergent. The relationship of an AE to study drug is recorded as not related, unlikely, possible, or probable.

For analysis purposes, 'related' AEs will be those reported as possibly related or probably related, or those for which the relationship is unknown.

Adverse events will be presented in data listings including dose cohort, patient, dates/times, study day of event, MedDRA System Organ Class, Preferred Term, 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 also be 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 interrupted)
- Related AEs leading to dose modifications (i.e., dose reduced or dose interrupted)
- 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 dose cohort for the full study period.

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

- System Organ Class, Preferred Term and lowest level term.
- System Organ Class, Preferred Term and worst CTCAE grade.
- System Organ Class, Preferred Term, lowest level term and worst CTCAE grade/severity.
- System Organ Class, Preferred Term and drug relationship (only for treatment-emergent AEs).

The incidence rate table for treatment-emergent AEs and treatment-emergent AEs related to treatment by System Organ Class, Preferred Term, lowest level term 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 study drug will be summarized by System Organ Class, Preferred Term, lowest level term and:

- Worst CTCAE grade and cycle of occurrence of first event
- Worst CTCAE grade during Cycle 1 and during the study overall

Treatment-emergent AEs leading to dose modifications or study drug discontinuation will be also summarized by System Organ Class and Preferred Term.

5.3.3 Laboratory evaluation

The laboratory tests for safety analyses comprise 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).
- Serum biochemistry: Serum creatinine, blood urea nitrogen (BUN), uric acid, sodium, potassium, chloride, calcium, inorganic phosphorus, glucose, albumin, total protein, AST, 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, red blood cells 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 v4.03.

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

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

The laboratory parameters will be presented in data listings sorted by 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).

The number and percentage of patients with laboratory values outside the marked reference range will also be tabulated by visit for each analyte.

A laboratory adverse change is defined as a change from baseline of either normal or high to low, or normal or low to high, as defined by the reference ranges.

A laboratory marked adverse change is defined as a change from baseline of either low, normal, high or marked high to marked low, or marked low, low, normal or high to marked high, as defined by the reference ranges and marked reference ranges.

The number and percentage of patients who have an adverse change (defined from the normal reference range) from baseline will be summarized by laboratory parameter and visit. The same analysis will be performed for marked adverse changes.

The number and percentage of patients with (1) any adverse change, (2) an adverse change that either occurs at the first post-treatment assessment or at two subsequent assessments, or (3) an adverse change that occurs on treatment and is not repeated at the subsequent assessment, will be tabulated. The same analysis will be performed for marked adverse changes.

5.3.4 Vital signs

Summary statistics by 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 and change from baseline (pre-dose on the study day on which infusion starts, to post-dose infusion timepoints 0.5, 1, 1,5, 2,…72 h according to schedule) will be presented by dose at study days C1D1, C1D8, C1D15, C2D1 C2D15 and C2D21. The mean maximum change from baseline (the average of the maximum change between baseline and all timepoints post baseline) will also be presented.

If blood pressure is collected on both arms, the average value of measurements from both arms and positions will be taken for the analyses.

The number of patients with values outside marked reference ranges will also be tabulated by dose cohort and scheduled time point.

The vital signs marked reference ranges are:

- Diastolic blood pressure: < 60 mmHg or > 100 mmHg.
- Systolic blood pressure: < 80 mmHg or > 180 mmHg.
- Pulse: < 40 beats/min or > 120 beats/min.
- Temperature: < 36.0 degrees Celsius or > 38.5 degrees Celsius.

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

5.3.5 ECG results

A summary of clinically-significant findings from the 12-lead ECG (CRF data) will be provided for each 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 administration of the first dose (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 QTcF interval reported in the CRF) and changes from baseline will be summarized using standard descriptive statistics by 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 (HR, RR, PR, QRS, QT, QTcB, QTcF)

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

5.3.5.1 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.

5.3.6 Physical examination

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

The incidence of abnormality in physical examination will be tabulated for each visit.

5.3.7 Prior and concomitant medications

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

The concomitant medications taken after the first administration of the study drug (i.e., medications which either starts before and stops after first study drug administration, or medications which start after first study drug administration) will be summarized by ATC term and dose group.

5.3.8 Chest X-ray/CT

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

5.3.9 ECOG performance status

All patients will be evaluated for ECOG performance status at Screening, at Day 1 (or within 72 hours prior to Day 1) of each treatment cycle prior to BAL101553 administration, and at the End of Study visit.

ECOG performance status will be presented in a frequency table by dose cohort and scheduled time point. ECOG performance status will also be presented for each patient in a data listing.

5.3.10 Transthoracic echocardiography

A transthoracic echocardiography (M-mode, 2D, or 3D) will be performed at Screening, and at the end of study visit to assess the left ventricular ejection fraction (LVEF) and regional wall motion abnormalities.

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

6 CHANGES FROM THE PLANNED ANALYSIS IN STUDY PROTOCOL

Not applicable.

7 REFERENCES

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(Rustin 2004) Rustin GJ, Quinn M, Thigpen T, et al. New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst. 2004;96(6):487–8.

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