Clinical Trial Protocol

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EudraCT No. **EU Trial No.**	2021-002392-20
BI Trial No.	1403-0008
BI Investigational Medicinal Products	BI 907828 (INN: Brigimadlin)
Title	Brightline-1: A Phase II/III, randomized, open-label, multi-center study of brigimadlin (BI 907828) compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Lay Title	Brightline-1: A study to compare brigimadlin (BI 907828) with doxorubicin in people with a type of cancer called dedifferentiated liposarcoma
Clinical Phase	Phase II/III
Clinical Trial Leader	[redacted] Phone: [redacted] Email:
Coordinating Investigators	[redacted] Phone [redacted] Email: [redacted] Phone: [redacted] Email:
Current Version and Date	Version 6.0, 02 May 2024
Original Protocol Date	18 Nov 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	18 Nov 2021
Revision date	02 May 2024
BI trial number **EU CT number**	1403-0008 2021-002392-20
Title of trial	Brightline-1: A Phase II/III, randomized, open-label, multi-center study of brigimadlin (BI 907828) compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Coordinating Investigators	[redacted] Phone [redacted] Email: [redacted] Phone: Email: [redacted]
Trial site(s)	Multi-center trial
Clinical phase	Phase II/III
Trial rationale	Brigimadlin (BI 907828) is an orally available MDM2-p53 antagonist that showed a manageable safety profile and preliminary signs of efficacy in Phase I studies especially in patients with dedifferentiated liposarcoma (DDLPS). The trial will compare different doses of brigimadlin (investigational arms) to doxorubicin (control arm) as first line systemic treatment of patients with advanced or metastatic DDLPS.
Trial objective(s)	The primary trial objective is to evaluate whether brigimadlin is superior to doxorubicin as first line systemic therapy for advanced or metastatic DDLPS. Additional trial objectives are to select an optimal dose of brigimadlin and to evaluate whether brigimadlin improves the objective response rate, duration of responses, overall survival, disease control rate, as well as tolerability and has a favorable impact on quality of life, compared to doxorubicin.

Trial endpoints	Primary endpoint Progression-free survival (PFS), defined as the time interval from randomization until tumor progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (based on blinded central independent review) or death from any cause, whichever occurs first. Secondary endpoints: • Objective response (OR), defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 (based on blinded central independent review) from the date of randomization until disease progression, death, or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent, whichever occurs first. • Duration of objective response (DOR), defined as the time interval from first documented confirmed OR until disease progression or death among patients with confirmed OR (based on blinded central independent review), whichever occurs first. • Overall survival (OS) at the end of Phase III, defined as the time interval from randomization until death from any cause. • Disease control (DC), defined as a best overall response of CR, PR, or stable disease (SD) according to RECIST version 1.1 (based on blinded central independent review). • Health-Related Quality of Life (HRQoL), based on data collected through specific questionnaires (Patient Reported Outcome Measures, PROMs), analyzed from baseline to Week 6 and to Week 18. The HRQoL endpoints are defined as the scores calculated from data collected through selected EORTC QLQ-C30 domains (physical functioning, fatigue, pain, and global health status / quality of life), fatigue and pain based on items from the EORTC QLQ-C30 and the EORTC Item Library, and the EQ-5D5L. • Occurrence of treatment-emergent adverse events (AEs). • Occurrence of treatment-emergent AEs leading to study drug discontinuation.
Trial design	Active-controlled, open-label, randomized, seamless Phase II/III parallel design comparison of 3 arms (Phase II) followed by 2 arms (Phase III). The Phase II part of the trial will start with 3 arms (2 investigational

Trial design (continued)	arms, 1 control arm) that will compare 2 different doses of brigimadlin (30 mg and 45 mg) versus doxorubicin (standard of care). An interim analysis for dose selection will be performed in the Phase II part for dose optimization, where one of the 2 investigational arms may be selected to continue full enrollment. Enrollment of patients to all 3 arms will continue while this interim analysis is conducted. The transition to Phase III is based on the number of patients enrolled. At the transition point from Phase II to Phase III, a total of 180 patients will have been randomized to the selected investigational arm and the control arm, and up to 90 patients randomized to the unselected investigational arm. An interim futility analysis of PFS will be performed after approximately 56 PFS events from the selected investigational arm and the control arm, which is expected to occur at approximately the same time as the end of Phase II. Enrollment of patients will continue whilst this analysis is performed. If the selected investigational arm passes the futility boundary, then the trial will continue to full enrollment. If enrollment is close to completion when the required number of 56 PFS events is reached, then the interim futility analysis of PFS may not be performed.
Total number of patients randomized	The overall sample size is approximately 390 patients. Up to 270 patients will be randomized 1:1:1 in Phase II. In Phase III, approximately 120 additional patients will be randomized 1:1 to either the selected investigational arm or the control arm. Randomization will be stratified by 'extent of disease' (locally advanced vs. metastatic disease).
Number of patients per treatment group	<u>Phase II:</u> Brigimadlin at 30 mg: Up to 90 patients Brigimadlin at 45 mg: Up to 90 patients Doxorubicin: 90 patients <u>Phase III:</u> Brigimadlin (at the selected dose level): Approximately 60 additional patients Doxorubicin: Approximately 60 additional patients
Diagnosis	Histologically proven locally advanced or metastatic dedifferentiated liposarcoma

Main inclusion and exclusion criteria	Main inclusion criteria: • Histologically proven locally advanced or metastatic, unresectable (surgery morbidity would outweigh potential benefits), progressive or recurrent DDLPS. Locally performed histopathological diagnosis will be accepted for entry into this trial. • Written pathology report indicating the diagnosis of DDLPS with positive MDM2 immunohistochemistry or MDM2 amplification as demonstrated by fluorescence *in situ* hybridization or NGS must be available. • Male or female patients ≥18 years old. • Formalin fixed paraffin embedded tumor blocks or slides must be available for retrospective histopathological central review. • Presence of at least one measurable target lesion according to RECIST version 1.1. • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • Patient willing to donate blood samples for the pharmacokinetics, pharmacodynamics, and tumor mutation analysis. • Patient willing to undergo a mandatory tumor biopsy. • Adequate organ function as defined by inclusion criteria detailed in the clinical trial protocol. Main exclusion criteria: • Known mutation in the TP53 gene (screening for TP53 status is not required). • Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to randomization or planned within 6 months after screening. • Prior systemic therapy for liposarcoma in any setting (including adjuvant, neoadjuvant, maintenance, palliative). • Previous or concomitant malignancies other than DDLPS or WDLPS, treated within the previous 5 years, except effectively treated non-melanoma skin cancers, carcinoma *in situ* of the cervix, ductal carcinoma *in situ,* or other malignancy that is considered cured by local treatment. • Previous treatment with anthracyclines in any setting (systemic treatment with other anti-cancer agents is allowed if completed at least 5 years prior to study entry with the exception of hormone therapy).

Main inclusion and exclusion criteria (continued)	• Patients who must or intend to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial.
Test product	Brigimadlin (BI 907828)
dose	Single dose on Day 1 every 21 days Starting dose will be 30 mg or 45 mg Patients with pre-specified adverse events or abnormal laboratory values can delay or reduce their dose. [redacted]
mode of administration	Oral
Comparator product	Doxorubicin
dose	75 mg/m^2 on Day 1 every 21-days
mode of administration	Intravenous
Duration of treatment	Treatment will be administered until documented disease progression, unacceptable adverse events, withdrawal of consent, or other reasons requiring treatment discontinuation, or for the doxorubicin arm for up to the maximum cumulative dose of 450 mg/m^2. Patients randomized to doxorubicin after confirmed disease progression by blinded central independent review will be allowed to cross-over to treatment with brigimadlin.
Statistical methods	<u>Phase II:</u> The interim analysis for dose selection will be conducted during the Phase II part based on the totality of safety data and PK/PD parameters as surrogates of clinical efficacy. After dose selection, enrollment into the unselected investigational arm will be stopped, and the rest of the Phase II and Phase III parts of the trial will continue with the selected dose of the investigational arm and the control arm. No PFS analysis between investigational arms and control arm is planned during this interim analysis for dose selection. The interim futility analysis of PFS will occur at the timepoint when about 56 PFS events occur from the selected investigational arm and the control arm using a stratified log-rank test (locally advanced vs. metastatic) as the primary analysis method. An alpha spending of 0.0005 (one-sided) and a non-binding futility boundary of HR = 0.80 for PFS are planned.

Statistical methods (continued)	If the selected investigational arm passes the futility boundary, then the trial will continue to full enrollment. Phase III: The primary PFS analysis will take place during Phase III at the time point when approximately 120 PFS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase II; and approximately 65 PFS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase III. The combination test approach as outlined by Lehmacher *et al.* will be applied for the primary analysis of PFS in the Phase III part to control the familywise error rate for the adaptive design of the trial. If statistical significance is obtained for PFS, then selected secondary endpoints (i.e. ORR and OS) will be tested following a hierarchical testing framework. The Cochran-Mantel-Haenszel method will be used to test for a difference between the selected investigational treatment arm and the doxorubicin control arm for ORR, and ORR will be tested at a one-sided alpha level of 0.0245 at the same time as the primary PFS analysis. The stratification factor will be adjusted for in the analysis (locally advanced vs. metastatic). If statistical significance is obtained for both PFS and ORR, then the alpha of one-sided level of 0.0245 will be carried over to the primary analysis and test of OS, occuring at the end of the Phase III part when approximately 133 OS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase II; and approximately 82 OS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase III. If statistical significance is obtained for PFS but not for ORR, then OS will continue to be followed up until the pre-specified number of OS events are met at the end of Phase III and then analyzed without being formally tested. The primary analysis of OS will be performed using the stratified log-rank test (locally advanced vs. metastatic), and OS would be tested at a one-sided level of 0.0245.

FLOWCHARTS

The flowchart in Table 1 gives details about brigimadlin (BI 907828) treatment, Table 2 provides details for the doxorubicin arm, and Table 3 gives details for the cross-over to treatment with brigimadlin.

Table 1 Flowchart brigimadlin treatment / trial 1403-0008

Brigimadlin arm	**Screening**		**Cycles 1 and 2** [1]			**Cycles 3 and 4** [1]		**Cycle ≥5** [1]	**EOT** [2]	**EOR** [3]	**FU for PD**	**FU for survival**
Time point	Day -28 to -1	Day -5 to 1	Day 1 [22]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	Day 15 (±2 d)	Day 1 (+3 d)	Within 7 days after EOT decision	Day 30 (+5 d) after last dose [4]	Every 6 weeks (± 7 d)	Every 12 weeks [21] (± 7 d)
Informed consent [5]	X											
Demographics / Medical history	X											
Review of inclusion and exclusion criteria [6]	X											
Randomization		X										
Physical examination, vital signs, ECOG PS [7]	X		X			X		X	X	X	X	
Hematology, biochemistry (safety laboratory [8])	X		X	X	X	X	X	X	X	X	X	
Coagulation, urinalysis (safety laboratory [8])	X		X			X		X	X	X	X	
Pregnancy test [9]	X		X			X		X	X	X	X	X
Single 12-lead ECG [10]	X		X			X		X	X	X		
Echocardiogram / MUGA scan [11]	X							X (C6)				
Archival tumor material / fresh biopsy [12]	X											
Fresh biopsy during treatment (mandatory) [12]			X (C2D2-4) [12]									
[redacted]												
Blood sample for circulating proteins [14]			X	X (C2)		X		X	X			

Brigimadlin arm	**Screening**		**Cycles 1 and 2** [1]			**Cycles 3 and 4** [1]		**Cycle ≥5** [1]	**EOT** [2]	**EOR** [3]	**FU for PD**	**FU for survival**
Time point	Day -28 to -1	Day -5 to 1	Day 1 [22]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	Day 15 (±2 d)	Day 1 (+3 d)	Within 7 days after EOT decision	Day 30 (+5 d) after last dose [4]	Every 6 weeks (± 7 d)	Every 12 weeks [21] (± 7 d)
Blood sample for GDF-15 [14]			X	X	X [14]	X		X	X			
Blood sample for miRNA analysis [14]			X			X		X	X			
Blood samples for PBMCs / MDSCs [14]			X	X [14]	X [14]				X			
Blood sample for tumor mutation analysis (ctDNA) [14]			X			X		X	X			
Blood sample for PGx (mandatory)			X (C1)									
PROMs: QLQ-C30, items pain & fatigue [15]			From C1D1 to Week 48 or PD, whichever occurs first, every 3 weeks; and from PD (or Week 48) onwards annually									
PROMs: EQ5D, PGIC, PGIS [15]			At C1D1; at Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 12 weeks; and from PD (or Week 48) onwards annually									
PRO-CTCAE [16]			From C1D1 until Week 15 weekly; from Week 15 to Week 48 or PD, whichever occurs first, every 3 weeks; no assessments after PD (or Week 48)									
Concomitant therapy [17]	X		X			X		X	X			
Analgesic quantification algorithm (AQA)	X		X			X		X	X			
Adverse events [18]	X		X	X	X	X	X	X	X	X	X	
Study treatment administration [19]			X			X		X				
Tumor assessment [20]	X		Every 6 weeks starting 6 weeks after C1D1								X [20]	
Termination of trial medication									X			
Patient status [21]												X

1. All cycles are 21 days in duration and may be extended if subsequent dosing is delayed e.g. due to toxicity. No new cycle should be started before at least 21 days have elapsed since the last treatment administration on Day 1 of the previous cycle. Patients may continue on treatment until any criteria for stopping medication are met (see Section 3.3.4.1). In general, Cycles 1 and 2 include visits on Days 1, 8, and 15; Cycles 3 and 4 include visits on Days 1 and 15; from Cycle 5 onwards visits are scheduled for Day 1.

2. EOT = End Of Treatment. All patients should undergo the EOT visit as soon as possible after permanent discontinuation of trial treatment (within 7 days of decision to stop treatment). An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment. If the decision to permanently discontinue trial medication is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. Please see Section 3.3.4. After the EOT visit, the investigator should report only any cancers of new histology, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.
3. EOR = End Of Residual effect period.
4. The residual effect period (REP) for brigimadlin is 30 days. The EOR visit must occur 30 days (+5 days) after last treatment. For patients who discontinue for a reason other than confirmed progression by central independent review, follow-up visits continue until confirmed disease progression by central independent review per the imaging schedule (refer to Section 5.1), lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6.
5. Written informed consent must be obtained before any protocol-specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent to collection of a blood sample for pharmacogenetics is mandatory (Section 5.4) unless precluded by local regulations.
6. Inclusion / exclusion criteria should be re-confirmed before treatment start. Safety laboratory tests do not need to be repeated if performed within 10 days prior to treatment start and there is no clinical reason to repeat laboratory tests.
7. The physical examination includes measurement of height (only at screening) and weight. Vital signs include systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. Additional physical examinations including vital signs may be conducted as clinically indicated at the investigator's discretion. Refer to Sections 5.2.1 and 5.2.2.
8. Safety laboratory assessments including hematology, serum biochemistry, coagulation, and urinalysis will be performed locally and should be performed or repeated within 10 days prior to treatment initiation (Cycle 1 Day 1) then within 72 h prior to each treatment administration (Day 1 of each cycle). On Day 1 of each treatment cycle the results must be available prior to treatment and evaluated to ensure that the patient is eligible to receive the next dose. Refer to Section 5.2.3.
   - Hematology and serum biochemistry laboratory tests must be performed weekly during the first 2 cycles, on Days 1 and 15 of Cycles 3 and 4, then within 72 h prior to Day 1 of each subsequent cycle.
   - Coagulation and urinalysis must be performed within 72 h prior to Day 1 of each cycle.
   - All safety laboratory tests can be repeated at any other time point, if clinically indicated, at the investigator's discretion.
   - After trial treatment discontinuation, all safety laboratory tests will be performed at EOT and at EOR. They may be repeated during FU if clinically indicated.
   - In case of any elevation of ALT/AST and bilirubin, please see Section 5.2.6.1.4.
9. A serum pregnancy test is mandatory for female patients of childbearing potential at screening. A urine or serum pregnancy test must be conducted within 72 hours prior to start of study treatment on Day 1 of Cycle 1, prior to treatment on Day 1 of every cycle from Cycle 2 Day 1 onwards, at EOT, and then monthly until 6 months after the last dose of treatment (refer to Sections 5.2.3 and 4.2.2.3 regarding restrictions for women of childbearing potential). Pregnancy testing after EOT can be performed remotely or at the clinic.
10. Electrocardiogram (ECG): Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be recorded (detailed timing see Appendix 10.1). To not confuse ECG recordings, PK samples should be taken after performing the ECG, and patient should rest in supine position for at least 10 minutes before starting ECG recordings (refer to Section 5.2.4). ECGs may be repeated as clinically indicated.
11. Echocardiograms or MUGA scans are to be performed prior to treatment start and in Cycle 6. Scans may be repeated during treatment if clinically indicated.

12. Archival tumor tissue MUST be provided for all patients to retrospectively test TP53 mutation status and MDM2 amplification by a central pathology laboratory. A block is preferred but slides are acceptable. The total volume of material provided (l×b×d) should not be less than 5 mm^3. If archival tissue is not available (or insufficient), a biopsy must be performed for collection of fresh tissue. In addition, 1 on-treatment biopsy is required in Cycle 2 (Day 2-4). Patients under anticoagulation treatment or patients with thrombocytopenia of CTCAE Grade 3 or 4 are not required to undergo the on-treatment tumor biopsy. See Section 5.4.2 for details.
13. [redacted]
14. Blood samples for biomarker analysis are mandatory. Details of blood sampling for all biomarker analyses are described in Section 5.4 and the detailed sampling schedule is available in Appendix 10.1.
    - Blood samples for GDF-15 will be collected as described in Appendix 10.1.
    - Blood samples for circulating protein biomarkers and miRNAs will be collected on Day 1 (pre-treatment) of all cycles and at EOT. An additional sample for circulating protein biomarkers will be collected at Cycle 2 Day 8.
    - Blood samples for peripheral blood mononuclear cells (PBMCs) and myeloid-derived suppressor cells (MDSCs) for flow cytometry analysis will only be collected for patients enrolled in the Phase II part.
    - Collection of blood samples for tumor mutation analysis (ctDNA) must be obtained at C1D1 prior to first drug administration, Day 1 of each treatment cycle, and at the time of progressive disease (at the EOT visit). Refer to Section 5.4.
15. [redacted]
16. [redacted]
17. For concomitant therapy and restrictions on concomitant therapy, refer to Sections 4.2.1 and 4.2.2.1.
18. Includes the review of safety laboratory tests if applicable. For details on Adverse Event reporting after treatment discontinuation, refer to Sections 5.2.6.2 and 6.2.3. Early and proactive management of side effects is essential to retention and the site is recommended to call the patient a few days after starting treatment to discuss whether the patient has side effects and how these can be treated. In addition, phone calls at any time are recommended e.g. in case of severe myelosuppression, and the patients should be instructed to contact the sites if applicable.

19. Brigimadlin will be dispensed on Day 1 of each cycle by investigator or authorized designee. Refer to Section 4.3.
20. Tumor assessment will be performed according to RECIST version 1.1. Tumor assessments should include computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest and abdomen/pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. bone) using an appropriate method (CT scan, MRI, or bone scan) should be performed. The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray, CT scan, MRI, or bone scan) should be performed and repeated at each tumor assessment.
    Assessments will be performed at the following time points, irrespective of scheduled protocol visits, until confirmed progressive disease by central independent review, or start of subsequent anti-cancer treatment:
    - Screening visit (within 28 days prior to first drug intake). A scan performed as part of routine clinical practice and prior to provision of informed consent and within the screening timeframe can be used if it meets the requirements described by the imaging laboratory and imaging manual.
    - Every 6 weeks ±7 days, relative to the C1D1 date. From Week 36 onwards every 12 weeks ±7 days.
    - In case of discrepancy between investigator and central independent review, refer to Section 5.1 for handling.
    - Assessment schedule should not be changed for any reason, including interruption / delay of treatment.
    - All imaging scans / timepoints (scheduled and unscheduled) are to be submitted for central independent review. Whenever the investigator assesses that a patient has progressive disease, the relevant scans must be flagged and submitted immediately for central independent review. The investigator should await the results of central independent review before permanent discontinuation of treatment. Refer to Section 5.1 and the imaging manual for additional details.
21. During FU for survival, patient visits to the clinic are not required unless required for pregnancy testing. Information may be collected from the patient notes, via telephone contact or through an edevice for PROMs. Patient status will be collected until death, lost to follow-up, withdrawal of consent, or end of the whole trial. In the case of death, date of death and cause of death will be collected. Patient death information can be collected from the patient's medical records, etc. if the patient had not withdrawn consent for trial participation.
22. Cycle 1 Day 1 assessments (physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done during screening within 72 h prior to treatment administration and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline.
    A window (+3 d) is acceptable for scheduling Cycle 2 Day 1.

Table 2 Flowchart doxorubicin arm / trial 1403-0008

Doxorubicin arm	**Screening**		**Cycles 1 and 2** [1]			**Cycles 3 to 6** [1]	**EOT** [2]	**EOR** [3]	**FU for PD**	**FU for survival**
Time point	Day -28 to -1	Day -5 to 1	Day 1 [20]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	21 days (±3 d) after last Cycle Day 1	Day 30 (+5 d) after last dose	Every 6 weeks (± 7 d)	Every 12 weeks [19] (± 7 d)
Informed consent [4]	X									
Demographics / Medical history	X									
Review of inclusion and exclusion criteria [5]	X									
Randomization		X								
Physical examination, vital signs, ECOG PS [6]	X		X			X	X	X	X	
Hematology, biochemistry (safety laboratory [7])	X		X			X	X	X	X	
Coagulation, urinalysis (safety laboratory [7])	X		X			X	X	X	X	
Pregnancy test [8]	X		X			X	X	X	X	X
Single 12-lead ECG [9]	X		X			X	X	X		
Echocardiogram / MUGA scan [10]	X					X (C6)				
Archival tumor material / fresh biopsy [11]	X									
Fresh biopsy during treatment (mandatory) [11]			X (C2D2-4)							
Blood sample for circulating proteins [12]			X			X	X			
Blood sample for miRNA analysis [12]			X			X	X			
Blood samples for PBMCs / MDSCs [12]			X	X [12]	X [12]		X			
Blood sample for tumor mutation analysis (ctDNA) [12]			X			X	X			
Blood sample for PGx (mandatory)			X (C1)							
PROMs: QLQ-C30, items pain & fatigue [13]			From C1D1 to Week 48 or PD, whichever occurs first, every 3 weeks; and from PD (or Week 48) onwards annually							
PROMs: EQ5D, PGIC, PGIS [13]			At C1D1; at Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 12 weeks; and from PD (or Week 48) onwards annually							

Doxorubicin arm	**Screening**		**Cycles 1 and 2** [1]			**Cycles 3 to 6** [1]	**EOT** [2]	**EOR** [3]	**FU for PD**	**FU for survival**
Time point	Day -28 to -1	Day -5 to 1	Day 1 [20]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	21 days (±3 d) after last Cycle Day 1	Day 30 (+5 d) after last dose	Every 6 weeks (± 7 d)	Every 12 weeks [19] (± 7 d)
PRO-CTCAE [14]			From C1D1 until Week 15 weekly; from Week 15 to Week 48 or PD, whichever occurs first, every 3 weeks; no assessments after PD (or Week 48)							
Concomitant therapy [15]	X		X			X	X			
Analgesic quantification algorithm (AQA)	X		X			X	X			
Adverse events [16]	X		X	X	X	X	X	X	X	
Pre-treatment [17]			X			X				
Study treatment administration [17]			X			X				
Tumor assessment [18]	X		Every 6 weeks starting 6 weeks after C1D1						X [18]	
Termination of trial medication							X			
Patient status [19]										X

1. All cycles are 21 days in duration and may be extended if subsequent dosing is delayed e.g. due to toxicity. Patients may continue on treatment with doxorubicin for up to the maximum cumulative dose of 450 mg/m^2 (approximately 6 cycles), or until any criteria for stopping medication are met (see Section 3.3.4.1). Patients who complete doxorubicin treatment will complete the EOT and EOR visit and will be followed until PD by central independent review and thereafter per local institutional guidelines/standards. In rare cases patients may receive more than 6 cycles of doxorubicin treatment. If this occurs, the study visits for the additional cycles will follow the same schedule as for Cycle 6. In general, Cycles 1 and 2 include visits on Days 1, 8, and 15; Cycles 3 to 6 include visits on Day 1.
2. EOT = End Of Treatment. This refers to completion of study treatment (as scheduled) as well as premature treatment withdrawal. Patients who received the maximum cumulative dose of doxorubicin should have the EOT visit 21 days (±3 d) after the last cycle Day 1. Patients who discontinue trial treatment prematurely should undergo the EOT visit as soon as possible (within 7 days of the decision to stop treatment). An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment. If the decision to permanently discontinue trial medication is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. Please see Section 3.3.4. After the EOT visit the investigator should report only any cancers of new histology, trial drug related SAEs, trial drug related AESIs. Reporting is to be done only via the BI SAE form, please see Section 5.2.6.2.1. Patients being considered for the cross-over arm may use the EOT visit assessments as “screening” (i.e. C1D1).
3. EOR = End Of Residual effect period. The residual effect period (REP) for doxorubicin is 30 days. For patients who discontinue for a reason other than confirmed progression by central independent review, continue with follow-up visits until confirmed disease progression by central independent review per the imaging schedule (refer to Section 5.1), lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6. Patients with confirmed PD by central imaging do not need to complete the EOR visit if they cross-over to treatment with brigimadlin.
4. Written informed consent must be obtained before any protocol-specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor’s instructions. The consent to collection of a blood sample for pharmacogenetics is mandatory (Section 5.4) unless precluded by local regulations.

5. Inclusion / exclusion criteria should be re-confirmed before treatment start. Safety laboratory tests do not need to be repeated if performed within 10 days prior to treatment start and there is no clinical reason to repeat laboratory tests.
6. The physical examination includes measurement of height (only at screening) and weight. Vital signs include systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. Additional physical examinations including vital signs may be conducted as clinically indicated at the investigator's discretion. Refer to Sections 5.2.1 and 5.2.2.
7. Safety laboratory assessments including hematology, serum biochemistry, coagulation, and urinalysis will be performed locally and should be performed or repeated within 10 days prior to treatment initiation (Cycle 1 Day 1) then within 72 h prior to each treatment administration (Day 1 of each cycle). On Day 1 of each treatment cycle the results must be available prior to treatment and evaluated to ensure that the patient is eligible to receive the next dose. Refer to Section 5.2.3.
   - Hematology and serum biochemistry laboratory tests must be performed within 72 h prior to Day 1 of each cycle.
   - Coagulation and urinalysis must be performed within 72 h prior to Day 1 of each cycle.
   - All safety laboratory tests can be repeated at any other time point or post treatment, if clinically indicated, at the investigator's discretion.
   - After trial treatment discontinuation, all safety laboratory tests will be performed at EOT and at EOR and may be repeated during FU if clinically indicated.
   - In case of any elevation of ALT/AST and bilirubin, please see Section 5.2.6.1.4.
8. A serum pregnancy test is mandatory for female patients of childbearing potential at screening. A urine or serum pregnancy test must be conducted within 72 hours prior to Cycle 1 Day 1 before start of study treatment, prior to treatment on Day 1 of every cycle from Cycle 2 Day 1 onwards, at EOT, and then monthly until 6 months after the last dose of treatment (refer to Sections 5.2.3 and 4.2.2.3 regarding restrictions for women of childbearing potential). Pregnancy testing after EOT can be performed remotely or at the clinic.
9. Electrocardiogram (ECG): Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be recorded. Patient should rest in supine position for at least 10 minutes before starting ECG recordings. Refer to Section 5.2.4. Single 12-Lead ECGs are done at screening, pre-treatment on Day 1 of every treatment cycle, at EOT and EOR. ECGs may be repeated at the investigator's discretion following local guidelines for doxorubicin treatment, or as clinically indicated.
10. Echocardiograms or MUGA scans are to be performed prior to treatment start and in Cycle 6. After Cycle 6 (for patients with resting LVEF >50%), perform echocardiograms or MUGA scans every 3 months (±2 weeks) or per local guidelines until the patient completes the trial, including cross-over treatment and follow up if applicable. For patients with LVEF <50% or with another cardiac dysfunction, scans should be performed more frequently, if clinically indicated. Patients who stop doxorubicin prior to Cycle 6 will undergo the same cardiac monitoring frequency as described above.
11. Archival tumor tissue MUST be provided for all patients to retrospectively test TP53 mutation status and MDM2 amplification by a central pathology laboratory. A block is preferred but slides are acceptable. The total volume of material provided (l×b×d) should not be less than 5 mm^3. If archival tissue is not available (or insufficient), a biopsy must be performed for collection of fresh tissue. In addition, 1 on-treatment biopsy is required in Cycle 2 (Day 2-4). Patients under anticoagulation treatment or patients with thrombocytopenia of CTCAE Grade 3 or 4 are not required to undergo the on-treatment tumor biopsy. See Section 5.4.2 for details.
12. Blood samples for biomarker analysis are mandatory. Details of blood sampling for all biomarker analyses are described in Section 5.4.
    - Blood samples for circulating protein biomarkers and miRNAs will be collected on Day 1 (pre-treatment) of all cycles and at EOT.
    - Blood samples for peripheral blood mononuclear cells (PBMCs) and myeloid-derived suppressor cells (MDSCs) for flow cytometry analysis will only be collected for patients enrolled in the Phase II part. Sampling time points are C1D1 prior to first drug administration, C1D8, C1D15, C2D1, and at EOT.
    - Collection of blood samples for tumor mutation analysis (ctDNA) must be obtained at C1D1 prior to first drug administration, Day 1 of each treatment cycle, and at the time of progressive disease (at the EOT visit). Refer to Section 5.4.

13. PROM = Patient Reported Outcome Measures; QLQ = Quality of Life Questionnaire QLQ; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity.
    QLQ-C30, items pain and fatigue will be assessed from C1D1 to Week 48 or PD, whichever occurs first, every 3 weeks (+2 days); and from PD (or Week 48) onwards annually.
    EQ5D, PGIC, PGIS will be assessed at C1D1; at Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 12 weeks (+2 days); and from PD (or Week 48) onwards annually. Please note that the PGIC assessment is not required at C1D1.
    Patients without PD who start subsequent anti-cancer treatment prior to Week 48, will switch to annual PROM assessment.
    Patients may complete the assessments either on provided edevices or access to PROMs/QoL remotely with their own devices. Patients are not required to attend the clinic on non-dosing days to complete the questionnaires. On clinic days, it is recommended that patients complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status.
14. Patient assessments of pre-specified AEs will be collected starting on C1D1 and continued weekly (+2 days) through Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 3 weeks (+2 days); there will be no assessments after PD (or Week 48).
    Patients without PD who start subsequent anti-cancer treatment prior to Week 48 do not need any further PRO-CTCAE assessments.
    Patients may complete self-assessments on provided edevices or access to PROMs/QoL remotely with their own devices. Patients are not required to attend the clinic on non-dosing days to complete the questionnaires. On clinic days, it is recommended that patients complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status.
15. For concomitant therapy and restrictions on concomitant therapy, refer to Sections 4.2.1 and 4.2.2.1.
16. Includes the review of safety laboratory tests if applicable. For details on Adverse Event reporting after treatment discontinuation, refer to Sections 5.2.6.2 and 6.2.3.
    Early and proactive management of side effects is essential to retention and the site is recommended to call the patient a few days after starting treatment to discuss whether the patient has side effects and how these can be treated. In addition, phone calls at any time are recommended e.g. in case of severe myelosuppression, and the patients should be instructed to contact the sites if applicable.
17. Doxorubicin will be given as standard-of-care dose of 75 mg/m^2 for up to the maximum cumulative dose of 450 mg/m^2 (approximately 6 cycles). For the prevention of cardiotoxicity, patients may be pre-treated with e.g. dexrazoxane at the investigator's discretion, following institutional guidelines / clinical practice and prescribing information (see Section 4.1.2).
18. Tumor assessment will be performed according to RECIST version 1.1. Tumor assessments should include computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest and abdomen/pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. bone) using an appropriate method (CT scan, MRI, or bone scan) should be performed. The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray, CT scan, MRI, or bone scan) should be performed and repeated at each tumor assessment.
    Assessments will be performed at the following time points, irrespective of scheduled protocol visits, until confirmed progressive disease by central independent review, or start of subsequent anti-cancer treatment:
    - Screening visit (within 28 days prior to first drug intake). A scan performed as part of routine clinical practice and prior to provision of informed consent and within the screening timeframe can be used if it meets the requirements described by the imaging laboratory and imaging manual.
    - Every 6 weeks ±7 days, relative to the C1D1 date. From Week 36 onwards every 12 weeks ±7 days.
    - In case of discrepancy between investigator and central independent review, refer to Section 5.1 for handling.

- Assessment schedule should not be changed for any reason, including interruption / delay of treatment. All imaging scans / timepoints (scheduled and unscheduled) are to be submitted for central independent review. Whenever the investigator assesses that a patient has progressive disease, the relevant scans must be flagged and submitted immediately for central independent review. The investigator should await the results of central independent review before permanent discontinuation of treatment. Patients who do not have a confirmed PD by central independent review will not be offered to cross-over to brigimadlin treatment. Refer to Section 5.1 and the imaging manual for additional details.

19. During FU for survival, patient visits to the clinic are not required unless required for pregnancy testing. Information may be collected from the patient notes, via telephone contact or through an edevice for PROMs. Patient status will be collected until death, lost to follow-up, withdrawal of consent, or the end of the whole trial. In the case of death, date of death and cause of death will be collected. Patient death information can be collected from the patient's medical records, etc. if the patient had not withdrawn consent for trial participation.
20. Cycle 1 Day 1 assessments (physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done during screening within 72 h prior to treatment administration and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline.
    A window (+3 d) is acceptable for scheduling Cycle 2 Day 1.

Table 3 Flowchart cross-over to brigimadlin treatment / trial 1403-0008

Cross-over to brigimadlin	**Screening** [1]	**Cycles 1 and 2** [2]			**Cycles 3 and 4** [2]		**Cycle ≥5** [2]	**EOT** [3]	**EOR** [4]	**FU for PD** [4]	**FU for survival**
Time point	Day -21 to -1	Day 1 [22]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	Day 15 (±2 d)	Day 1 (+3 d)	Within 7 days after EOT decision	Day 30 (+5 d) after last dose	Every 6 weeks (± 7 d)	Every 12 weeks [21] (± 7 d)
Re-consent [5]	X										
Review of inclusion and exclusion criteria [6]	X										
Physical examination, vital signs, ECOG PS [7]	X	X			X		X	X	X	X	
Hematology, biochemistry (safety laboratory [8])	X	X	X	X	X	X	X	X	X	X	
Coagulation, urinalysis (safety laboratory [8])	X	X			X		X	X	X	X	
Pregnancy test [9]	X	X			X		X	X	X	X	X
Single 12-lead ECG [10]	X	X			X		X	X	X		
Echocardiogram / MUGA scan [11]	X	X [11]									
Fresh biopsy during treatment (mandatory) [12]		X (C2D2-4) [12]									
[redacted]											
Blood sample for GDF-15 [14]		X	X		X			X			
Blood sample for circulating proteins [14]		X	X (C2)		X		X	X			
Blood sample for miRNA analysis [14]		X			X		X	X			
Blood samples for PBMCs / MDSCs [14]		X	X	X				X			
Blood sample for tumor mutation analysis (ctDNA) [14]		X			X		X	X			
PROMs: QLQ-C30, items pain & fatigue [15]		From C1D1 to Week 48 or PD, whichever occurs first, every 3 weeks; and from PD (or Week 48) onwards annually									
PROMs: EQ5D, PGIC, PGIS [15]		At C1D1; at Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 12 weeks; and from PD (or Week 48) onwards annually									
PRO-CTCAE [16]		From C1D1 until Week 15 weekly; from Week 15 to Week 48 or PD, whichever occurs first, every 3 weeks; no assessments after PD (or Week 48)									
Concomitant therapy [17]	X	X			X		X	X			

Cross-over to brigimadlin	**Screening** [1]	**Cycles 1 and 2** [2]			**Cycles 3 and 4** [2]		**Cycle ≥5** [2]	**EOT** [3]	**EOR** [4]	**FU for PD** [4]	**FU for survival**
Time point	Day -21 to -1	Day 1 [22]	Day 8 (±1 d)	Day 15 (±1 d)	Day 1 (+3 d)	Day 15 (±2 d)	Day 1 (+3 d)	Within 7 days after EOT decision	Day 30 (+5 d) after last dose	Every 6 weeks (± 7 d)	Every 12 weeks [21] (± 7 d)
Analgesic quantification algorithm (AQA)	X	X			X		X	X			
Adverse events [18]	X	X	X	X	X	X	X	X	X	X	
Study treatment administration [19]		X			X		X				
Tumor assessment [20]	X	Every 6 weeks starting 6 weeks after the first dose of brigimadlin								X [20]	
Termination of trial medication								X			
Patient status [21]											X

1. Patients randomized to the doxorubicin arm will be eligible to cross-over to receive brigimadlin following confirmed PD by central independent review and if eligibility criteria are met. Patients crossing over can use either their EOT, EOR or FU-PD visit assessments as part of screening or can have a complete screening visit. Patients who are screened but do not meet the criteria for cross-over must complete the required follow-up assessments for the doxorubicin arm (Table 2), including EOR and FU survival.
2. All cycles are 21 days in duration and may be extended if subsequent dosing is delayed e.g. due to toxicity. Patients will retain their originally assigned patient number and will start once again at Cycle 1. No new cycle should be started before at least 21 days have elapsed since the last treatment administration on Day 1 of the previous cycle. Patients may continue on treatment until any criteria for stopping medication are met (see Section 3.3.4.1). In general, Cycles 1 and 2 include visits on Days 1, 8, and 15; Cycles 3 and 4 include visits on Days 1 and 15; from Cycle 5 onwards visits are scheduled for Day 1.
3. EOT = End Of Treatment. All patients should undergo the EOT visit as soon as possible after permanent discontinuation of trial treatment (within 7 days of decision to stop treatment). An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment. If the decision to permanently discontinue trial medication is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. Please see Section 3.3.4. After the EOT visit the investigator should report only any cancers of new histology, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.
4. EOR = End Of Residual effect period. The residual effect period (REP) for brigimadlin is 30 days. The REP visit must occur 30 days (+5 days) after last treatment. For patients who discontinue for a reason other than confirmed progression, follow-up for PD visits continue per the imaging schedule (refer to Section 5.1), until disease progression, lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6. Wherever possible, follow-up for PD visits should continue until disease progression confirmed by central independent review.
5. Patients must re-consent prior to starting treatment with brigimadlin. Assessments for screening may be completed prior to re-consent as they have been collected during participation in the doxorubicin arm. Re-consenting while on study may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
6. Inclusion / exclusion criteria need to be re-confirmed before treatment start. Safety laboratory tests do not need to be repeated if performed within 10 days prior to treatment start and there is no clinical reason to repeat laboratory tests.

7. The physical examination includes measurement of weight. Vital signs include systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. Additional physical examinations including vital signs may be conducted as clinically indicated at the investigator's discretion. Refer to Sections 5.2.1 and 5.2.2.
8. Safety laboratory assessments including hematology, serum biochemistry, coagulation, and urinalysis will be performed locally and should be performed or repeated within 10 days prior to treatment initiation (Cycle 1 Day 1) then within 72 h prior to each treatment administration (Day 1 of each cycle). On Day 1 of each treatment cycle the results must be available prior to treatment and evaluated to ensure that the patient is eligible to receive the next dose. Refer to Section 5.2.3.
   - Hematology and serum biochemistry laboratory tests must be performed weekly during the first 2 cycles, on Days 1 and 15 of Cycles 3 and 4, then within 72 h prior to Day 1 of each subsequent cycle.
   - Coagulation and urinalysis must be performed within 72 h prior to Day 1 of each cycle.
   - All safety laboratory tests can be performed at any other time point or post treatment, if clinically indicated, at the investigator's discretion.
   - After trial treatment discontinuation, all safety laboratory tests will be performed at EOT and at EOR and may be repeated during FU if clinically indicated.
   - In case of any elevation of ALT/AST and bilirubin, please see Section 5.2.6.1.4.
9. A serum pregnancy test is mandatory for female patients of childbearing potential at screening. A urine or serum pregnancy test must be conducted within 72 hours prior to Cycle 1 Day 1 before start of study treatment, prior to treatment on Day 1 of every cycle from Cycle 2 Day 1 onwards, at EOT, and then monthly until 6 months after the last dose of treatment (refer to Sections 5.2.3 and 4.2.2.3 regarding restrictions for women of childbearing potential). Pregnancy testing after EOT can be performed remotely or at the clinic.
10. Electrocardiogram (ECG): Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be recorded (detailed timing see Appendix 10.1). To not confuse ECG recordings, PK samples should be taken after performing the ECG, and patient should rest in supine position for at least 10 minutes before starting ECG recordings (refer to Section 5.2.4). ECG may be repeated as clinically indicated.
11. Echocardiograms or MUGA scans are to be performed following the schedule from doxorubicin treatment and per local guidelines for post-doxorubicin treatment. Scans may be repeated during treatment if clinically indicated.
12. One on-treatment biopsy is required in Cycle 2 (Day 2-4), unless exemption applies. Patients under anticoagulation treatment or patients with thrombocytopenia of CTCAE Grade 3 or 4 are not required to undergo the on-treatment tumor biopsy. See Section 5.4.2.2 for details.
13. [redacted]
14. Blood samples for biomarker analysis are mandatory. Details of blood sampling for all biomarker analyses are described in Section 5.4 and Appendix 10.1.
    - Blood samples for GDF-15 will be collected as described in Appendix 10.1.
    - Blood samples for circulating protein biomarkers and miRNAs will be collected on Day 1 (pre-treatment) of all cycles and at EOT. An additional sample for circulating protein biomarkers will be collected at Cycle 2 Day 8.
    - Blood samples for peripheral blood mononuclear cells (PBMCs) and myeloid-derived suppressor cells (MDSCs) for flow cytometry analysis will only be collected for patients enrolled in the Phase II part.
    - Collection of blood samples for tumor mutation analysis (ctDNA) must be obtained at C1D1 prior to first drug administration, Day 1 of each treatment cycle, and at the time of progressive disease (at the EOT visit). Refer to Section 5.4.

15. PROM = Patient Reported Outcome Measures; QLQ = Quality of Life Questionnaire QLQ; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity.
    QLQ-C30, items pain and fatigue will be assessed from C1D1 to Week 48 or PD, whichever occurs first, every 3 weeks (+2 days); and from PD (or Week 48) onwards annually.
    EQ5D, PGIC, PGIS will be assessed at C1D1; at Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 12 weeks (+2 days); and from PD (or Week 48) onwards annually. Please note that the PGIC assessment is not required at C1D1.
    Patients without PD who start subsequent anti-cancer treatment prior to Week 48, will switch to annual PROM assessment.
    Patients may complete the assessments either on provided edevices or access to PROMs/QoL remotely with their own devices. Patients are not required to attend the clinic on non-dosing days to complete the questionnaires. On clinic days, it is recommended that patients complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status.
16. Patient assessments of pre-specified AEs will be collected starting on C1D1 and continued weekly (+2 days) through Week 15; from Week 15 to Week 48 or PD, whichever occurs first, every 3 weeks (+2 days); there will be no assessments after PD (or Week 48).
    Patients without PD who start subsequent anti-cancer treatment prior to Week 48 do not need any further PRO-CTCAE assessments.
    Patients may complete self-assessments on provided edevices or access to PROMs/QoL remotely with their own devices. Patients are not required to attend the clinic on non-dosing days to complete the questionnaires. On clinic days, it is recommended that patients complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status.
17. For concomitant therapy and restrictions on concomitant therapy, refer to Sections 4.2.1 and 4.2.2.1.
18. Includes the review of safety laboratory tests if applicable. For details on Adverse Event reporting after treatment discontinuation, refer to Sections 5.2.6.2 and 6.2.3.
    Early and proactive management of side effects is essential to retention and the site is recommended to call the patient a few days after starting treatment to discuss whether the patient has side effects and how these can be treated. In addition, phone calls at any time are recommended e.g. in case of severe myelosuppression, and the patients should be instructed to contact the sites if applicable.
19. Brigimadlin will be dispensed on Day 1 of each cycle by investigator or authorized designee. Refer to Section 4.3.
20. Tumor assessment will continue according to RECIST version 1.1. Tumor assessments should include computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest and abdomen/pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. bone) using an appropriate method (CT scan, MRI, or bone scan) should be performed. The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray, CT scan, MRI, or bone scan) should be performed and repeated at each tumor assessment.
    Assessments will be performed at the following time points, irrespective of scheduled protocol visits, until confirmed disease progression, or start of subsequent anti-cancer treatment. Wherever possible assessments should continue until confirmed progressive disease by central independent review:
    - Baseline (screening) scans of all anatomical regions as described above are required if more than 6 weeks have passed since the last set of scans.
    - Every 6 weeks ±7 days, relative to the date of the first administration of brigimadlin. From Week 36 onwards every 12 weeks ±7 days.
    - In case of discrepancy between investigator and central independent review, refer to Section 5.1 for handling.
    - Assessment schedule should not be changed for any reason, including interruption / delay of treatment.
    - All imaging scans / timepoints (scheduled and unscheduled) are to be submitted for central independent review. Refer to Section 5.1 and the imaging manual for additional details.

21. During FU for survival, patient visits to the clinic are not required unless required for pregnancy testing. Information may be collected from the patient notes, via telephone contact or through an edevice for PROMs. Patient status will be collected until death, lost to follow-up, withdrawal of consent, or end of the whole trial. In the case of death, date of death and cause of death will be collected. Patient death information can be collected from the patient's medical records, etc. if the patient had not withdrawn consent for trial participation.
22. Cycle 1 Day 1 assessments (physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done during screening within 72 h prior to treatment administration and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline.
    A window (+3 d) is acceptable for scheduling Cycle 2 Day 1.

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ALT/WDLPS	Atypical Lipomatous Tumor / Well-Differentiated Liposarcoma
[redacted]	
AQA	Analgesic Quantification Algorithm
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
C1D1	Cycle 1 Day 1
CA	Competent Authority
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
COVID	Coronavirus disease 2019
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Report
CYP	Cytochrome P
DBL	Database Lock
DC	Disease Control
DCR	Disease control rate
DDI	Drug-drug interaction
DDLPS	Dedifferentiated Liposarcoma
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DOR	Duration of Objective Response
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EEA	European economic area

EOR	End of residual effect period
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EWOC	Escalation With Overdose Control
FACT-GP5	Functional Assessment of Cancer Therapy - Global Physical item #5
FUP	Follow-up
GCP	Good Clinical Practice
GIST	Gastrointestinal stromal tumors
GMP	Good Manufacturing Practice
HA	Health Authority
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
INN	International non-proprietary name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LMS	Leiomyosarcoma
LPLT	Last patient last treatment
LPS	Liposarcoma
LVEF	Left ventricular ejection fraction
MDM2	Mouse double minute 2 homolog
[redacted]	
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
NGS	Next Generation Sequencing
OATP	Organic Anion Transporting Polypeptide

OPU	Operative Unit
OR	Objective response
ORR	Overall response rate
OS	Overall survival
p53	Tumor protein P53
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFS2	Progression-free survival 2
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
PS	Performance status
q3w	Once every 3 weeks
QLQ	Quality of Life Questionnaire
RA	Regulatory Authority
RCI	Repeated Confidence Interval
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual effect period
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable Disease
SmPC	Summary of product characteristics
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
STS	Soft tissue sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVR	Sustained Viral Response
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial Master File
TP53	Tumor protein 53
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UPS	Undifferentiated pleiomorphic sarcoma

WDLPS	Well-differentiated liposarcoma
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise <1% of all adult malignancies and 12% of paediatric cancers. Approximately 80% of sarcomas originate from soft tissue, and the rest originate from bone. More than 100 histologically and biologically distinct subtypes of sarcoma are recognized with the majority being soft tissue sarcomas (STS). The most common STS subtypes in adults are undifferentiated / unclassified STS, undifferentiated pleiomorphic sarcoma (UPS), leiomyosarcoma (LMS), gastrointestinal stromal tumors (GIST) and liposarcoma (LPS). Some 13,000 new patients with STS are reported each year in the US [R21-0706; R21-0712; R21-0693; R21-0694]. The RARECARE project involving 76 population-based cancer registries reported an estimated 23,574 new cases of STS in the EU each year, with age-standardized incidence rates per 100,000 ranging from 3.3 in Eastern Europe to 4.7 in Northern Europe [R21-1225]. A recent report by Orphanet in January 2021 estimated the prevalence of STS in Europe to be 30.0 per 100,000 and the incidence to be 4.74 per 100,000 [R21-1251].

While surgical management remains the mainstay of the treatment of localized STS, several different chemotherapy regimens are used in advanced or metastatic STS. First line systemic therapy has not changed substantially for the last 45 years and is still based on doxorubicin-containing chemotherapy. The latest trials enrolling patients with STS showed a median progression-free survival of 7 months and a median overall survival of around 18 months. However, since patients' prognosis varies from one histology to another, PFS and OS can be quite different depending on the specific STS histology [R21-0713; R21-0720; R21-0721].

LPS represents 20% of STS and includes 4 different subtypes, among which well-differentiated and dedifferentiated subtypes display MDM2 (Mouse Double Minute 2) amplification in over 90% of the cases. Interestingly, early genetic studies in LPS revealed that mutations in the TP53 gene are not observed in tumors carrying MDM2 amplification [R21-1630], suggesting these events are mutually exclusive, thus providing a strong molecular rational for sensitivity to treatment with a MDM2-p53 antagonist.

The dedifferentiated LPS subtype (DDLPS) represents 15-20% of all LPS cases. DDLPS is typically a high-grade tumor that metastasizes in more than 20% of cases (lungs, liver, bone, skin, or brain). The mainstay of first line therapy for advanced DDLPS remains an anthracycline-based regimen despite its moderate efficacy in this setting (ORR <15%; median PFS: 2 to 4 months; median OS: 8 to 12 months [R21-0711; R21-0715; R21-0716; R21-0720]). In addition, doxorubicin yields many side effects among them irreversible cardiac toxicity [R21-1309; R21-1310; R21-1311; R21-1312].

No evidence of added benefit in terms of overall survival was shown for the doxorubicin-based combination compared to doxorubicin monotherapy in studies with mixed types of STS [R21-1533; R21-1534; R21-1535] and there are, to our knowledge, no studies demonstrating the potential added benefit in terms of OS for a doxorubicin-based combination over doxorubicin monotherapy in patients with DDLPS. Considering the above-mentioned reasons, doxorubicin monotherapy is considered the standard of care for DDLPS in the first line setting.

Brigimadlin is an orally available MDM2-p53 antagonist that showed a manageable safety profile and preliminary signs of efficacy in Phase I studies especially in patients with DDLPS. Given the heterogeneity of STS with different oncogenic drivers and diverse outcomes, it is considered that histotype-specific and biomarker-directed studies in sarcomas may better define the efficacy of novel therapies in this population.

1.2 DRUG PROFILE

Mode of action

The MDM2-p53 antagonist brigimadlin is a new small molecule that inhibits the interaction between the tumor suppressor TP53 and its negative regulator MDM2. Inhibition of this protein-protein interaction leads to stabilization of TP53 followed by target gene induction, which may result in cell cycle arrest or apoptosis in tumors with TP53 wild type status. For further details, please refer to the Investigator's Brochure (IB [c15936970]).

Key pharmacokinetic characteristics

Brigimadlin has a t_{max} [redacted]
Brigimadlin has a low clearance/F (4.5 to 11 mL/min) and a low volume of distribution (23.6 to 35.1 L). Inter-individual variability in exposure is medium to high. The human bioavailability and metabolism profile are not known to date. Based on animal data, brigimadlin is excreted via the bile with very low renal excretion of parent or metabolites.

Drug interactions

[redacted]

Brigimadlin reduces [redacted] and may therefore increase the exposure of drugs that are [redacted] substrates. Therefore, coadministration of any known [redacted] substrates are not allowed. [redacted]

Residual Effect Period

The Residual Effect Period (REP) is the period after the last administration of trial medication with measurable drug levels and/or pharmacodynamics effects still likely to be present.

- REP for brigimadlin will be 30 days
- REP for doxorubicin will be 30 days

Data from nonclinical studies

Nonclinical data suggest that the anti-tumor efficacy of brigimadlin in tumors harboring wild-type TP53 is based on 2 modes of action: (1) direct anti-tumor activity via activation of wild-type TP53 function and induction of apoptosis in cancer cells, and (2) immunomodulatory activity. Detailed non-clinical results are available in the IB [c15936970] and show that

brigimadlin is a potent MDM2-p53 antagonist [redacted] and a high bioavailability in several species. Available data support clinical investigation of brigimadlin in various malignancies with TP53 wild-type status, including tumors with MDM2 amplification.

Genotoxicity studies showed that brigimadlin was not mutagenic in the bacterial reverse mutation (Ames) test; but was clastogenic in the *in vitro* chromosomal aberration test. It was negative in the rat bone marrow assay, but induced DNA damage in the liver and duodenum of rats as assessed by the comet assay.

Data from clinical studies

There are currently several ongoing clinical trials of brigimadlin in patients with advanced or metastatic solid tumors. Trial 1403-0001 is a Phase Ia/Ib, open-label, multicenter, dose-escalation study of brigimadlin monotherapy. Trial 1403-0002 is a Phase Ia/Ib, open-label, dose-escalation study of the combination of brigimadlin with ezabenlimab.

For a detailed description of the brigimadlin profile, please refer to the IB [c15936970] and for doxorubicin to the Summary of Product Characteristics (SmPC) or US Package Insert.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Dedifferentiated liposarcoma (DDLPS) represents 15-20% of liposarcoma and represents a high-grade MDM2-amplified tumor with low responsiveness to doxorubicin, the standard of care approved in first line treatment (that showed a median PFS between 2 and 4 months, and a median OS between 8 and 12 months; see [R21-0715; R21-0716; R21-0720]). In addition, doxorubicin yields many side effects which include irreversible cardiac toxicity [R21-1309, R21-1310, R21-1311, R21-1312]. Therefore, a treatment with a manageable safety profile that is superior to doxorubicin as first line systemic therapy for advanced or metastatic DDLPS is needed.

Brigimadlin is an orally available MDM2-p53 antagonist that showed a manageable safety profile and preliminary signs of efficacy in Phase I studies (1403-0001 and 1403-0002) especially in patients with DDLPS; an MDM2-driven malignancy fitting brigimadlin's mechanism of action.

To bring new treatments faster to a patient population with a high unmet medical need, a seamless Phase II/III study design is proposed. In accordance with the latest regulatory authority guidance [R21-3031], dose optimization of brigimadlin will be performed in the Phase II part and the chosen dose will be taken forward for comparison with the control arm in the Phase III part of the study.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

MDM2-p53 antagonists provide the opportunity to target the key tumor suppressor p53 (tumor protein p53). Brigimadlin is a tumor-targeting agent that leads to p53 activation, which triggers cell cycle arrest or apoptosis in cancer cells. Pharmacology data support that

the compound can also modulate the immune response. Overall, brigimadlin-induced p53 activation may trigger an adaptive immunity in TP53 wild type tumors.

Several MDM2-p53 protein-protein interaction inhibitors are currently being evaluated in clinical trials [P20-06431; R17-0975]. Reported clinical data with other MDM2-p53 antagonists showed both, a pharmacodynamic target activity, [redacted]

Brigimadlin is a highly potent MDM2-p53 antagonist with efficacy in preclinical mouse models of human cancer with intermittent dosing [P20-03237]. Brigimadlin is orally available and showed high exposures in patients in trial 1403-0001 [redacted]. The compound characteristics mentioned above allow an intermittent dosing schedule that mitigates serious adverse events.

Brigimadlin showed preliminary signs of efficacy in Phase I studies (1403-0001 and 1403-0002) especially in patients with DDLPS (see Section 1.2). The durable disease stabilizations seen in 12 patients with DDLPS (median PFS approximately 10.8 months) were noticeable as DDLPS has a reported median PFS between 2 and 4 months after doxorubicin first line therapy.

A clinically meaningful benefit in terms of prolonged PFS and an improved quality of life for these patients with locally advanced or metastatic DDLPS is expected with brigimadlin versus doxorubicin. Doxorubicin (standard of care) induces limited efficacy and shows many side effects including irreversible cardiac toxicity [R21-0711; R21-0715; R21-0716; R21-0720; R21-1309; R21-1310; R21-1311; R21-1312].

1.4.2 Risks

Brigimadlin has been administered to about 160 patients in the ongoing clinical trials. Based on safety data from these trials and data from in-class competitors, the following potential treatment-induced side effects were identified, i.e. myelosuppression and gastrointestinal AEs:

1) Myelosuppression

Myelosuppression, particularly thrombocytopenia and neutropenia, is the main toxicity associated with brigimadlin. Current data show that myelosuppression is dose dependent. Most of these AEs (neutropenia, thrombocytopenia, anemia) are of CTCAE Grade 3 or lower. Grade 3 or higher events were manageable with appropriate treatment and dose modification. The mean duration (median 1 – 2 weeks) for myelosuppressive events was 2 – 3 weeks; recovery periods >90 days were reported in some cases.

To mitigate and manage the AEs related to myelosuppression, the following measures have been implemented:

- Safety laboratory assessments at appropriate intervals to monitor the degree of myelosuppression and allow the investigators to properly treat the patients
- General recommendations for the management of AEs related to myelosuppression are detailed in Sections 4.1.4.2 and 4.2.1.
- Dose modification is allowed (see Section 4.1.4.2)

2) Gastrointestinal AEs

Data from the ongoing trials show that gastrointestinal AEs were common among treated patients: nausea (>75%), vomiting (>45%), and diarrhea (>35%). However, these AEs were predominantly of CTCAE Grade 1 or Grade 2. Less than 2% of the patients discontinued due to nausea and less than 3% of the patients had a dose reduction due to nausea.

General recommendations for the management of treatment-induced gastrointestinal AEs are detailed in Section 4.2.1.

Preliminary data suggest that brigimadlin has a moderate emetogenic risk level. Primary anti-emetic prophylaxis before Cycle 1 and before treatment on subsequent cycles are recommended in accordance with established national, international, and institutional guidelines based on the emetogenic risk level of brigimadlin (see Section 4.2.1).

Other risks and measures to reduce risks are described below:

- As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of lightheadedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. These risks will be addressed by careful safety monitoring and risk mitigation measures such as
  (a) compression
  (b) close clinical monitoring for AEs
  (c) selection of experienced sites and site staff
  (d) Safety recommendations provided in laboratory manual
- Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Patients treated with brigimadlin should be

monitored for signs of liver injury according to guidelines specified in Section 5.2.6.1.4.

- Tumor biopsies will be taken during the treatment period or after disease progression. There is an added risk for pain, swelling, and bleeding for those patients who will undergo tumor biopsies. For this reason, biopsies will only be performed when deemed safe by the investigator and if the platelet count is sufficient to allow for hemostasis. The biopsy results will provide valuable information and will assist clinical decisions for future patients. Hence, the benefit is assumed to outweigh the risks associated with the biopsy.
- Clinical imaging will expose the patient to a certain radiation burden. The imaging schedule is kept to the minimum in this trial. National regulations must be complied regarding the CT exposure for the purpose of this clinical trial.
- A data-monitoring committee (DMC) that is independent of the sponsor will review unblinded efficacy and safety analyses prepared by the sponsor [R21-3662]. Further details about the planned analyses are given in Section 7.2.8. Details about the DMC are provided in Section 8.7 and will also be provided in a DMC charter.
- A steering committee (SC) will act as an advisory body. It will consist of independent experts, sponsor representatives, and investigator representatives. Details about the SC are provided in Section 8.7 and will also be provided in an SC charter.

For patients treated with doxorubicin, the following risk has been identified:

Infusion-related reaction: doxorubicin will be administered intravenously. The anticipated adverse effect for this route of administration is a hypersensitivity reaction. Typical compound-related signs and symptoms of hypersensitivity reactions of mild to severe grading could include flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension.

In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of doxorubicin, the investigator should, in accordance with the severity of the reaction and the local standard of care, consider interrupting the infusion and treating the condition. Emergency medicines must be available, and the personnel must be aware how to handle such reactions.

1.4.3 Discussion

The nature of the target and the mechanism of action of brigimadlin are sufficiently understood.

In the context of the unmet medical need and the anticipated benefit of brigimadlin treatment, the benefit risk evaluation of the compound is favorable, based upon the available preclinical and clinical information. The expected benefit outweighs the potential risks.

Guidance related to COVID-19 infection

Patients in clinical trials with brigimadlin have advanced, late-stage cancer with limited treatment options. Given the life-threatening nature of the underlying disease, the approach

recommended by professional oncology organizations (e.g. ASCO, ESMO) remains to treat patients with cancer as under normal circumstances. No consensus on recommendations exists regarding holding or delaying anti-cancer treatments in patients with or susceptible to COVID-19. Withdrawing treatment in a patient with cancer who may have few or no alternative treatment options requires a careful, individual evaluation.

To date, there is no evidence suggesting an association between an increased susceptibility to COVID-19 infection and MDM2-p53 inhibition by brigimadlin. Considering the limited data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality of COVID-19 infection, there may be unknown risk factors associated with brigimadlin monotherapy. Information regarding relevant risk factors and recommendations from professional medical oncology organizations will be monitored.

There are no interactions expected between approved COVID-19 vaccines and the use of brigimadlin monotherapy. Patients treated with brigimadlin should be carefully monitored for myelosuppressive side effects before COVID-19 vaccination is started as guided by the vaccine labels. Interactions with COVID-19 therapeutics cannot be excluded, and restrictions should be considered (Section 4.2.2.1).

The inclusion of additional patients with cancer in trials with brigimadlin is evaluated on a single case basis, taking into account the totality of information related to each individual patient and the local COVID-19 situation. The sponsor, where required, will support the investigator in their decision finding.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will assess the efficacy and safety of brigimadlin compared to doxorubicin as first line systemic therapy for advanced or metastatic DDLPS.

The primary objective of the trial is to evaluate whether brigimadlin is superior to doxorubicin as first line systemic therapy for advanced or metastatic DDLPS.

The secondary objectives of the Phase II part of the trial are to select an optimal dose of brigimadlin and to evaluate prior to the Phase III part whether the expected benefits of brigimadlin as first line systemic therapy for advanced or metastatic DDLPS outweigh any risks. The secondary objectives of the Phase III part of the trial are to evaluate whether brigimadlin as first line systemic therapy for advanced or metastatic DDLPS improves the objective response rate, duration of responses, overall survival, disease control rate, tolerability and has a favorable impact on quality of life, compared to doxorubicin. Safety of brigimadlin will be investigated in both parts of the trial.

The primary comparison will be made for randomized patients, regardless of the extent of adherence to the protocol and regardless of premature discontinuation of trial medication due to any reason; however, the primary comparison will exclude effects of any subsequent anti-

cancer therapy started before documented progression. In other words, in primary analyses of PFS, any PFS events occurring after subsequent anti-cancer therapy begins will be censored.

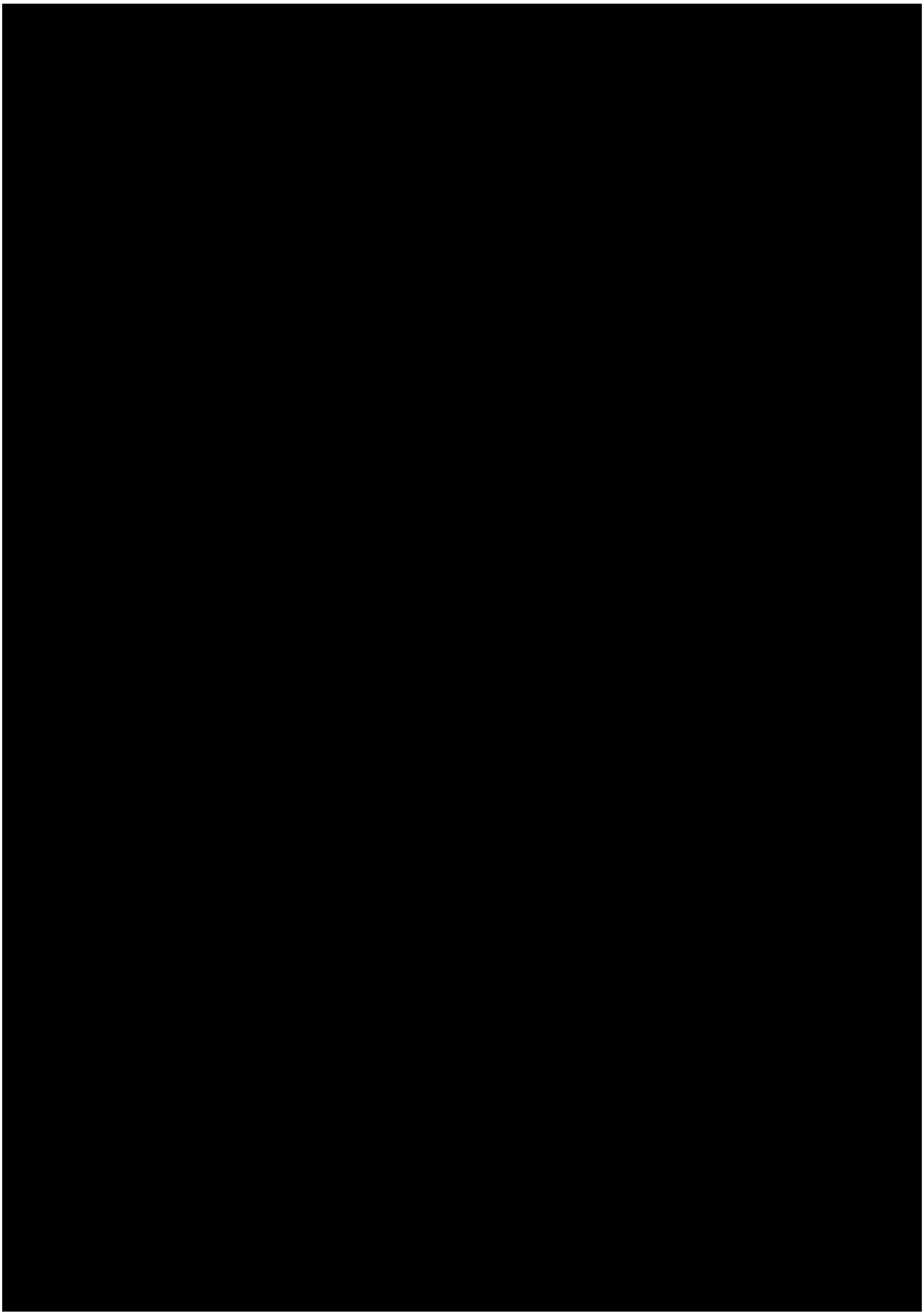
2.1.2 Primary endpoint(s)

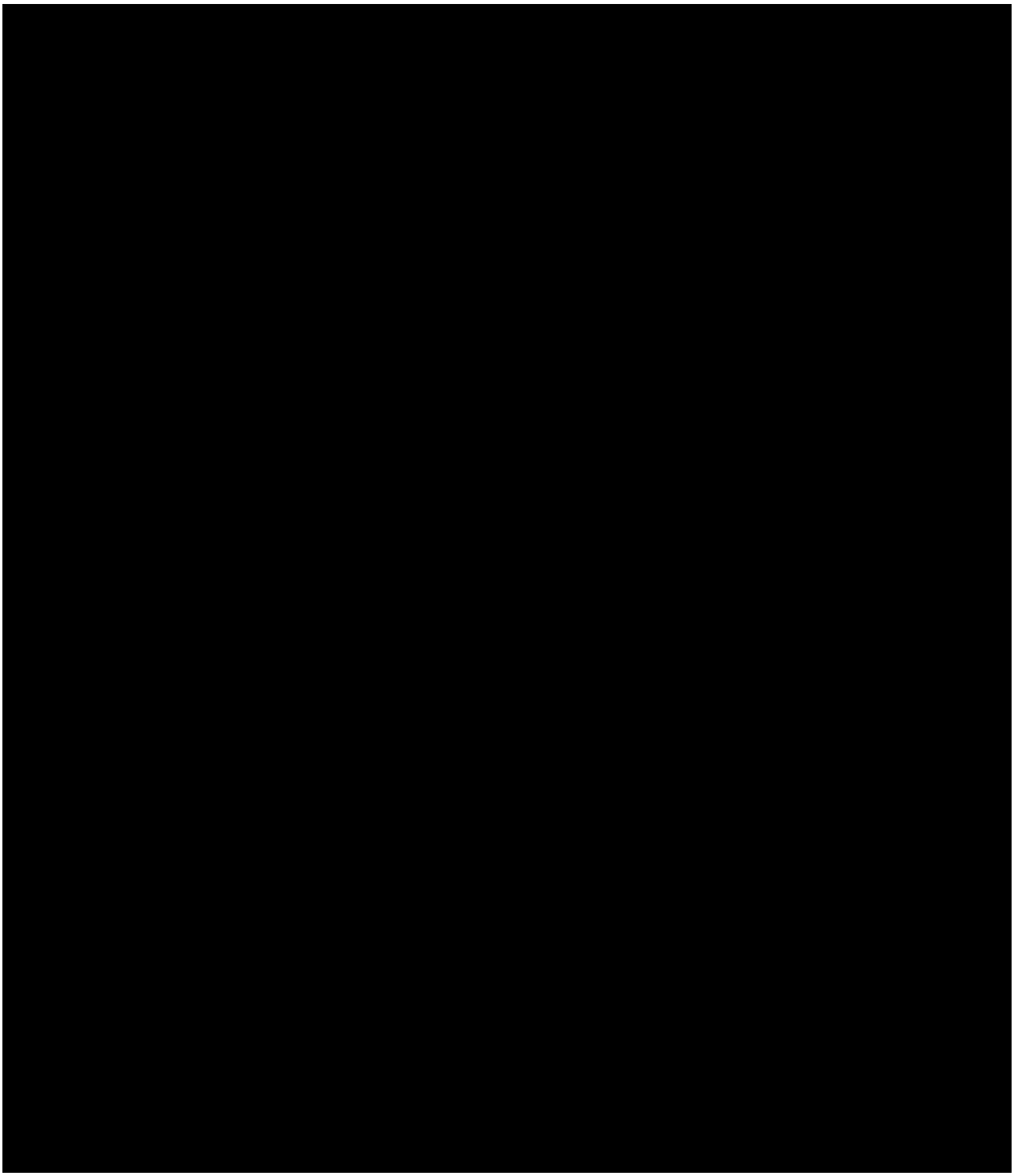
The primary endpoint of the trial is progression-free survival (PFS). PFS based on central independent review will be assessed at the interim futility analysis at approximately the same time as the end of Phase II, and the primary PFS analysis will take place during the Phase III part. For each patient, PFS is defined as the time interval from randomization until tumor progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (solely based on blinded central independent review) or death from any cause, whichever occurs first.

2.1.3 Secondary endpoint(s)

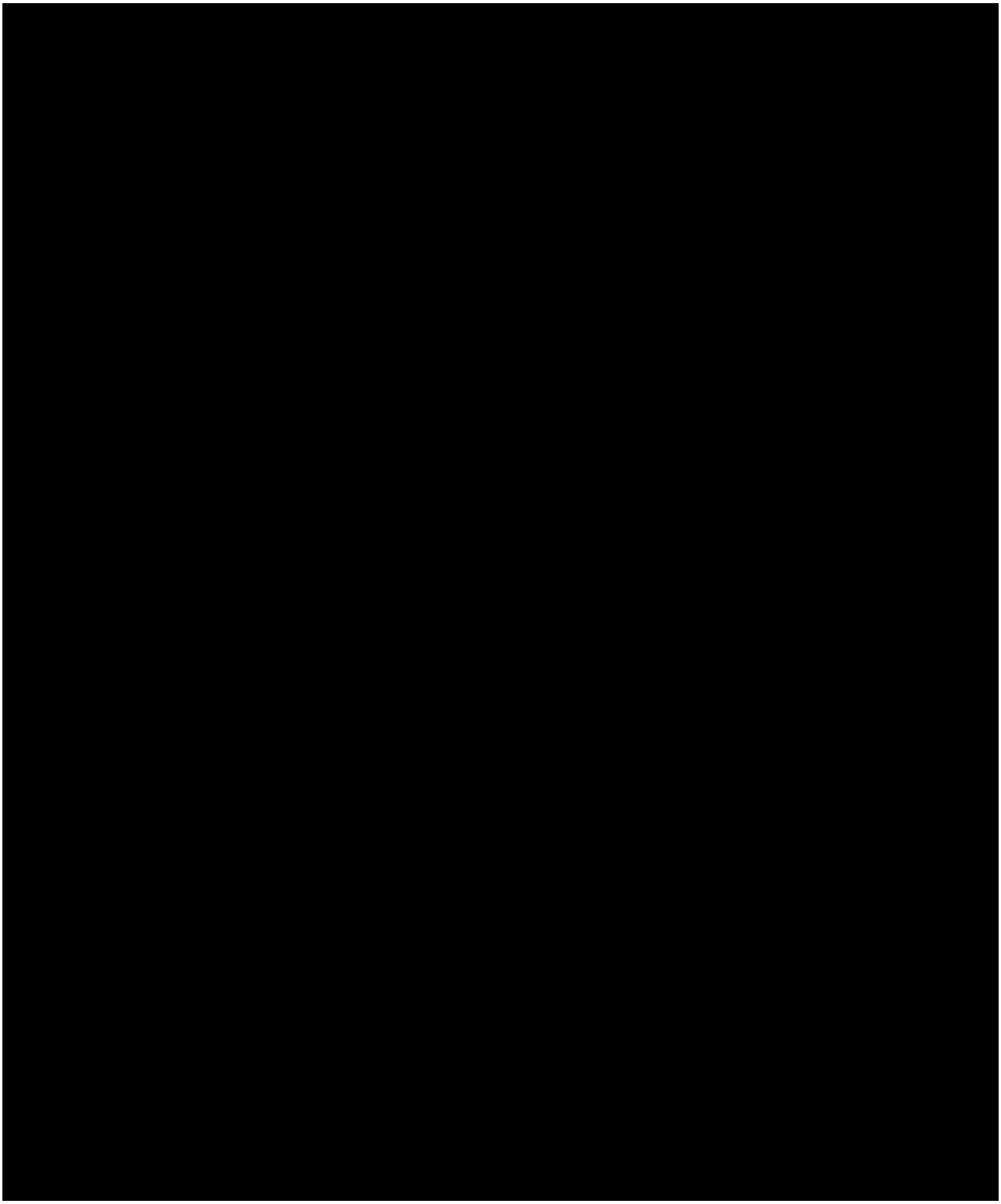
The secondary endpoints in this trial are:

- Objective response (OR), defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 (based on blinded central independent review) from the date of randomization until disease progression, death, or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent, whichever occurs first.
- Duration of objective response (DOR), defined as the time interval from first documented confirmed OR until disease progression or death among patients with confirmed objective response (based on blinded central independent review), whichever occurs first.
- Overall survival (OS) will be assessed at the end of the Phase III part of the trial. OS is defined as the time interval from randomization until death from any cause.
- Disease control (DC), defined as a best overall response of CR, PR, or stable disease (SD) according to RECIST version 1.1 (based on blinded central independent review).
- Health-Related Quality of Life (HRQoL), based on data collected through specific questionnaires (Patient Reported Outcome Measures, PROMs), analyzed from baseline to Week 6 and to Week 18. The HRQoL endpoints are defined as the scores calculated from data collected through selected EORTC QLQ-C30 domains (physical functioning, pain, fatigue, and global health status / quality of life), fatigue and pain based on items from the EORTC QLQ-C30 and the EORTC Item Library, and the EQ-5D5L.
- Occurrence of treatment-emergent adverse events (AEs).
- Occurrence of treatment-emergent AEs leading to study drug discontinuation.





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION



3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A randomized, open-label, seamless Phase II/III parallel design was considered most appropriate to assess the efficacy, safety, and tolerability of brigimadlin versus doxorubicin as first line systemic therapy for advanced or metastatic DDLPS. A seamless Phase II/III

design was chosen to bring new treatments faster to a patient population with a high unmet medical need.

The mainstay of first line therapy for advanced DDLPS remains an anthracycline-based regimen. In studies with mixed types of STS, no evidence of added benefit in terms of overall survival was shown for the doxorubicin-based combination compared to doxorubicin monotherapy [R21-1533; R21-1534; R21-1535]. In patients with DDLPS, there are no known studies demonstrating the potential added benefit in terms of OS for a doxorubicin-based combination over doxorubicin monotherapy; doxorubicin monotherapy is considered to be an appropriate comparator representing clinical practice and standard of care for the treatment of DDLPS in the first line setting.

The trial has an open-label design due to the doxorubicin-specific cumulative cardiac toxicity potential and the requirement to discontinue doxorubicin once the maximum cumulative dose is reached. These distinctive features of doxorubicin make the use of blinding in the trial design unfeasible. The open-label nature of the design should not alter the data quality, as the outcome is based on objective endpoints which are assessed by blinded independent reviewers.

PFS was chosen as primary endpoint of the trial due to its wide acceptance as a primary endpoint in STS and its capacity to show clinical benefit. This is supported by 2 recent meta-analyses conducted on trials in first- and second-line STS. A meta-analysis of 33 randomized clinical trials performed between 1995 and 2014 in patients with STS found that PFS was the predominant selected primary endpoint (70% of the cases), while OS was the primary endpoint in only 6% of the trials [R21-1540]. A second meta-analysis of 52 randomized clinical trials of mixed first line or pre-treated settings [R21-1540] reported a highly significant correlation between PFS and OS (R = 0.61), the highest among any other measurements correlated with OS including ORR, 3-month PFS, and 6-month PFS. In addition, since treatment with brigimadlin will be allowed after objective PD is observed among patients in the doxorubicin arm of this trial, and because receipt of subsequent anti-cancer therapy is expected to occur at a high rate, OS may not be an appropriate primary endpoint in the first line setting of DDLPS. Details about the cross-over from the doxorubicin arm to treatment with brigimadlin are available in Section 4.1.3.

Cross-over to treatment with brigimadlin is provided for eligible patients who have disease progression following doxorubicin treatment. The purpose is to give access to the investigational treatment for a population with high unmet need where available therapies have limited benefit.

A central imaging vendor will conduct blinded reads (‘central independent review’) on a regular basis to support the interim and final analysis of efficacy endpoints based on RECIST; real-time reads will be performed to assess patients’ tumor response and to independently document disease progression if applicable. The imaging vendor’s roles and responsibilities will be described in an imaging charter.

During this open-label trial, a DMC independent of the sponsor will be established to review unblinded efficacy and safety analyses prepared by the sponsor [R21-3662]. Further details

about the DMC are in Section 8.7 and will also be provided in a DMC charter. Further details about the planned interim analyses are given in Section 7.2.8.

3.3 SELECTION OF TRIAL POPULATION

The Phase II part of the trial will be conducted in about 125 sites in multiple countries and regions. For the Phase III part of the trial, additional sites might be added as needed to fulfill the planned enrollment. If site(s) are unable to recruit patients, additional sites may be opened, and non-enrolling sites may be closed.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomization if eligible.

Assessments may be repeated within the screening period if patients do not initially meet the inclusion / exclusion criteria. Eligibility must always be assessed using the latest results available. In addition, up to 2 re-screenings of patients who have previously failed screening will be permitted.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been randomized in error (= did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

The trial will include patients with histologically proven locally advanced or metastatic dedifferentiated liposarcoma.

Criteria to assist with the differentiation of locally advanced vs. metastatic disease are provided below (randomization in this trial will be stratified by ‘extent of disease’ as described in Section 4.1.4, i.e. locally advanced vs. metastatic disease):

- Locally advanced DDLPS is defined here for the purpose of this trial as DDLPS without metastatic spread via the blood vessels or the lymphatic system. A huge, inoperable retroperitoneal DDLPS or DDLPS elsewhere in the body should be considered locally advanced disease.
- Metastatic DDLPS is defined here for the purpose of this trial as DDLPS with metastatic spread via the blood vessels or the lymphatic system. A relapse of retroperitoneal DDLPS after earlier surgery with or without radiotherapy should be considered metastatic disease.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

Patients will only be included in the trial if they meet all the following criteria:

1. Provision of signed and dated, written informed consent form ICF in accordance with ICH-GCP and local legislation prior to any trial-specific procedures, sampling, or analyses.
2. Male or female patients ≥18 years old at the time of signature of the ICF. Women of childbearing potential (WOCBP; for a definition see Section 4.2.2.3) and men able to father a child must be ready and able to use 2 medically acceptable methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation, and until 6 months and 12 days after last dose. A list of contraception methods meeting these criteria is provided in the patient information.
3. Histologically proven locally advanced or metastatic, unresectable (surgery morbidity would outweigh potential benefits), progressive or recurrent DDLPS *. Locally performed histopathological diagnosis will be accepted for entry into this trial but will be confirmed by independent pathological review while the patients receive treatment in this trial.
4. Written pathology report indicating the diagnosis of DDLPS with positive MDM2 immunohistochemistry or MDM2 amplification as demonstrated by fluorescence *in situ* hybridization or NGS must be available.
5. Formalin fixed paraffin embedded tumor blocks or slides must be available for retrospective histopathological central review.
6. Presence of at least one measurable target lesion according to RECIST version 1.1. In patients who only have one target lesion, the baseline imaging must be performed at least 2 weeks after any biopsy of the target lesion.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8. Patient must be willing to donate blood samples for the pharmacokinetics, pharmacodynamics, and tumor mutation analysis.
9. Patient willing to undergo a mandatory tumor biopsy at the time point specified in the flowchart unless exempt (see Section 5.4.2.2 for details).
10. Adequate organ function, defined as meeting all criteria in Table 3.3.2: 1.

* Histology of DDLPS according to the WHO classification of tumors [R21-3615]: transition from atypical lipomatous tumor / well-differentiated liposarcoma (ALT/WDLPS) to non lipogenic sarcoma with a variable extent of dedifferentiation; the transition can be abrupt or

gradual and the well-differentiated lipomatous component can be easily or hardly identifiable. Patients with purely well-differentiated liposarcomas are excluded from trial participation.

Table 3.3.2: 1 Screening reference laboratory values

System	*Laboratory Value*
Hematological	
Absolute neutrophil count	$\geq 1.5\times10^9$/L (or $\geq 1.5\times10^3$/µL or ≥ 1500/mm^3)
Platelets	$\geq 100\times10^9$/L (or $\geq 100\times10^3$/µL or $\geq 100\times10^3$/mm^3)
Hemoglobin	≥8.5 g/dL or ≥5.3 mmol/L or ≥85 g/L
Hepatic	
Total bilirubin	≤1.5×upper limit of normal (ULN), (patients with Gilbert's syndrome, total bilirubin must be ≤3×ULN)
AST and ALT	≤2.5×ULN OR ≤5×ULN for patients with liver metastases
Renal	
Creatinine *	≤1.5×ULN Patients may enter if creatinine is >1.5×ULN provided that the estimated glomerular filtration rate (eGFR) is >50 mL/min (assessed by Chronic Kidney Disease Epidemiology [CKD-EPI] creatinine equation); confirmation of eGFR is only required when creatinine is >1.5×ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5×institutional ULN Patients taking low dose warfarin must have their INR followed closely and according to institutional guidelines
* Creatinine can be assessed by any of these methods: CREE (enzymatic serum creatinine assay), CREJIDMS (IDMS standardized Jaffe), or CREJ (non-IDMS standardized Jaffe).	

3.3.3 Exclusion criteria

Patients will be excluded from the trial if they meet any of the following criteria:

1. Known mutation in the TP53 gene (screening for TP53 status is not required).
2. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to randomization or planned within 6 months after screening.
3. Prior systemic therapy for liposarcoma in any setting (including adjuvant, neoadjuvant, maintenance, palliative).
4. Previous or concomitant malignancies other than DDLPS or WDLPS, treated within the previous 5 years, except effectively treated non-melanoma skin cancers, carcinoma *in situ* of the cervix, ductal carcinoma *in situ*, or other malignancy that is considered cured by local treatment.
5. Previous treatment with anthracyclines in any setting (systemic treatment with other anti-cancer agents is allowed if completed at least 5 years prior to study entry with the exception of hormone therapy).

6. Patients who must or intend to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
7. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) or receiving other investigational treatment(s).
8. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
9. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast feeding from the start of study treatment until 6 months and 12 days after last dose of study treatment.
10. Patients with known history of human immunodeficiency virus (HIV) infection who meet one or more of the following criteria:
    - CD4+ count <350 cells/µL
    - Viral load >400 copies/mL (local laboratory assessment)
    - Not receiving antiretroviral therapy
    - Receiving established antiretroviral therapy for <4 weeks prior to the start of study treatment
    - History of AIDS-defining opportunistic infections within 12 months prior to start of study treatment

    Patients with a history of HIV who do not meet any of the criteria above are eligible to participate but the patient must be under the care of a HIV/Infectious Diseases specialist or a HIV/Infectious Diseases specialist must be consulted prior to inclusion.
11. Patients with a history of HCV infection who meet any of the following criteria:
    - Currently receiving curative antiviral treatment or not yet achieved sustained viral response (SVR)
    - HCV viral load is above the limit of quantification (HCV RNA positive)
12. Patients with chronic HBV infection with active disease who meet the criteria for anti-HBV therapy (according to local / institutional standard) and who have not been treated with suppressive antiviral therapy prior to initiation of study treatment.
13. Any history or presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the trial drug (e.g. nausea, vomiting, Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) in the opinion of the investigator.
14. Known hypersensitivity or contraindication to the trial drugs or their excipients.
15. Active major infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at treatment start in this trial.
16. History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥III or IV, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator. Myocardial infarction or stroke within 6 months prior to randomization.

17. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTcF) >470 msec
    - Any clinically important abnormalities (as assessed by the investigator) in rhythm, conduction, or morphology of resting ECGs, e.g. complete left bundle branch block, third degree heart block
    - Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval
    - Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard

18. Patients with brain metastasis, unless they meet all below criteria:
    - Patients with treated or stable CNS metastasis:
        - Therapy for CNS metastasis was completed at least 4 weeks prior to first administration of trial drug.
        - No evidence of CNS metastatic progression (based on CNS imaging) following therapy for CNS metastasis (patients manifesting progression in lesions previously treated with stereotactic radiosurgery might still be eligible if pseudoprogression can be demonstrated by appropriate means).
        - Any CNS metastasis is asymptomatic.
        - Without corticosteroids or on a stable dose of corticosteroids for at least 14 days prior to first administration of trial medication, (except for physiological/replacement doses of about 5 mg per day prednisolone or equivalent).
        - Without antiepileptic drugs (for malignant disease) or on a stable dose of antiepileptic drugs (for malignant disease) for at least 14 days prior to first administration of trial medication.
19. Active bleeding, significant risk of haemorrhage (e.g. previous severe gastrointestinal bleeding, previous haemorrhagic stroke at any time), or current bleeding disorder (e.g. haemophilia, von Willebrand disease).
20. Any history of, or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the trial or interfere with the evaluation of the safety and efficacy of the trial drug.

3.3.3.1 Eligibility criteria for cross-over to brigimadlin treatment

Patients randomized to the doxorubicin arm will be offered the option to receive brigimadlin as subsequent therapy upon PD by central independent review (for more information please refer to Sections 4.1.3 [assigning patient to treatment group] and 6.2.1 [details about screening]). For cross-over to brigimadlin, patients need to fulfill all of the following inclusion and exclusion criteria:

Inclusion criteria:

1. Received a minimum of 1 dose of doxorubicin.
2. PD according to RECIST version 1.1 based on central independent review after receiving a minimum of 1 dose of doxorubicin.
3. Adequate organ function, defined as meeting all criteria in Table 3.3.2: 1.
4. Recovered from any doxorubicin-related toxicity to CTCAE Grade 1 or baseline (except for alopecia and peripheral neuropathy which must be ≤CTCAE Grade 2, and amenorrhea / menstrual disorders which can be any grade).

Exclusion criteria:

1. In the judgment of the investigator, any serious condition affecting compliance with trial requirements or considered relevant for the evaluation of safety of brigimadlin.
2. Intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

However, if the patients agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrollment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

The patient must attend all remaining visits including follow-up for progression assessments if discontinued from treatment prior to confirmed progression by the central independent review. Should the patient not agree, at least phone contacts should occur at the scheduled visit time points. Should that not be acceptable, a phone contact once a year or at the end of the planned observation period should occur to collect the most relevant information: vital status (please see Section 5.2.6.2.1), outcome events, adverse events, or last contact date in case of lost to follow-up.

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons such as surgery, adverse events, other diseases, or pregnancy. This includes specified adverse events requiring discontinuation as described in Section 4.1.4.2.
- The patient has radiological documentation of progressive disease by central independent review on the current treatment (see Section 5.1) with the exception of patients receiving doxorubicin, who may be offered cross-over to treatment with brigimadlin. If the patient has radiological progression by investigator assessment while tolerating trial treatment, the treatment should be continued. The decision to withdraw treatment must be based on documentation of progressive disease according to RECIST version 1.1 based on central independent review.
- If a patient becomes pregnant during the trial, treatment with brigimadlin or doxorubicin must be stopped immediately. The patient will be followed up until delivery or termination of pregnancy.

In case of a temporary reason for pausing treatment, trial treatment should be restarted if medically justified; please see Section 4.1.4.

After completion of the final OS analysis (see Section 7), the sponsor may remove patients on treatment with brigimadlin from the trial if the patient has access to brigimadlin via an alternative clinical trial, marketed product, an expanded access program, named patient use program, compassionate use protocol or other means based on local regulation. The cost of any ongoing supply of brigimadlin will be incurred by the sponsor until disease progression or any other reason for treatment discontinuation occurs. If a patient is removed from the trial treatment in these circumstances, an end of treatment and follow-up visit will be performed to ensure all adverse events are followed up and then the patient will be considered to have

completed the trial. Follow-up for overall survival may continue if required by the sponsor (see Section 6.2).

An interim analysis for dose selection will be performed in Phase II, and an interim futility analysis will be performed at approximately the same time as the end of Phase II (see Section 7.2.8 for details). If the trial is stopped for futility or an investigational arm is discontinued, ongoing patients will be informed of this, and the possibility to continue receiving their assigned treatment will be discussed with the investigator.

If new efficacy or safety information becomes available, BI will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and will undergo the procedures for early treatment discontinuation and follow-up as outlined in the flowchart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision. If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the clinical trial protocol, or the contract impairing the appropriate conduct of the trial.
4. All efficacy analyses (see Section 7) are complete and all patients have either ended trial treatment or are eligible to receive brigimadlin under the conditions listed in Section 3.3.4.1.

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the investigational medicinal products

This trial investigates brigimadlin (BI 907828) monotherapy and doxorubicin monotherapy.

Brigimadlin (BI 907828)

Table 4.1.1: 1 Brigimadlin (BI 907828)

Substance:	Brigimadlin (BI 907828)
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Single dose on Day 1 every 21 days Starting dose will be 30 mg or 45 mg [redacted]
Mode of administration:	Oral

Doxorubicin

Table 4.1.1: 2 Doxorubicin

Substance:	Doxorubicin
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Commercial supply provided by BI
Unit strength:	2 mg/mL: 200 mg per 100 mL vial
Posology:	75 mg/m^2 on Day 1 of each 21-day cycle Maximum cumulative dose of 450 mg/m^2
Mode of administration:	Intravenous infusion / injection

4.1.2 Selection of doses in the trial and dose modifications

Selected doses of brigimadlin (investigational arms) for the Phase II/III trial are derived from the Phase I monotherapy trial (1403-0001). The dose escalation part of trial 1403-0001 has recently been completed. Based on exploratory safety and efficacy analyses, 60 mg q3w (once every 3 weeks) was determined as the maximum tolerated dose (MTD) and 45 mg q3w was selected as the recommended dose for expansion (RDE).

The 2 doses of brigimadlin proposed for dose optimization in trial 1403-0008 are 45 mg and 30 mg q3w. The 45 mg dose was determined as the highest dose fulfilling the EWOC (escalation with overdose control) criterion from a Bayesian Logistic Regression Model (BLRM) analysis, taking into account the AEs of interest during the entire treatment period (and not only during the MTD evaluation period); the AEs considered for the BLRM sensitivity analysis were analyzed for all cycles and included the following: hematologic DLTs, hematologic AEs Grade 4, hematologic AEs leading to dose delay / dose reduction / discontinuation, time for platelet count recovery (to over 100,000/mm^3) >21 days, time for neutrophil count recovery (to over 1,500/mm^3) >21 days. The 30 mg dose was selected as the next lower and potentially efficacious dose. An interim analysis for dose selection in Phase II will enable the selection of 1 of the 2 investigational arms for further enrollment.

The dose for doxorubicin is 75 mg/m^2 given as intravenous infusion on Day 1 of each 21-day cycle. Patients will continue receiving doxorubicin for up to the maximum cumulative dose of 450 mg/m^2. Investigators should consult the approved package insert for complete prescribing information and follow institutional procedures / clinical practice for the administration of doxorubicin.

The sponsor will determine the optimal Phase III dose based on the Phase II data, taking into consideration any recommendations from the Steering Committee and the Data Monitoring Committee. More details about the interim analysis for dose selection are provided in Section 7.2.8.

4.1.3 Method of assigning patients to treatment groups

Patients will be randomized to one of the available treatment groups using an Interactive Response Technology (IRT) system. The company that provides the IRT system will receive the randomization list from Boehringer Ingelheim Clinical Trial Support Group or a CRO appointed by the sponsor. The BI standard validated random number generating system will be used to generate the randomization schedules.

Patient numbers will be assigned at enrollment (screening) via the IRT system. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT system). Initial medication number(s) will be assigned at time of the randomization call. If a patient withdraws from the trial, then the enrollment code cannot be re-used.

Cross-over to treatment with brigimadlin

Patients randomized to the doxorubicin arm will be offered the option to receive brigimadlin as subsequent therapy upon confirmed PD by central independent review. Patients must not have received any other anti-cancer therapy since commencing trial treatment with doxorubicin. Palliative radiotherapy is permitted; however, the irradiated area cannot be used for further tumor response assessment. These patients will be randomized 1:1 to receive either 30 mg or 45 mg brigimadlin until a dose for Phase III is selected, after which all patients assigned to one of the brigimadlin dose groups will be allowed to continue on the same dose (unless there are toxicity concerns) or change to the selected dose (if different from the current dose at the investigator's discretion), with the exception that patients who have previously had a dose reduction due to toxicity are not allowed to change to a higher dose.

The crossed over patients will re-consent, be re-assessed for inclusion and exclusion criteria and undergo assessments as described in the cross-over Flowchart prior to being registered in the IRT for the new treatment arm. Patients crossing over from the doxorubicin arm will not contribute to the total number of required patients needed in the investigational arm(s) as noted in the trial design.

4.1.4 Drug assignment and administration of doses for each patient

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomized to treatment groups according to a randomization plan in a 1:1:1 ratio at Cycle 1 Day 1 (-5 days) via an IRT. Randomization will be stratified by 'extent of disease' (locally advanced vs. metastatic disease). After the interim analysis for dose selection, patients will be randomized in a 1:1 ratio at Cycle 1 Day 1 (-5 days).

All trial medication will be prepared and handled according to the 'Medication Handling Instruction', which will be filed in the ISF. Upon notification that a patient will be treated in the trial, the pharmacy will prepare the trial medication at the assigned dosage for administration to the patient.

4.1.4.1 Administration of study medications

Administration of brigimadlin

Brigimadlin film-coated tablets are developed in 3 dosage strengths: [redacted]

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. [redacted]

Brigimadlin will be stored at each investigational site.

In all treatment cycles, brigimadlin should only be administered if all of the following criteria are met:

- Absolute neutrophil count is $\geq 1.5 \times 10^9$/L
- Platelet count is $\geq 100 \times 10^9$/L (in case of platelet transfusion after the last drug administration, this criterion must be met in a measurement taken at least 72 hours after the last platelet transfusion)
- Haemoglobin is ≥8.5 g/dL
- Any related SAE/AE which required a dose delay (see Section 4.1.4.2) has recovered to ≤CTCAE Grade 1 or to baseline value.

Brigimadlin will be administered at a fixed dose of either 30 mg or 45 mg, independent of the patient's body surface area (weight and height).

The medication will be administered in the clinic, as a single oral dose, with about 240 mL (approximately 8 U.S. ounces) water, in the standing or sitting position, under supervision of the investigating physician or an authorized designee in the morning of Day 1 of each cycle.

Patients with emesis should not take a replacement dose. Any occurrence of vomiting within 12 hours of brigimadlin administration should be documented in the medical record and the eCRF.

Pre-dose laboratory samples will be collected ≤72 hours prior to receiving each single dose.

[redacted]

Administration of doxorubicin

Doxorubicin will be administered intravenously at a dose of 75 mg/m^2 on Day 1 every 21 days, for up to the maximum cumulative dose of 450 mg/m^2. Doxorubicin will be administered according to institutional guidelines and SmPC/US Package Insert as an intravenous injection or as an infusion. Route as well as administration start and end times will be recorded in the eCRF.

4.1.4.2 Guidance for dose delays and dose reductions for brigimadlin

Adverse events requiring discontinuation

Treatment will be permanently discontinued if the following events related to brigimadlin occur:

- CTCAE Grade 4 AEs with the exception of myelosuppressive AEs of CTCAE Grade 4 (e.g. neutropenia, thrombocytopenia, anaemia) for which treatment options and blood transfusion are available (Section 4.2.1).
- Adverse events which cause a dose delay and do not recover within the allowed time window, as described in the sections below.
- Patient requires more than 2 dose reductions.

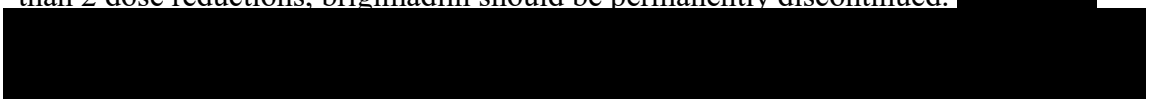
Guidance for dose delays of brigimadlin due to low platelet and/or neutrophil count

Platelet and neutrophil count are assessed on the planned Day 1 of (or within 72 hours prior to) each treatment cycle. Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle.

[redacted]

Brigimadlin dose reduction guidelines

- Any dose reduction will be permanent (i.e. dose re-escalation is NOT allowed).
- Up to 2 dose reductions of brigimadlin are allowed. For patients who require more than 2 dose reductions, brigimadlin should be permanently discontinued.



4.1.4.3 Guidance for treatment with brigimadlin after selection of Phase III dose

During the Phase II part of the trial, a dose of either 30 mg or 45 mg brigimadlin will be selected for Phase III (see Section 3.1). From then on, all new patients who enter the trial and are randomized to brigimadlin will receive the selected brigimadlin dose.

If the 45 mg dose of brigimadlin is selected for Phase III, then all patients who at that time are already on treatment with brigimadlin at the 30 mg dose, and did not reduce their dose, will be offered to increase their dose to 45 mg brigimadlin but may also choose to continue on the 30 mg dose.

If the 30 mg dose of brigimadlin is selected for Phase III, patients on the 45 mg dose may continue (assuming there are no safety concerns) or may switch to the 30 mg dose.

4.1.4.4 Guidance for dose delays, modifications, and discontinuation of doxorubicin

Doxorubicin will be administered according to the current SmPC or US Package Insert of the supplied medication and according to institutional guidelines.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The eCRF will contain information on randomized treatment.

For a discussion explaining the rationale for why this controlled trial is open-label, please see Section 3.2.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labeled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. Investigator information is omitted from the labels due to use of an IRT system.

For details of packaging and the description of the label, refer to the ISF.

Due to potential regional restriction for locally sourcing doxorubicin, doxorubicin will be sourced, packaged, labeled, and provided to the sites. Should BI supply become unavailable, sites will be allowed to use local source supply. Investigator information is omitted from the labels due to use of an IRT system. The visit number is not relevant for the label of doxorubicin as the product will remain at the clinical site.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,

- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this clinical trial protocol. They must not be forwarded to other investigators or clinics.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

For patients treated with doxorubicin, supportive reatment should be given as needed and in accordance with current SmPC or US Package Insert of the supplied medication.

Rescue medications to reverse the actions of brigimadlin are not available. Therefore, potential side effects must be treated symptomatically or as specifically noted below.

[redacted]

For patients with thrombocytopenia of CTCAE Grade 3 or 4 who are under treatment with anticoagulants, weekly controls of the blood counts and coagulation parameters should be performed.

Patients under anticoagulation treatment or patients with thrombocytopenia of CTCAE Grade 3 or 4 are not required to undergo the on-treatment tumor biopsy.

The use of the medications or therapies listed below is allowed, as clinically indicated:

- Erythropoietic therapy when used in accordance with the American Society of Clinical Oncology (ASCO)/American Society of Hematology or the National Comprehensive Cancer Network (NCCN) guidelines. In Japan, erythropoietic therapy is not approved for anemia caused by cancer chemotherapies.
- Colony-stimulating factor (granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor) when used in accordance with the ASCO guidelines.
- Blood transfusions are allowed at any time during the trial when clinically indicated.
- Corticosteroids.
- Bisphosphonates for patients with lytic bone metastases.
- Anti-diarrheal agents e.g. loperamide.
- After study enrollment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for further tumor response assessment. During palliative radiotherapy, study treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is delayed for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator.
- Gonatropin-releasing hormone or luteinizing hormone-releasing hormone analogs for patients with prostate adenocarcinoma or breast cancer can be continued but should not be initiated during trial.
- Prevention and treatment of gastrointestinal adverse events

  Preliminary data suggest that brigimadlin has a moderate emetogenic risk level. Primary anti-emetic prophylaxis before Cycle 1 and on subsequent treatment days is recommended in accordance with established national, interna[redacted]al guidelines based on the emetogenic risk levels of brigimadlin. [redacted] The recommendations for prevention and management of nausea and vomiting are as follows:

[redacted] in addition to continuing the standard antiemetic regimen (ASCO / MASCC / ESMO / NCCN [P22-02579; P22-05918; P22-05968])

- Continue or modify anti-emetic strategy based on clinical judgement, patients' condition, and response.

Auxiliary Medicinal Product

Supportive treatment for doxorubicin should be given as needed and in accordance with the SmPC, package insert, and institutional guidelines.

Dexrazoxane may be administered for the prevention of cardiotoxicity associated with doxorubicin. The dosing and administration are at the discretion of the investigator and/or according to institutional guidelines.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the CRF during the screening and treatment periods, starting at the date of signature of informed consent and ending after the residual effect period (REP). After the REP, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the CRF, on a separate page of follow-up therapy, different from the concomitant therapy pages.

[redacted]

- Brigimadlin is an inhibitor of P-gp and BCRP in *in vitro* studies with IC_{50} values of 8.6 µM and 7.2 µM, respectively. Assessment of the DDI likelihood according to FDA guidelines suggest that the inhibition of intestinal P-gp and BCRP would likely occur at brigimadlin dose levels exceeding 12 mg and 10 mg, respectively. P-gp or BCRP substrates with a narrow therapeutic window or index (NTI) are prohibited during the trial. P-gp or BCRP substrates without a narrow therapeutic index may be used with caution or should be replaced with alternatives wherever possible. For a list of P-gp substrates with an NTI see Table 4.2.2.1: 1.
- Based on clinical data brigimadlin can be considered a weak, transient CYP3A4 inducer at the clinically relevant dose and dosing schedule (45 mg q3w). Coadministration of brigimadlin with CYP3A4 sensitive substrates, for which minimal concentration changes may lead to therapeutic failures of the substrate, should be avoided. If coadministration cannot be avoided, follow recommendations for CYP3A4 inducers provided in their approved product label.
- Brigimadlin is a potential inducer of CYP1A2, based on in vitro studies. Drugs that are known CYP1A2 substrates may have reduced exposure and therefore reduced efficacy when given together with brigimadlin. Alternatives with less potential for CYP1A2-based interactions or concomitant drug dose adjustment should be considered if possible.
- Brigimadlin is in part metabolized by CYP3A4 according to *in vitro* hepatocyte data. Thus, the exposure of brigimadlin might be influenced by concomitant medications that are inducers and inhibitors of CYP3A4. Concomitant medications that are inhibitors or inducers of CYP3A4 should be administered with care and the patient should be more closely monitored.
- Brigimadlin reduces CYP2C9 mRNA and CYP2C19 enzyme activity *in vitro*. Drugs that are known CYP2C9 and CYP2C19 substrates may have increased exposure and therefore increased risk for side effects when given together with brigimadlin. Specifically, sensitive substrates and substrates with narrow therapeutic window or index (NTI) e.g. warfarin, should be used with caution or should be replaced with alternatives with less potential for CYP2C9 and CYP2C19-based interactions.
- Brigimadlin is a substrate of the OATP1B1 and OATP1B3, hence inhibitors for both transporters are not allowed as concomitant therapies. Inhibitors of OATP1B1 and OATP1B3 are listed in Table 4.2.2.1: 1.

Anti-viral treatments have recently been approved for use in some countries for the treatment of mild to moderate COVID-19 infection. [redacted]. Other treatments are allowed taking into consideration the restrictions detailed in this section and in Section 4.2.1.

In addition to the restrictions detailed above, the following concomitant medications are prohibited:

- Live attenuated vaccines are prohibited during the trial and until 30 days after the last dose of brigimadlin.

Herbal preparations / medications and nutritional supplements are allowed throughout the trial at the discretion of the investigator. Potential interactions described above should be taken into consideration.

[redacted]

[redacted]

For restrictions during treatment with doxorubicin, please refer to the current SmPC or US Package Insert of the supplied medication. Table 4.2.2.1: 2 provides on overview.

Table 4.2.2.1: 2 Examples of restricted comedications during treatment with doxorubicin

Strong CYP3A4 inhibitors	Not Permitted	Boceprevir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, chloramphenicol, ketoconazole, itraconazole, posaconazole, voriconazole, nefazodone, cobicistat
Strong CYP2D6 inhibitors	Not Permitted	Fluoxetine, paroxetine, bupropion, quinidine, quinine, cinacalcet, ritonavir
Strong P-glycoprotein inhibitors	Not Permitted	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, ritonavir, propafenone, quinidine, ranolazine, saquinavir telaprevir, tipranavir, verapamil

COVID-19 vaccine

It is recommended that the treating physician consider vaccination against SARS-CoV-2 using the vaccines that have been authorized by the regulatory agencies for the patients participating in these BI clinical trials, provided that a benefit-risk assessment by the treating physician is favorable. Given the mode of action of brigimadlin, it is not anticipated that it would adversely interfere with the response to the vaccines.

This recommendation is consistent with the recommendation by professional oncology organizations (e.g. ASCO, ESMO, and SITC).

4.2.2.2 Restrictions on diet and lifestyle

Patients treated with brigimadlin should be instructed to avoid consumption of [redacted] and their products on days when brigimadlin is administered, as these are CYP3A4 inhibitors.

For all cycles, [redacted]

For restrictions during treatment with doxorubicin, please refer to the current SmPC or US Package Insert of the supplied medication.

4.2.2.3 Contraception requirements

A woman is considered of child-bearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

WOCBP and men able to father a child must use 2 medically approved methods of birth control throughout the trial. They must use one barrier method, i.e. condom or occlusive cap with spermicide, and one highly effective non-barrier method including oral, injected, or implanted hormonal contraceptives, intrauterine device or system. These requirements also apply regardless of whether the male is vasectomized.

Male patients:

Men receiving brigimadlin whose partner is a WOCBP must use a condom (regardless of whether the male is vasectomized) and their female partner must use a highly effective form of contraception, during the study and until 102 days after the last dose of brigimadlin (calculated as the period of relevant systemic exposure (5 half-lives plus 90 days).

Men receiving doxorubicin whose partner is a WOCBP must use a condom (regardless of whether the male is vasectomized) and their female partner must use a highly effective form of contraception, during the study and until 3 months and 10 days after the last dose of doxorubicin.

Female patients:

WOCBP must use a highly effective method of birth control (as outlined in the patient information) per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation, and until 6 months and 12 days after the last dose of brigimadlin (calculated as the period of relevant systemic exposure (5 half-lives plus 6 months) or until 6 months and 10 days after the last dose of doxorubicin.

Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Alternatively, patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral

hormonal contraceptives and experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.

Treatment in this trial carries a potential risk of reduced fertility in both male and female participants, which could be permanent. Prior to treatment initiation, investigators must advise trial participants (men and WOCBP) on the conservation of gametes. Additionally, ovum or sperm donation is not permitted during the periods of contraception.

4.3 TREATMENT COMPLIANCE

The investigational product should only be used as directed in this clinical trial protocol. Brigimadlin will be administered orally and only if considered safe by the investigator.

Brigimadlin will be taken at the investigational site under the supervision of the investigator and/or an authorized and trained designee. Therefore, actual dosing is expected to precisely follow the assigned dose. Dosing will be recorded in the eCRF.

Doxorubicin will be administered by intravenous infusion / injection at the investigational site under the supervision of the investigator and/or an authorized and trained designee, according to the current SmPC or US Package Insert of the supplied medication. Therefore, actual dosing is expected to precisely follow the assigned doses. Missed or interrupted doses will be recorded in the eCRF with the associated reasons.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Imaging

Tumor response will be evaluated according to RECIST version 1.1 [R09-0262].

Baseline imaging should include imaging of all known or suspected sites of disease using an appropriate method. The investigator (or a designee) will record the target and non-target lesions in the eCRF. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. The same method of assessment and the same imaging technique must be used at each subsequent time point to characterize each reported lesion throughout treatment and during follow-up.

All imaging-related endpoints will also be assessed by central independent review (in a blinded fashion) according to RECIST version 1.1. All decisions in this trial will be taken based on central independent review. Instructions for obtaining images and the shipment / transfer of image data will be provided in the imaging manual located in the ISF.

Tumor assessment will be performed at the time points indicated in the flowchart and must continue until confirmation of disease progression by central independent review. Wherever possible, the assessment schedule should not be changed. Additional unscheduled tumor assessments may be performed at the investigator's discretion. If the patient stops trial medication for a reason other than disease progression by central independent review, tumor

assessment according to RECIST version 1.1 will continue until progression by central independent review (or until death, lost to follow-up, or end of the trial).

Management of imaging discrepancies

If there is a discrepancy in the assessment of PD between investigator and central independent evalution, this will be handled as follows:

- If the patient has PD according to investigator assessment, but not according to central independent review, the patient must continue treatment and be re-assessed at the next scheduled time point. The patient must be kept on trial until central independent review concludes that the patient has progressive disease. Patients receiving doxorubicin will only be eligible for cross-over to treatment with brigimadlin after PD *based on central independent review*.

- If the patient is receiving doxorubicin and has PD according to central independent review, but not according to investigator assessment, the patient must stop doxorubicin. The patient is eligible for cross-over to treatment with brigimadlin.

- If the patient is receiving brigimadlin and has PD according to central independent review, but not according to investigator assessment, the patient must stop brigimadlin. Further treatment outside of the trial will be at the discretion of the investigator.

For patients in the cross-over arm, assessments should, wherever possible, continue until confirmed PD by central independent review.

The assessment schedule will be as follows:

- Every 6 weeks (42 days ±7 days), relative to the C1D1 date (for patients after cross-over to brigimadlin: relative to the date of the first administration of brigimadlin). From Week 36 onwards every 12 weeks ±7 days

Clinical imaging data acquired in this trial might be analyzed further for changes in tumor texture features, e.g. using radiomics, and assessment tumor growth kinetics using lesion volumes. If such exploratory analyses are conducted, then the exploratory analyses may be performed in collaboration with an independent third party nominated by the sponsor.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Additional physical examinations may be conducted, as clinically indicated, at the investigator's discretion.

Measurement of height (in cm) and body weight (in kg) and the evaluation of the ECOG performance score will be performed at the time points specified in the flowchart. The results must be included in the source documents available at the site.

Body weight measurements should be done on the same scale for each patient. To get comparable body weight values, body weight measurements should be performed as follows:

- shoes and coat or jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points, please refer to the flowchart.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling / processing and sample shipping are provided in the Laboratory Manual in the ISF.

It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6.1.1).

If the criteria for hepatic injury are fulfilled, a number of additional measures may need to be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF and EDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3: 1 Safety laboratory tests

Category	*Parameters*
Hematology	Hemoglobin, red blood cell count, hematocrit, mean corpuscular volume, white blood cell count, and differential blood count (preferably expressed in absolute values), and platelets.
Biochemistry	Glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, total protein, albumin, uric acid and creatinine kinase (CK; if CK is elevated, then patient should be further evaluated according to local standard of care). If symptoms of pancreatitis are observed, amylase and lipase should be tested at the discretion of the investigator.
Liver function	AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values)
Renal function	Blood urea or blood urea nitrogen, and creatinine. Note: Creatinine can be assessed by any of these methods: CREE (enzymatic serum creatinine assay), CREJIDMS (IDMS standardized Jaffe), or CREJ (non-IDMS standardized Jaffe).
Coagulation	Activated partial thromboplastin time (aPTT) and prothrombin time (PT) (expressed either in seconds or as percentage) or International Normalized Ratio (INR)
Urinalysis	pH, glucose, erythrocytes (hemoglobin / blood), leukocytes, protein, and nitrite analyzed by dipstick (semi-quantitative measurements)
Pregnancy	Beta human chorionic gonadotropin (β-HCG) pregnancy test in serum performed for women of childbearing potential at Screening Urine or serum test performed within 72 h prior to start of study treatment, prior to treatment on Day 1 of every cycle from Cycle 2 Day 1 onwards, at EOT, and then monthly until 6 months after the last dose of treatment.

All screening laboratory assessments should be performed or repeated within 10 days prior to treatment initiation, except for the pre-treatment urine or serum pregnancy test which should be conducted within 72 hours of treatment start; all other screening assessments are performed within 28 days of treatment start (Day 1). On-treatment laboratory assessments can be performed up to 72 hours prior to Day 1 of each cycle.

5.2.4 Electrocardiogram

Recording
Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be digitally recorded at various time points (see the flowchart and Appendix 10.1). In addition, safety ECGs will be performed as single measurements.

All ECG recordings will be obtained after the patient has rested in supine position for at least 10 minutes prior to the indicated time points. All ECGs should be recorded with the patient in the same physical position.

To avoid disruption of ECG recordings, blood samples for a particular time point should be taken after performing the ECG.

ECG recordings may be repeated for quality reasons, e.g. due to alternating current artefacts, muscle movements, or electrode dislocation.

Additional ECGs may be recorded for safety reasons. These ECGs are single recordings and will be assigned to the most previous scheduled time point in the sponsor's database.

All ECG recordings must be analyzed and checked for abnormalities by the investigator (or a designated physician) who will calculate the QTcF value for each time point. Abnormal findings, if deemed clinically relevant by the investigator, will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate. CTCAE version 5.0 will be used for the grading of prolonged QTcF intervals, T wave flattening or unspecific ST segment changes.

In case of QTcF prolongation of >500 msec after receiving therapy, the investigator will initiate further ECG monitoring and diagnostics (e.g. check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation per local standards) and, if required, provide adequate treatment according to medical standards.

In case of occurrence of symptoms suggestive of arrhythmia related to QTcF prolongation, a cardiologic evaluation will be performed, and treatment will be provided according to medical standards at the discretion of the investigator.

5.2.5 Other safety parameters

5.2.5.1 Left Ventricular Ejection Fraction

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or Multiple Gated Acquisition (MUGA) scan will be assessed at the time points specified in the flowchart. The same method of measurement must be used throughout the trial. LVEF assessment does not need to be repeated at the screening visit if there is valid result available from an assessment which was performed as part of routine clinical practice within 28 days prior to treatment start.

Echocardiography
Echocardiography will be performed to assess the LVEF according to the standard guidelines of the American Society of Echocardiography [R06-1414].

MUGA scan
MUGA scan is recommended for the assessment of diseases of the heart muscle. It is used for the monitoring of the ejection fraction of the cardiac ventricles, especially the LVEF.

Patients randomized to doxorubicin and who have completed their treatment will continue to undergo monitoring for cardiotoxicity following local guidelines / clinical practice for cardiotoxicity post doxorubicin treatment. Results will be captured in the eCRF. In addition,

those patients who cross-over to brigimadlin treatment will continue to have LVEF monitored following local guidelines.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease if certain conditions are met – refer to Section 5.2.6.2.5
- Worsening of pre-existing conditions other than the underlying disease
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least 1 of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

For Japan only: An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Every occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.3. AESIs need to be reported only for patients receiving brigimadlin.

In this trial, hepatic injury, hematological AEs, gastrointestinal AEs, and fatigue are considered as AESIs. Details are provided below:

1. Hepatic injury

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- For patients with normal aminotransaminase levels:
  - An elevation of AST (Aspartate Aminotransferase) and / or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other

  OR
  - ALT and / or AST elevations ≥10-fold ULN.

- For patients with abnormal aminotransaminase levels,
  ALT and AST are both between >1 and <3×ULN at baseline:
  - An elevation of AST and/or ALT ≥3×the baseline value combined with an elevation of bilirubin ≥2×ULN (if bilirubin is normal at baseline) or ≥2×the baseline value (if bilirubin is elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other

  OR
  - Aminotransferase elevations (ALT and/or AST ≥5×the baseline value).

- For patients with abnormal aminotransaminase levels,
  ALT and/or AST between ≥3 and <5×ULN at baseline:
  - An elevation of AST and/or ALT ≥2×the baseline value combined with an elevation of bilirubin ≥2×ULN (if bilirubin is normal at baseline) and/or ≥2×the baseline value (if bilirubin is elevated at baseline) measured in the same blood sample or in samples drawn within 30 days of each other

  OR
  - Aminotransferase elevations (ALT and/or AST ≥3×the baseline value).

For further details, see the figure below:

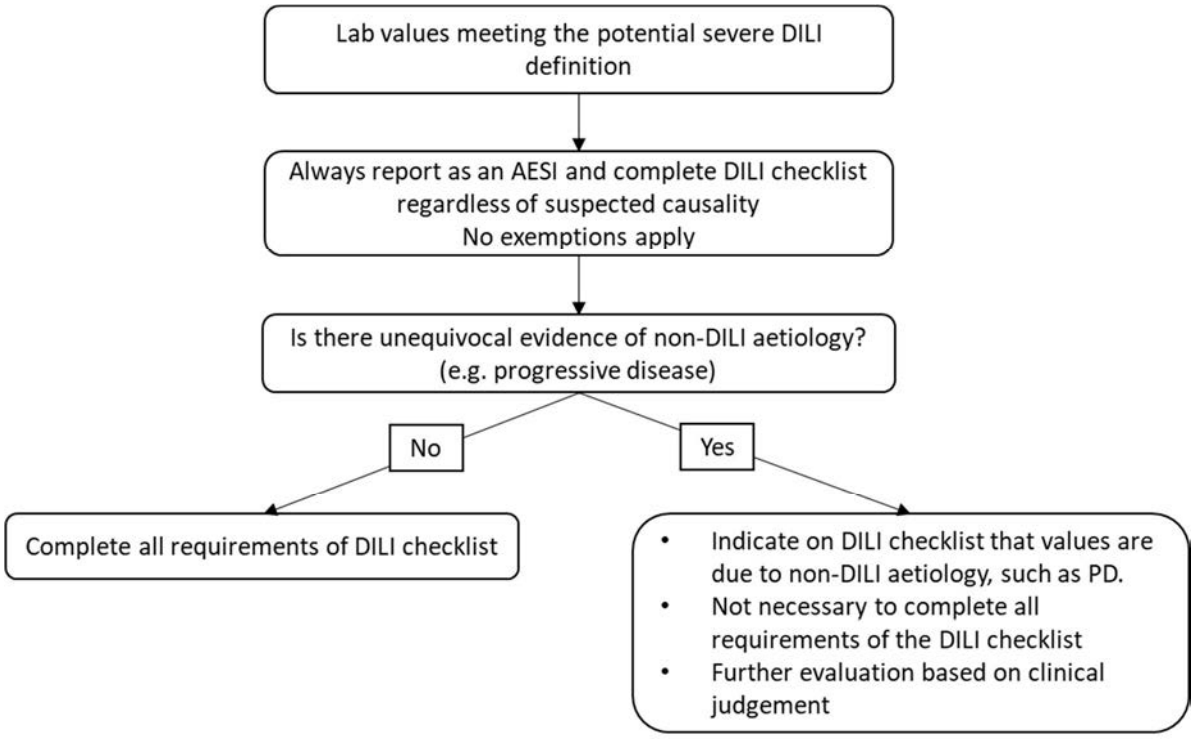


Figure 5.2.6.1.4: 1 Potential severe DILI reporting

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up according to the “DILI checklist” provided in the EDC system.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analyzed, if necessary, in an unscheduled blood test. If the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

2. Hematological AEs

- Thrombocytopenia of CTCAE Grade ≥3
- Neutropenia of CTCAE Grade ≥3
- Thrombocytopenia or anemia requiring transfusion per local or international guidelines

3. Gastrointestinal AEs

- Nausea of CTCAE Grade ≥3
- Vomiting of CTCAE Grade ≥3
- Diarrhoea/colitis of CTCAE Grade ≥3

4. Fatigue

- Fatigue of CTCAE Grade 3 if it lasts for ≥7 days despite adequate medical interventions and if baseline fatigue was of CTCAE Grade ≤1

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If the CTCAE grade of an AE changes, a new separate AE should be recorded in the eCRF.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the trial drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of treatment, including the Residual Effect Period (REP):
  all AEs (serious and non-serious) and all AESIs.
- After the end of treatment (including the REP) until the individual patient's end of trial:
  cancers of new histology, all trial drug related SAEs and all trial drug related AESIs.
- After the individual patient's end of the trial:
  the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.3), but not on the CRF.

The rules for Adverse Event Reporting exemptions still apply, please see Section 5.2.6.2.5.

5.2.6.2.2 Vital Status Data Collection

Patients who discontinue trial treatment prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report any occurrence of cancer, report all deaths / fatal AEs regardless of relationship, and trial drug related SAEs and trial drug related AESIs the investigator becomes aware of.

5.2.6.2.3 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form must be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and / or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.5 Exemptions to AE/SAE reporting

The outcome "progressive disease (PD)" is used to assess trial endpoints for the analysis of efficacy and will be recorded on the appropriate page of the eCRF.

If the disease progression does not meet standard seriousness criteria (see Section 5.2.6.1.2), then it is exempt from AE/SAE reporting, and will only be recorded on the appropriate page of the eCRF. For example, asymptomatic disease progression detected on a routine scan would be exempt from AE/SAE reporting, even if disease progression is on the "always serious" list.

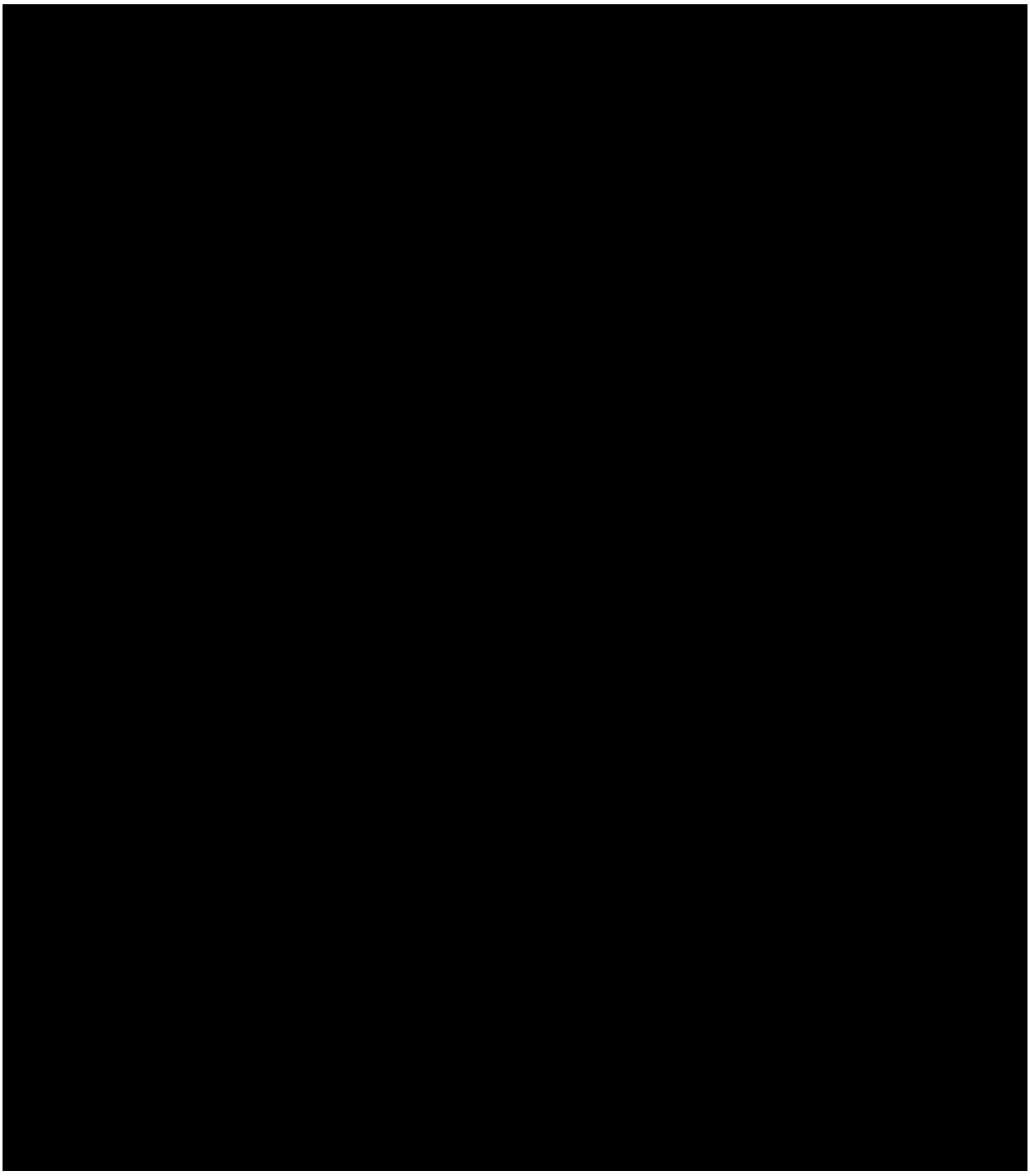
However, if there is evidence suggesting a causal relationship between the investigational drug and the progression of the underlying malignancy, the event must be recorded as an SAE on the AE page in the eCRF and reported as an SAE on the SAE form.

If disease progression meets the standard seriousness criteria (see Section 5.2.6.1.2) it will be recorded on the AE page in the eCRF and on the SAE form and the SAE reporting process will be followed.

Laboratory values meeting the potential severe DILI definition in Section must always be reported as AESI, even if the most likely cause is disease progression. No exemption in AE reporting applies.

Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of disease progression of the patient's underlying malignancy meet standard seriousness criteria, they will additionally be reported as SAEs on the SAE form and the SAE reporting procedures will be followed. If signs and symptoms are attributable to a diagnosis, reporting the diagnostic term is preferable, e.g. pulmonary embolism rather than dyspnoea, intestinal obstruction rather than abdominal pain.

Exempted events are reviewed at appropriate time intervals by an independent DMC and the sponsor. The objectives of the DMC are described in Sections 3.2, 8.7 and in the DMC charter.



5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Planned exploratory analyses of biomarkers during the trial may be reduced or stopped based on new information in the literature or early analyses.

5.4.1 Handling of samples and biomarker results

Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF. All required materials and labels will

be provided. If local regulations allow, any excess materials at the central laboratory will be shipped and stored at BI's central laboratory until all required validations have taken place or until it is decided that there is no requirement for validation. Samples will be destroyed no later than 5 years after trial completion.

A brief description of the biomarker analyses to be performed is provided below. All tumor and blood samples will be obtained at the time points specified in the flowchart. The results of the biomarker analyses performed by the central screening laboratory will be reported to investigators, upon request.

5.4.2 Tumor tissue samples

5.4.2.1 Tumor tissue samples at screening

Patients with a written pathology report indicating the diagnosis of DDLPS with positive MDM2 immunohistochemistry and/or MDM2 amplification are eligible for enrollment into the trial (see Section 3.3.2). Patients may be enrolled based on local testing of tumor tissue which establishes the MDM2 gene amplification status of their tumor. Test results from a liquid biopsy are not acceptable. If there is a local test result from tumor tissue and from liquid biopsy, the test result from the tumor tissue must be used to determine eligibility.

If a fresh biopsy is conducted for the baseline (Screening) assessment of TP53 and MDM2 amplification, a sample from the same procedure may be used as baseline (pre-treatment) sample for other biomarker analyses.

A sample of archival tumor tissue must be provided for every randomized patient for the retrospective testing of the TP53 and MDM2 gene status in a central pathology laboratory nominated by the sponsor. As central laboratory testing is conducted retrospectively for patients deemed eligible per local testing, if test results are inconsistent, the investigator will be informed, and the patient will continue at the investigator's discretion, taking into consideration the patient's clinical benefit.

A fresh biopsy taken for the patient's primary or a metastatic lesion is preferred for biomarker testing but archival sample from a tumor biopsy taken at disease diagnosis is acceptable.

Tumor samples should be provided in the form of a formalin-fixed paraffin embedded (FFPE) block (preferred). Please refer to the laboratory manual for further details on sample preparation.

5.4.2.2 Fresh biopsies on treatment

The use of freshly taken biopsies will enable to generate correlative biomarker data from tumor tissue which help to better understand the treatment benefit but also contributes to the better understanding of the mechanism of action of brigimadlin. Tissue-based biomarker analyses may also be used to support the dose selection. However, the retrospective correlative studies are exploratory and will not be powered to demonstrate statistical significance.

At Cycle 2 Day 2-4, patients will be required to undergo a biopsy (see flowchart) for assessment of the biomarkers listed below. This is a mandatory assessment; however, if in the judgment of the investigator, the biopsies are not feasible (e.g. considering tumor accessibility, patient safety) for a particular patient, the fresh biopsy procedure will not be conducted.

Patients with only one measurable target lesion are not required to undergo the on-treatment biopsy. This is because of the potential effects of a biopsy on the assessment of the lesion and thus the efficacy endpoints.

5.4.2.3 Tumor tissue sample processing and storage

Refer to the laboratory manual for additional detail [redacted]

[redacted]

5.4.3 Circulating biomarkers

5.4.3.1 Circulating tumor DNA

The isolation of DNA from blood originating from the tumor (circulating tumor DNA, or ctDNA) provides a minimally invasive means of monitoring changes in the biology of the tumor resulting from the trial medication. [redacted]

[redacted]

The plasma will also be used to analyze changes in tumor- derived circulating microRNAs, or circulating markers such as cytokines, chemokines, and other circulating protein markers, which may be affected by the therapy. Plasma samples will be destroyed no later than 5 years after study completion.

5.4.3.2 Circulating micro RNA

The p53 pathway also controls the expression of short length RNA species called microRNAs (miRNA) [redacted]

[redacted]

5.4.3.3 Circulating proteins

Circulating proteins such as cytokines, chemokines and hormones will be measured to determine the potential predictive or pharmacodynamic impact of these biomarkers of the treatment benefit.

[redacted]

5.4.4 Flow cytometry

Flow cytometry studies will be carried out to measure or monitor drug-related changes on circulating immune cells such as T cells, dendritic cells, and myeloid-derived suppressor cells (MDSCs). [redacted]

[redacted]

5.4.5 Pharmacogenetics

Pharmacogenetics (PGx) investigates genetic variations in patients to explain and to predict their individual response to drugs. The pharmacogenetic analysis is mandatory but a whole genome sequencing is excluded.

[redacted]

5.5 BIOBANKING

Not applicable for this trial.

5.6 OTHER ASSESSMENTS

5.6.1 Patient reported outcomes

Patient-reported outcomes (PRO) will be measured throughout the trial using the below multidimensional questionnaires. Patients will use digital devices to complete the questionnaires. During the conduct of the trial, the sponsor may decide to implement paper questionnaires.

- EORTC QLQ-C30 v3, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) [R07-2064; R99-1213].

- EQ-5D5L health status self-assessment questionnaire [R96-2382]
- Fatigue: A selection of items from the EORTC PRO item library.
- Pain: A selection of items from the EORTC PRO item library.
- Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) [R21-2016]

The questionnaires will be completed at the time points specified in the flowchart. To minimize the possibility of bias, on clinic days it is recommended that patients should complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status. The responses recorded on the questionnaires will not be recorded as adverse events. Adverse events are collected during protocol specified study visits with the clinician.

The questionnaires generally take about 15 to 30 minutes to complete. Validated translations exist for all questionnaires for all countries participating in the trial, and patients will receive the questionnaires in their native language.

The patient perspective is considered a supportive contribution to inform physicians on the clinical utility of brigimadlin compared to doxorubicin in patients with DDLPS. In addition, the EQ-5D5L, HRQoL assessment will inform a later health economic (cost-effectiveness) analysis.

EORTC QLQ-C30
The QLQ-C30 comprises 30 questions. The QLQ-C30 incorporates both multi-items scales and single-item measures. These include 1 global health status/QoL scale, 5 functional scales, 3 symptoms scales and 6 single items to assess dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Each of the multi-item scales includes a different set of items – no item occurs in more than one scale [R07-2064].

PROMs for fatigue and pain symptoms
A selection of Likert scale items from the EORTC item library will be used to assess pain and fatigue. These items are selected based on patient preferences and are considered relevant and specific for patients with soft-tissue sarcoma, including liposarcoma.

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are FDA-recommended anchors to detect meaningful change. Both single item PROMs are scored through a Likert response scale: the PGIS is scored on a 4-point Likert scale (1 = none, 4 = severe) while the PGIC is scored on a 5-point Likert scale (1 = much better, 5 = much worse).

EQ-5D5L
The EQ-5D5L is a disease-generic instrument that has been widely used and has been found to capture HRQoL changes in soft-tissue sarcoma, including liposarcoma [R21-2293]. The EQ-5D5L comprises the following 2 components:

1. The EQ-5D5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises 5 levels (no problems, slight problems, moderate problems, severe problems, unable to/extreme problems).
2. The EQ-VAS records the respondents self-rated health status on a vertical graduated (0-100) visual analogue scale.

For the EQ-5D5L, the respondent is asked to indicate his/her health state by placing a cross in the box against the most appropriate statement in each of the 5 dimensions. Additional instructions are provided in the ISF.

PRO-CTCAE
The PRO-CTCAE was previously developed to elicit symptomatic toxicity information directly from participants in cancer clinical trials. The PRO-CTCAE has demonstrated favorable validity, reliability, and responsiveness in a sample of 975 patients who had received cancer-directed therapy in the prior 2 weeks. PRO-CTCAE exhibited acceptable test-retest reliability across the subset of items tested. There is also evidence that the 1-week recall corresponds most closely to daily reporting, supporting the validity of the 7-day recall period [R21-2312].

The PRO-CTCAE Item Library is comprised of 78 symptomatic adverse events, assessed by 124 items. It has been linguistically validated in more than 30 languages. Items from this library were selected to assess the following pre-defined adverse events: abdominal pain, nausea, vomiting, diarrhea, mouth sores, decreased appetite, cough, fatigue. One item to assess the global experience of side effects (FACT-G item GP5) will be added to the PRO-CTCAE items.

5.6.2 Analgesic quantification algorithm

The use of analgesic medications for pain will be assessed throughout the trial, at the same schedule as concomitant medication (see flowchart). The investigator (or a designee) will complete the AQA (Analgesic Quantification Algorithm), a measure of analgesic use. The AQA will be used as a component of the clinical trial secondary PRO endpoint (pain as a symptom of the disease), to determine whether changes in pain assessments are due to the intervention or due to changes in analgesic use.

5.7 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumors.

The US National Cancer Institute (NCI) CTCAE is used in the assessment of adverse events in cancer patients. In the present trial, CTCAE version 5.0 will be used.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war), the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, the sponsor and investigator may agree on alternative, back-up or

rescue methodology which may include but will not be limited to: virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. The implementation of these measures will depend on the patient's consent, operational feasibility, and local laws and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed consent may be signed by the patient prior to the screening visit. A separate written informed consent must be obtained for patients crossing over from the doxorubicin arm to treatment with brigimadlin. Imaging scans performed as part of routine clinical practice and prior to provision of informed consent and within the screening timeframe can be used if they meet the imaging requirements.

Eligible patients will be randomized to their trial medication and receive the assigned trial medication until any of the criteria for stopping medication is met (see Section 3.3.4.1), or the maximum cumulative dose of doxorubicin is met for the doxorubicin arm.

During the treatment phase, visits should be performed weekly during Cycles 1 and 2, and once or twice per cycle (as indicated in the flowchart) from Cycle 3 onwards, within 2 days of the scheduled date. The scheduled time interval for each visit is relative to the initiation of trial medication (C1D1). Following discontinuation of all trial medications, an EOT visit must occur as soon as possible (within 7 days after the EOT decision). An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment. After the EOT visit, the patient must undergo a follow-up safety evaluation (after the REP of the assigned trial medication). Then the patient will enter the follow-up period until trial completion. Please see the flowchart for the detailed visit schedule.

Unscheduled visits can be performed as necessary, and assessments will be performed as required at the discretion of the investigator. In case a patient missed a visit and the patient reports to the investigator between the missed visit and the next scheduled visit, the date of the report and the reason for the delayed visit should be noted in the patient's chart. The next visit, however, should take place at the scheduled time. In the event of any interruption / delay of treatment, the imaging schedule should not be changed.

In COVID-19-related or similar exceptional situations, sites should adhere to the required protocol procedures as close as possible while implementing measures to reduce the risk of transmission of infections; however, where a patient is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor. Patient safety must be ensured when determining if a visit may be remote.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

An overview of all assessments to be performed at the respective visit is given in the flowchart; detailed explanations of procedures or observations are given in Section 5.

6.2.1 Screening

The screening visit should be performed between 28 days and 1 day prior to first administration of treatment.

Before or during the screening visit, prior to any study procedures, all patients will need to sign the Informed Consent Form (ICF) for trial participation.

Examinations and assessments will be conducted as depicted in the flowchart. Patients' medical history and demographic information will be collected, and inclusion and exclusion criteria must be assessed (see details below).

A tumor-tissue biopsy (archival or fresh) will be submitted to the central laboratory. This is a mandatory requirement for study enrollment.

Demographics
During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female to describe the subject's sex at birth)
- Gender identity (male, female, other to describe how the subject self-identifies regardless of their genotypic or phenotypic sex)
- For women: of childbearing potential yes / no to characterize the patient population and as a basis for contraception requirements
- Ethnicity and race to sufficiently characterize the patient population, to support possible subgroup analyses, unless not acceptable according to local regulations.

Baseline Conditions
Baseline conditions and concomitant therapies present during screening will be recorded in the eCRF.

Medical History
Medical history for each tumor type will be obtained during screening and documented in the eCRF, this includes:

- Date of first histological diagnosis
- Primary tumor site
- Number and location of metastatic sites at screening (bone, brain, liver, pleural effusion, other)
- Previous anti-cancer treatments including any surgery, radiotherapy, and or systemic therapy, including start and end dates as well as the outcome

Pre-existing tumor molecular marker information (e.g. Next Generation Sequencing data) will be collected where possible.

Baseline imaging
Imaging scans performed as part of routine clinical practice prior to provision of informed consent and within the screening timeframe can be used if they meet the imaging

requirements, provided it is clear from source documents that the imaging was not performed for the purpose of the present trial.

Cross-over to treatment with brigimadlin

Patients randomized to the doxorubicin arm will be offered the option to receive brigimadlin as subsequent therapy (see Section 4.1.3 for further details). The crossed over patients will re-consent, undergo a screening visit, and will be re-assessed for inclusion and exclusion criteria (see Section 3.3.3.1).

Special rules apply for the screening visit of crossed over patients:

- EOT, EOR, and FU for PD assessments from the doxorubicin arm can be used if they had been completed within 21 days of C1D1.
- At maximum a 12-week window is permitted from the date of confirmed PD by central independent review to C1D1 of the cross-over arm.
- Imaging scans do not need to be repeated and can be used as baseline if performed within 6 weeks prior to C1D1.
- If the patient fails screening for the cross-over arm, the patient needs to complete the EOR visit and the follow-up assessments of the doxorubicin arm.

6.2.2 Treatment period(s)

Eligible patients will be randomized through IRT and will be administered trial medication in 21-day treatment cycles until criteria for treatment discontinuation are met (see Section 3.3.4) or the maximum cumulative dose of doxorubicin is met for the doxorubicin arm. Treatment visits are specified in the flowchart and must be conducted as scheduled and outlined there.

Eligible patients for the for the cross-over arm will either be randomized to the 30 mg or 45 mg dose of brigimadlin during Phase II or be assigned to the selected brigimadlin dose in Phase III.

All procedures will be conducted on Day 1 of the cycle. Selected procedures, pharmacokinetics and pharmacodynamics sampling (refer to Appendix 10.1), as well as PROM / PRO-CTCAE assessment will also be performed on subsequent days (Days 8 and 15). A treatment delay should not affect the imaging schedule – the imaging schedule continues, based on the randomization date or C1D1 date of the cross-over arm.

6.2.3 Follow-up period and trial completion

6.2.3.1 End of Treatment visit (EOT)

For patients in the doxorubicin arm who complete the maximum treatment, the EOT visit is performed 21 days (±3 days) after the last dose of doxorubicin.

For all other patients, after permanent discontinuation of trial medication for any reason, the EOT visit must be performed as soon as possible and within 7 days after EOT decision. An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment.

If the decision to permanently discontinue trial medication is taken during a scheduled visit, the EOT (End of Treatment) visit should be performed instead of the scheduled visit. In the event of early discontinuation for reasons other than confirmed progressive disease, the tumor assessment schedule as outlined in Section 5.1.1 should continue to be followed.

After permanent discontinuation of trial medication, further therapy will be decided by the investigator.

6.2.3.2 Safety follow-up visit (End of Residual Effect period, EOR)

After the last administration of trial medication, all patients are required to attend the EOR visit to evaluate safety. The EOR visit is conducted as indicated in the flowchart. In cases where the EOT may be after the EOR period, the EOT and EOR can be done as a single visit. The purpose of this visit is primarily to collect all new AEs that occurred after last administration of trial medication and to follow-up on ongoing adverse events. The EOR visit should occur for all patients, including those patients with confirmed disease progression and/or start of subsequent anti-cancer treatment. For AE reporting after EOT, see Section 5.2.6.2.3.

6.2.3.3 Follow-up period

If a patient does not have documented progression by central independent review prior to or at the safety follow-up visit (EOR) he / she will continue to have regular follow-up visits (FU-PD) and tumor assessments in accordance with the trial schedule. Assessments will be performed as indicated on the flowchart. The end of FU-PD will occur at the timepoint of the earliest event of the following:

- Disease progression
- Start of further anti-cancer treatment
- Loss to follow-up
- Death
- End of the whole trial as specified in Section 8.6

After disease progression the patient will continue to be followed-up for survival as described below.

The following will be obtained and/or performed every 6 weeks during the follow-up for PD:

- For each reportable SAE/AESI, the investigator should provide the information about concomitant medication and the medication administered to treat the AE on the appropriate CRF pages and the SAE form including trade name, indication, and dates of administration.
- Perform tumor imaging and assessment.
- Pregnancy testing as required according to the flowchart.
- Treatment and date with any subsequent anti-cancer drug / therapy including the name and type of the anti-cancer drug and/or best supportive care (if applicable).

- Outcome (date and cause of death [if applicable]; for PD, the actual date of PD.

During this period, imaging scans will continue to be collected as per the imaging manual and submitted to central imaging laboratory.

Follow-up for survival:
After disease progression, the patient will enter the follow-up for survival. No visits will be performed for the purposes of the trial, but data on further anti-cancer treatment and survival will be collected from medical records or via telephone. Patients will also be asked to complete the PROMs. For WOCBP, pregnancy testing will continue as applicable and according to the flowchart. ***Survival*** data will be collected every 12 weeks (±7 days) starting from last contact (EOT and/or EOR) and may also be collected at additional timepoints when a snapshot of data is required (e.g. at the time of analysis). Data collection will continue until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 8.6).

The following information will be collected during the follow-up for OS period:

- Date of contact
- Subsequent anti-cancer therapy (if applicable)
- Related SAE/AESI and concomitant medication
- Outcome event (e.g. death; date of and reason for outcome event/death)

For patients who discontinue for a reason other than confirmed progression by central independent review, follow-up visits continue until confirmed disease progression per the imaging schedule (refer to Section 5.1.1), lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The overall trial design is an active-controlled, randomized, open-label, seamless Phase II/III parallel design to evaluate whether brigimadlin is superior to doxorubicin as first line systemic therapy for advanced or metastatic DDLPS. The primary endpoint, progression-free survival (PFS), will be used to determine superiority. Randomization will be stratified by 'extent of disease' (locally advanced vs. metastatic disease).

The selected investigational arm (brigimadlin at the 30 mg dose or at the 45 mg dose) will be compared with the control arm for the primary endpoint of PFS (based on blinded central independent review). The weighted inverse normal method described by Lehmacher and Wassmer [R14-1197] combining one-sided p-values from a stratified log-rank test (locally advanced vs. metastatic) will be the primary analysis method for PFS. The Lehmacher and Wassmer method is a generalization of the method described by Cui *et al*. [R08-2069]. Family-wise type I error rate will be strongly controlled under the level of 2.5% (one-sided) using the technique detailed in Section 10.2 and as described in [R14-2334; R15-5218; R20-0234; R21-0907;]. Details regarding hypothesis testing, alpha-spending/control, and interim analyses are provided in the following sections.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The primary endpoint PFS will be assessed and compared between the selected investigational arm and the doxorubicin control arm at an interim futility analysis (which is expected to occur at approximately the same time as the end of Phase II) and at the primary analysis of PFS during Phase III.

The one-sided null hypothesis of the primary PFS endpoint is:

H_0: $S_{PFS;\,MDM2}(t) \leq S_{PFS;Doxorubicin}(t)$ for all $t > 0$,

versus the alternative hypothesis:

H_A: $S_{PFS;\,MDM2}(t) > S_{PFS;Doxorubicin}(t)$ for some $t > 0$.

$S_{PFS}(t)$ is the probability that a patient passes time t without experiencing a PFS event. The further subscripts represent the 2 treatment arms, i.e. MDM2 denotes the selected investigational arm of brigimadlin, and Doxorubicin denotes the doxorubicin control arm.

The weighted inverse normal combination test approach will be applied to the primary analysis of PFS. Details of the combination test approach can be found in Appendix 10.2.

For the primary endpoint PFS, a technical one-sided alpha of 0.0005 will be spent at the interim futility analysis and the rest one-sided alpha of 0.0245 will be spent at the primary analysis. There is no plan to test or claim for superiority at the interim futility analysis. If statistical significance is obtained for PFS at the primary PFS analysis during Phase III, then selected secondary endpoints (i.e. ORR and OS) will be tested following a hierarchical testing framework. Due to the hierarchical testing procedure chosen, no alpha adjustment is required to account for multiple testing. ORR will be tested at one-sided level 0.0245 at the same time as the primary PFS analysis. If statistical significance is obtained for both PFS and ORR, then the alpha of one-sided level of 0.0245 will be carried over to the primary analysis and test of OS, occuring at the end of Phase III. If statistical significance is obtained for PFS but not for ORR, then OS will continue to be followed up until the pre-specified number of OS events are met at the end of Phase III and then analyzed without being formally tested.

For ORR, the Cochran-Mantel-Haenszel method will be used to test for a difference between the selected investigational treatment arm and the doxorubicin control arm. The one-sided p-value to test ORR will be generated from the Cochran-Mantel-Haenszel test statistic. The stratification factor will be adjusted for in the analysis (locally advanced vs. metastatic). The one-sided null hypothesis of the ORR endpoint is:

H_0: $ORR_{MDM2} \leq ORR_{Doxorubicin}$,

versus the alternative hypothesis:

H_A: $ORR_{MDM2} > ORR_{Doxorubicin}$.

The subscripts represent the 2 treatment arms, i.e. MDM2 denotes the selected investigational arm of brigimadlin, and Doxorubicin denotes the doxorubicin control arm.

For OS, the primary analysis will be performed using the stratified log-rank test (locally advanced vs. metastatic). The one-sided null hypothesis of the OS endpoint is:

H_0: $S_{OS;\,MDM2}(t) \leq S_{OS;Doxorubicin}(t)$ for all $t > 0$,

versus the alternative hypothesis:

H_A: $S_{OS;\,MDM2}(t) > S_{OS;Doxorubicin}(t)$ for some $t > 0$.

$S_{OS}(t)$ is the probability that a patient passes time t without experiencing death. The further subscripts represent the 2 treatment arms, i.e. MDM2 denotes the selected investigational arm of brigimadlin, and Doxorubicin denotes the doxorubicin control arm.

The weighted inverse normal method described by Lehmacher and Wassmer [R14-1197] combining one-sided p-values will be the analysis method for ORR and OS.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The primary endpoint of PFS (based on central independent review) will be assessed and compared between the selected investigational arm and the doxorubicin control arm at an interim futility analysis (which is expected to occur at approximately the same time as the end of Phase II) and at the primary PFS analysis during Phase III. For more details about the interim futility analysis, see Section 7.2.8 below. Analysis of the primary endpoint of PFS will follow the intention-to-treat principle and will therefore include all randomized patients regardless of whether the patient is treated with trial medication or not.

If statistical significance is obtained for the primary analysis of PFS during Phase III, then the alpha will be carried over, and selected secondary endpoints ORR and OS will be tested following a hierarchical testing framework. These analyses would follow the intention-to-treat principle and would therefore include all randomized patients regardless of whether the patient is treated with trial medication or not.

The final analysis of the secondary endpoint of OS will occur at the end of Phase III. The final analysis of OS will also follow the intention-to-treat principle and will therefore include all randomized patients regardless of whether the patient is treated with trial medication or not.

Safety analyses will include all patients in the treated set (TS), i.e. all patients treated with at least 1 dose of trial medication.

The PK set includes all patients in the TS who provide at least one observation for at least 1 PK endpoint without important protocol deviations relevant to the evaluation of PK.

Any other analysis sets will be defined in the TSAP.

No per protocol set will be used in the analysis. However, important protocol deviations will be identified and listed in the Clinical Trial Report (CTR).

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest in this trial are:

- Start of subsequent anti-cancer therapy before a PFS event based on blinded central independent review
- Treatment switching from doxorubicin to brigimadlin before a PFS event based on blinded central independent review
- Start of a restricted medication (see Section 4.2.2.1)
- Loss to follow-up
- Withdrawal of informed consent by patient
- Missed visits, or 2 or more consecutively missed tumor assessments
- Treatment discontinuation
- Death

The strategies for handling intercurrent events in this trial are as follows:

Primary strategy

The primary strategy for the analysis of the primary endpoint PFS is to handle intercurrent events by studying the effect of randomizing patients to a treatment arm regardless of the actual treatment taken. Different strategies will be used for the expected intercurrent events. Start of subsequent anti-cancer therapy, cross-over from doxorubicin to brigimadlin, loss to follow-up, withdrawal of informed consent, missed visits, or 2 or more consecutively missed tumor assessments before the event of interest occurs will be handled using the “hypothetical approach” as defined in ICH E9 (R1). Use of the “hypothetical approach” considers the effect of what would have happened if the intercurrent event (e.g., start of subsequent therapy) did not occur.

Intercurrent events of treatment discontinuation and start of restricted medications will be handled using the “treatment policy” approach as defined in ICH E9 (R1). Use of the “treatment policy” approach disregards the intercurrent event and uses the value of the variable regardless of the occurence of the intercurrent event (e.g., start of a restricted medication).

The intercurrent event of death will be handled using the composite strategy as defined in ICH E9 (R1), where the intercurrent event becomes part of the endpoint.

Table 7.2.2: 1 Handling of intercurrent events as per ICH E9 (R1) within the different strategies

Intercurrent event	*Primary strategy*
Start of subsequent anti-cancer therapy before a PFS event by blinded central independent review	Hypothetical (censored; see Section 7.3)
Cross-over from doxorubicin to brigimadlin before a PFS event by blinded central independent review	Hypothetical (censored)
Start of a restricted medication	Treatment policy
Loss to follow-up	Hypothetical (censored)
Withdrawal of informed consent by patient	Hypothetical (censored)
Missed visits or 2 or more consecutively missed tumor assessments	Hypothetical (censored)
Treatment discontinuation	Treatment policy
Death	Composite

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this clinical trial protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Any handling of intercurrent events not listed above will be decided during blinded review and documented in the TSAP.

7.2.3 Primary objective analyses

The primary endpoint of PFS is defined in Section 2.1.2.

The primary endpoint of PFS (based on central independent review) will be assessed and compared between the selected investigational arm and the doxorubicin control arm at an interim futility analysis (which is expected to occur at approximately the same time as the end of Phase II) and at a primary PFS analysis during Phase III. The interim futility analysis will be performed once the required number of approximately 56 PFS events have occurred between the selected investigational arm and the control arm. The primary PFS analysis during Phase III will be performed once approximately 120 PFS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase II and approximately 65 PFS events have occurred in patients enrolled in Phase III according to option A (patient separation approach) in Jenkins *et al*. [R15-5218].

For patients with known date of progression based on blinded central independent review or death:

PFS [days] = earlier date of progression based on blinded central independent review or death – date of randomization + 1.

For patients who will be censored:

PFS [days] = date of last imaging assessment without disease progression based on blinded central independent review – date of randomization + 1.

Censoring rules for PFS are provided in Section 7.3.

The analysis of the primary endpoint PFS (based on blinded central independent review) will be performed using the weighted inverse normal method described by Lehmacher and Wassmer [R14-1197]. Stage 1 (Phase II) is defined as the time period until 180 patients have been enrolled between the selected investigational arm and the control arm, and Stage 2 (Phase III) is defined as the time period after that (when 120 additional patients have been enrolled between the selected investigational arm and the control arm). Two one-sided p-values will be calculated, one for each stage. P-values for comparisons of PFS based on stratified log-rank tests are produced separately for those patients recruited to Stage 1 and those recruited to Stage 2. For the patients enrolled at the first stage, the p-value is based on the one-sided Dunnett test [R97-1269] adjusted p-value for dose selection, derived from the stratified log-rank test statistics for PFS. The follow up time of Stage 1 patients is prespecified until 120 PFS events are observed from the selected investigational arm and the control arm. This Stage 1 adjusted p-value for primary PFS analysis can only be calculated when the prespecified number of events for patients enrolled at Stage 1 has been reached. For the patients enrolled at the second stage, the p-value is based on the one-sided p-value derived from the stratified log-rank test statistics for PFS. The follow up time of Stage 2 patients is planned until 65 PFS events are observed from the selected investigational arm and the control arm. Patients who are randomized to the unselected dose level and change to the selected dose (after dose selection), will be censored at the time when dose change occurs (if there is no PFS event before that). The test for statistical significance at the primary PFS analysis will then be based on combining these p-values via the weighted inverse combination function. The above-mentioned process is based on independent, normally distributed stratified log-rank test statistics, which ensures control of the type I error rate [R15-0928]. Additional technical details of the combination test approach can be found in Appendix 10.2.

Kaplan-Meier estimates of the survival function of PFS, median PFS and the corresponding 95% confidence interval using Greenwood variance that is incorporated into the Brookmeyer and Crowley method [R09-6372] with a loglog transformation, as well as the p-value of stratified log-rank test (stratified by locally advanced vs. metastatic) on PFS will be provided.

To estimate the HR for PFS, the median unbiased estimator [R14-2334] will be used as the primary estimator. The 95% confidence interval for the HR will then be calculated as repeated confidence interval (RCI) according to [R15-0928]. In addition, as a secondary estimator, the partial maximum likelihood estimator from the stratified Cox proportional hazards model (stratified by locally advanced vs. metastatic) will be used.

7.2.4 Secondary objective analyses

No key secondary endpoints are defined for the trial.

Secondary endpoints are defined in Section 2.1.3.

The hierarchical testing framework for testing selected secondary endpoints (i.e. ORR and OS) is described in Section 7.1.

In addition to the details described below, further details may be specified in the TSAP.

Objective response

Objective response (OR) is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 (based on blinded central independent review) from the date of randomization until disease progression, death, last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent, whichever occurs first. Each patient will be assigned as

having a best overall response of one of the following RECIST categories: CR, PR, SD (stable disease), PD (progressive disease), or NE (not evaluable).

A best overall response of CR or PR must be confirmed by a subsequent tumor assessment, i.e., a confirmed response requires a repeat observation at least 4 weeks apart.

Unconfirmed PR or CR will be presented as a sub-category of confirmed SD. SD must last for at least 42 days to be presented as SD. SD lasting less than 42 days and followed by PD will be presented as a sub-category of PD. SD lasting less than 42 days and without evaluable response thereafter will be listed as "Not evaluable". Any assessments done in compliance with the pre-specified (-)7-day assessment window will also be accounted for as within the 42-day duration.

Objective tumor response rate (ORR) gives the percentage of patients with objective tumor response. The Cochran-Mantel-Haenszel method will be used to test for a difference between arms for ORR. The stratification factor will be adjusted for in the analysis (locally advanced vs. metastatic). The two-sided p-value will be generated from the Cochran-Mantel-Haenszel test statistic. The one-sided p-value will then be inferred from the two-sided p-value. The weighted inverse normal method described by Lehmacher and Wassmer [R14-1197] combining one-sided p-values from two stages will be the analysis method. The Stage 1 p-value will be calculated only based on patients enrolled at Stage 1, and the Stage 2 p-value will be calculated only based on patients enrolled at Stage 2.

To estimate the odds ratio for ORR, the median unbiased estimator [R14-2334] will be used as the primary estimator. The 95% confidence interval for the odds ratio will then be calculated as repeated confidence interval (RCI) according to [R15-0928]. In addition, as a secondary estimator, an odds ratio and corresponding 95% confidence interval will be generated using the likelihood ratio confidence interval.

Overall survival

Overall survival (OS) will be assessed at the end of Phase III. OS is defined as the time interval from randomization until death from any cause.

For patients with known date of death of any cause:

> OS [days] = date of death - date of randomization + 1.

For patients who died but with unknown date of death of any cause:

> OS [days] = date of last contact when the patient is known to be alive - date of randomization + 1.

For patients who will be censored:

> OS [days] = date of last contact when the patient is known to be alive - date of randomization + 1.

The primary analysis of OS will be assessed and compared between the selected investigational arm and the doxorubicin control arm at the end of Phase III once approximately 133 OS events have occurred in patients enrolled in Phase II and approximately 82 OS events have occurred in patients enrolled in Phase III, and the testing process will be similar to the analysis described for PFS.

Kaplan-Meier estimates of the survival function of OS, median OS, and the corresponding 95% confidence interval using Greenwood variance that is incorporated into the Brookmeyer and Crowley method [R09-6372] with a loglog transformation, as well as the p-value of stratified log-rank test (stratified by locally advanced vs. metastatic) on OS, will be provided.

To estimate the HR for OS, the median unbiased estimator [R14-2334] will be used as the primary estimator. The 95% confidence interval for the HR will then be calculated as repeated confidence interval (RCI) according to [R15-0928]. In addition, as a secondary estimator, the partial maximum likelihood estimator from the stratified Cox proportional hazards model (stratified by locally advanced vs. metastatic) will be used.

To address cross-over effects, a sensitivity analysis of OS is planned. Details will be provided in the TSAP.

Duration of objective response

Duration of objective response (DOR) is defined as the time interval from first documented confirmed OR until disease progression or death among patients with confirmed objective response (based on blinded central independent review), whichever occurs first.

DOR can only be calculated for patients with confirmed objective response.

For patients with disease progression based on blinded central independent review or death:

DOR [days] = date of outcome - date of first assessment indicating objective response + 1.

For patients without disease progression based on blinded central independent review or death:

DOR (censored) [days] = date of outcome - date of first assessment indicating objective response + 1.

The censoring rules for DOR will be provided in the TSAP. Only radiological assessments after first assessment indicating objective response should be taken into consideration.

Kaplan-Meier methods will be used for the calculation of DOR.

Disease control

Disease control is defined as a best overall response of CR, PR, or SD according to RECIST version 1.1 (based on blinded central independent review).

Disease control rate gives the percentage of patients with disease control. Logistic regression will be used to explore the difference between arms for disease control rate. The stratification factor will be included as a covariate in the logistic regression model (locally advanced vs. metastatic).

Health-Related Quality of Life

Health-Related Quality of Life (HRQoL), based on data collected through specific questionnaires (Patient Reported Outcome Measures, PROMs). Scores will be calculated from data collected through the QLQ-C30, EQ-5D5L, fatigue, pain, Patient Global Impression questionnaires, PRO-CTCAE, and FACT-GP5 as described in Section 5.6.1 at the time points specified in the flowchart.

Secondary HRQoL endpoints analyzed will be:

- Mean change from baseline to Week 18 in the following QLQ-C30 scores:
  - Physical functioning
  - Pain
  - Fatigue
  - Global health status / quality of life
- Mean change from baseline to Week 18 in the following scores obtained using items from the EORTC QLQ-C30 and Item Library
  - Fatigue
  - Fatigability
  - Pain
  - Fatigue impact
  - Pain impact
- Mean change from baseline to Week 6 of all the EORTC QLQ-C30 scores listed above
- Mean change from baseline to Week 6 of all the scores obtained using items from the EORTC QLQ-C30 and Item Library listed above

Piecewise linear mixed models will be used for the main analysis of secondary HRQoL endpoints. Responder analyses will complement the main analysis of HRQoL. In addition, PROMs will be analysed descriptively. Further details on the analyses of PROMs will be provided in the TSAP.

Analyses for the secondary safety endpoints

Please refer to Section 7.2.6 where the safety analyses are described.

[redacted]

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between treatment start and end of the REP will be assigned to the on-treatment period for evaluation. The REP is the period after the last administration of trial medication with measurable drug levels and/or pharmacodynamics effects still likely to be present. For more details about the REP, please refer to Section 1.2.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing for safety analyses is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between treatment start and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analyzed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarized. Treatment groups will be compared descriptively regarding distribution parameters as well as regarding frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the trial, and at the end-of-trial evaluation will be assessed regarding possible changes compared to findings before treatment start.

[redacted]

7.2.8 Interim analyses

Interim analysis for dose selection

The interim analysis for dose selection will be conducted during Phase II based on the totality of safety data and PK/PD parameters as surrogates of clinical efficacy. This interim analysis is estimated to take place approximately 8 months after the start of enrollment when PK/PD and safety data from at least 20 evaluable patients treated with 30 mg of brigimadlin and 20 evaluable patients treated with 45 mg of brigimadlin become available. Patients must have received at least 1 dose of brigimadlin and have evaluable PK/PD data in Cycle 1 to be considered evaluable. If the overall safety profile is assessed to be tolerable and manageable (i.e. manageable gastrointestinal AEs and acceptable risk of hematological side effects) and at least [redacted] increase of PK/PD parameters are observed at the 45 mg dose as compared to the 30 mg dose, then the brigimadlin 45 mg dose will be selected. Otherwise, the brigimadlin 30 mg dose will be selected. All available data (i.e safety, dose modification rates, PK/PD parameters, and preliminary anti-tumor activity) from all patients enrolled until the data lock point for this interim analysis will be used to support the final dose selection. Enrollment of both investigational arms will continue until the dose selection decision is made, which may be before or at the end of Phase II. Additional details will be provided in the TSAP.

Interim futility analysis

An interim futility analysis of the primary endpoint of PFS will take place when there are approximately 56 PFS events from the selected investigational arm and the control arm, which is expected to occur at approximately the same time as the end of Phase II. Enrollment of patients will continue whilst this analysis is performed. Only PFS will be analyzed at the interim futility analysis; no other endpoints are planned to be tested at this timepoint. If the selected investigational arm passes the non-binding futility boundary of HR = 0.80 for PFS (based on blinded central independent review), then the study will continue to full enrollment. If enrollment is close to completion when the required number of 56 PFS events is reached, then the interim futility analysis of PFS may not be performed.

Primary PFS analysis

The primary PFS analysis will take place during Phase III at the time point when approximately 120 PFS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase II and approximately 65 PFS events from the selected investigational arm and the control arm have occurred in patients enrolled in Phase III. The primary PFS analysis is expected to take place around [redacted] after the trial starts. If statistical significance is obtained for PFS at this analysis, then the secondary endpoints will be tested following a hierarchical testing framework.

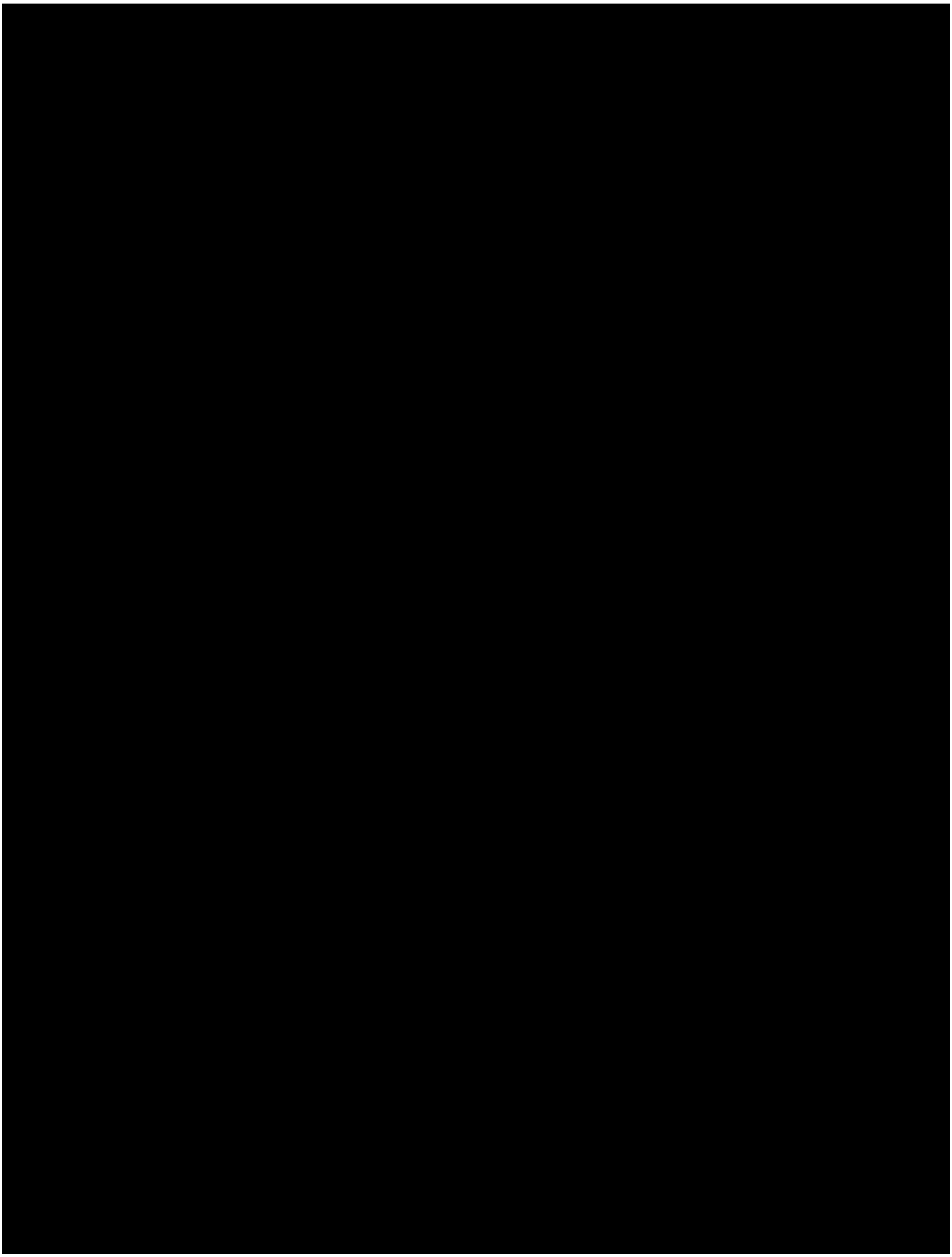
DMC analyses

During this open-label trial, an independent DMC will review unblinded interim efficacy and safety analyses prepared by the sponsor.

Though the trial is open-label, a minimum number of sponsor internal team members will view unblinded data aggregated by treatment arm before the end of the trial as defined in Section 8.6. These precautions will be taken to reduce potential bias during trial conduct.

The independent DMC will review the unblinded analyses at the interim analysis for dose selection, at the interim futility analysis (which is expected to occur at approximately the same time as the end of Phase II), and as needed during the conduct of the trial.

For more details about the DMC, please see Section 8.7.



7.4 RANDOMIZATION

The trial will use randomization for assignment of patients to the different trial arms. This is an open-label trial, and during trial conduct, treatment assignments will be available to all personnel in the trial.

As mentioned in Section 7.2.8 above, though the trial is open-label, a minimum number of sponsor internal team members will view unblinded data aggregated by treatment arm before the end of the trial as defined in Section 8.6. These precautions will be taken to reduce potential bias during trial conduct.

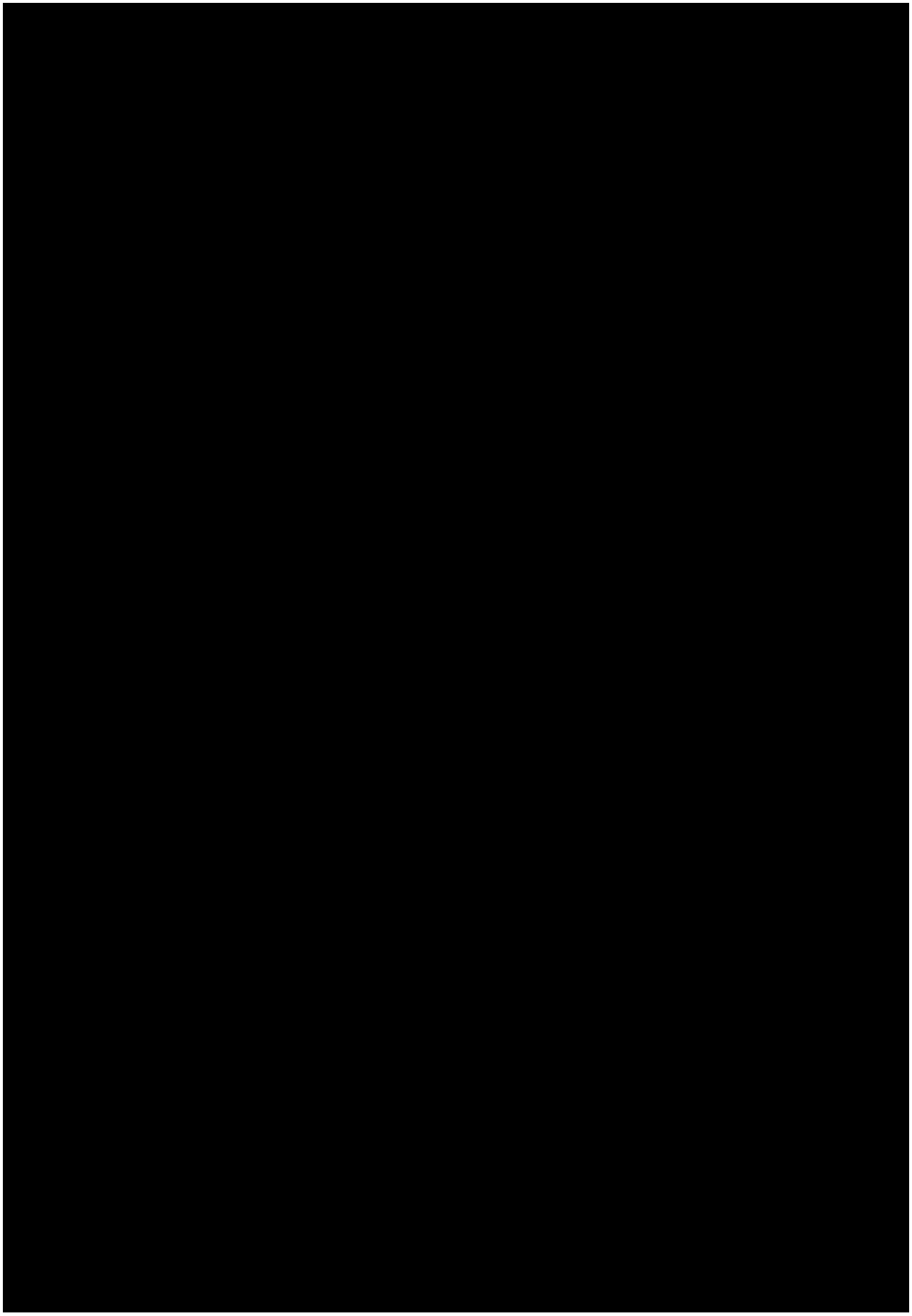
First, in the Phase II part, up to 270 patients will be randomized with a 1:1:1 ratio to brigimadlin at the 30 mg dose, brigimadlin at the 45 mg dose, or the doxorubicin control arm.

Patients randomized to the doxorubicin arm who receive brigimadlin as subsequent therapy (cross-over arm) will be randomized 1:1 to receive either 30 mg or 45 mg of brigimadlin until a dose for Phase III is selected, after which all crossed over patients will be offered the selected dose (see Section 4.1.3).

In the Phase III part, an additional 120 patients will be randomized with a 1:1 ratio to either the selected investigational arm or the doxorubicin control arm.

An IRT will be used to perform the randomization centrally across all study sites. The randomization list will be generated by BI using a validated pseudo-random number generator, yielding reproducible and non-predictable results.

Randomization will be stratified by ‘extent of disease’ (locally advanced vs. metastatic disease).



8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor regarding publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and it is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee

(IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial patient protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal, and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for tumor assessments will be provided to blinded central independent review. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant

meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

For patient-reported outcomes that were provided via an edevice or remotely, the electronic record is the source document.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

COVID-19 restrictions may limit the options for onsite source data verification and other onsite monitoring tasks.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.6.2.5.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage, and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalized treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection and future use of biological samples and clinical data, in particular:

- Sample and data usage must be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, including audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").The "Last Patient Last Treatment" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this clinical trial protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI). In EU/EEA countries, the trial is sponsored by Boehringer Ingelheim International GmbH, [redacted]

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A steering committee (SC) will act as an advisory body and oversees the execution and the dissemination of the trial. It will consist of independent experts, sponsor representatives from different disciplines, and investigator representatives. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor and will also be summarized in an SC charter.

A DMC will be established for the trial. Voting members of the DMC are independent of BI; they are physicians with relevant expertise, and a statistician. The DMC will review unblinded efficacy and safety analyses prepared by the sponsor. The independent DMC will review the unblinded analyses at the interim analysis for dose selection, at the interim futility analysis around the end of Phase II, and as needed during the conduct of the trial. Further details about the planned interim analyses are given in Section 7.2.8. While DMC members are unblinded to treatment arm assignment, measures are in place to ensure that during trial conduct, a minimum number of sponsor internal team members will view unblinded data aggregated by treatment arm. The DMC will recommend continuation, modification, or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs) / Health Authorities (HAs), IRBs / ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader responsible for coordinating all required activities,

- to manage the trial in accordance with applicable regulations and internal SOPs,
- to direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- to ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries, the trial will be performed by the respective local or regional BI-organization (Operating Unit, OPU) in accordance with applicable regulations and BI

SOPs, or by a Contract Research Organization (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned to organize, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, a central images service (responsible for the blinded central independent review), and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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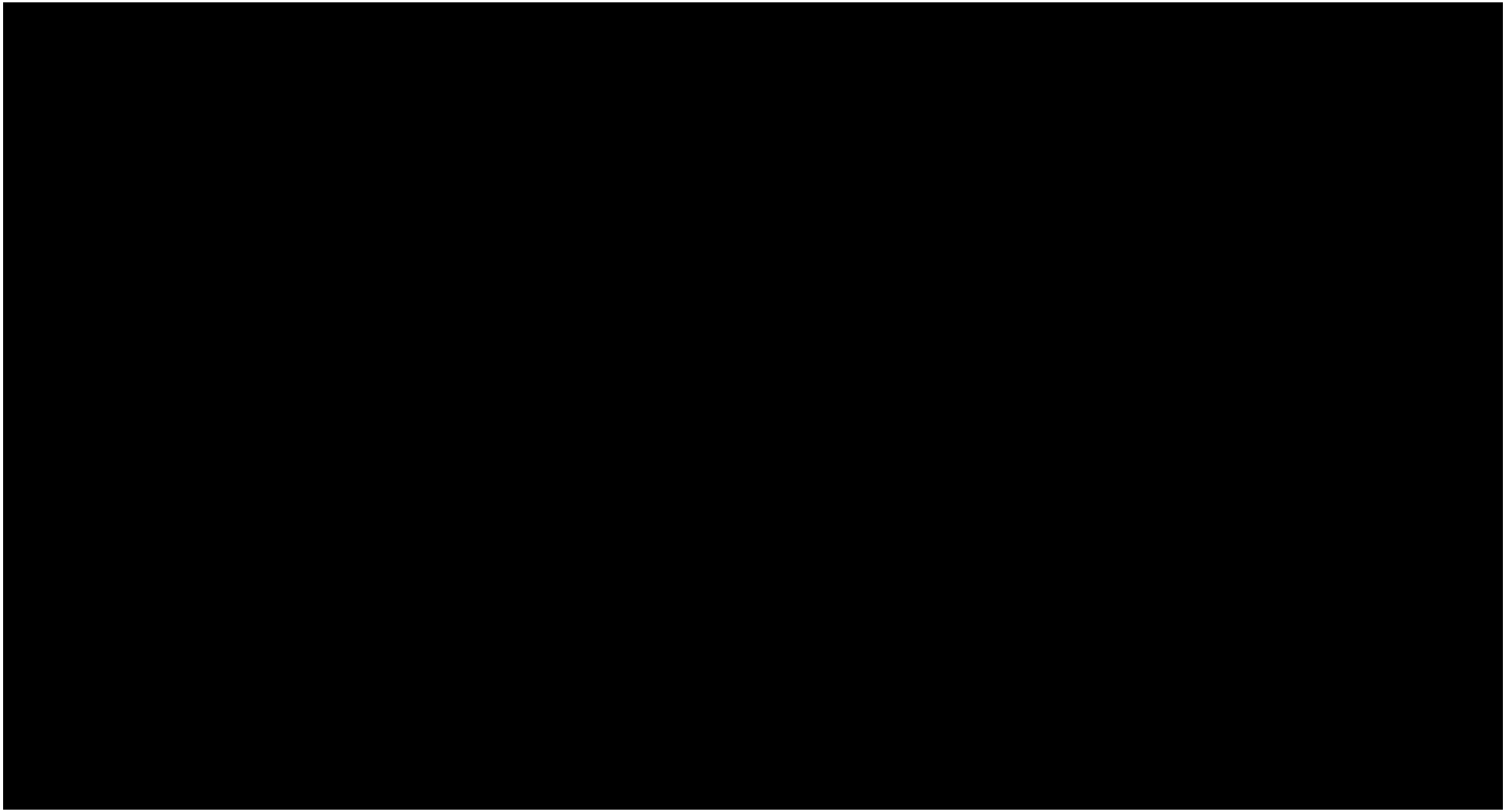
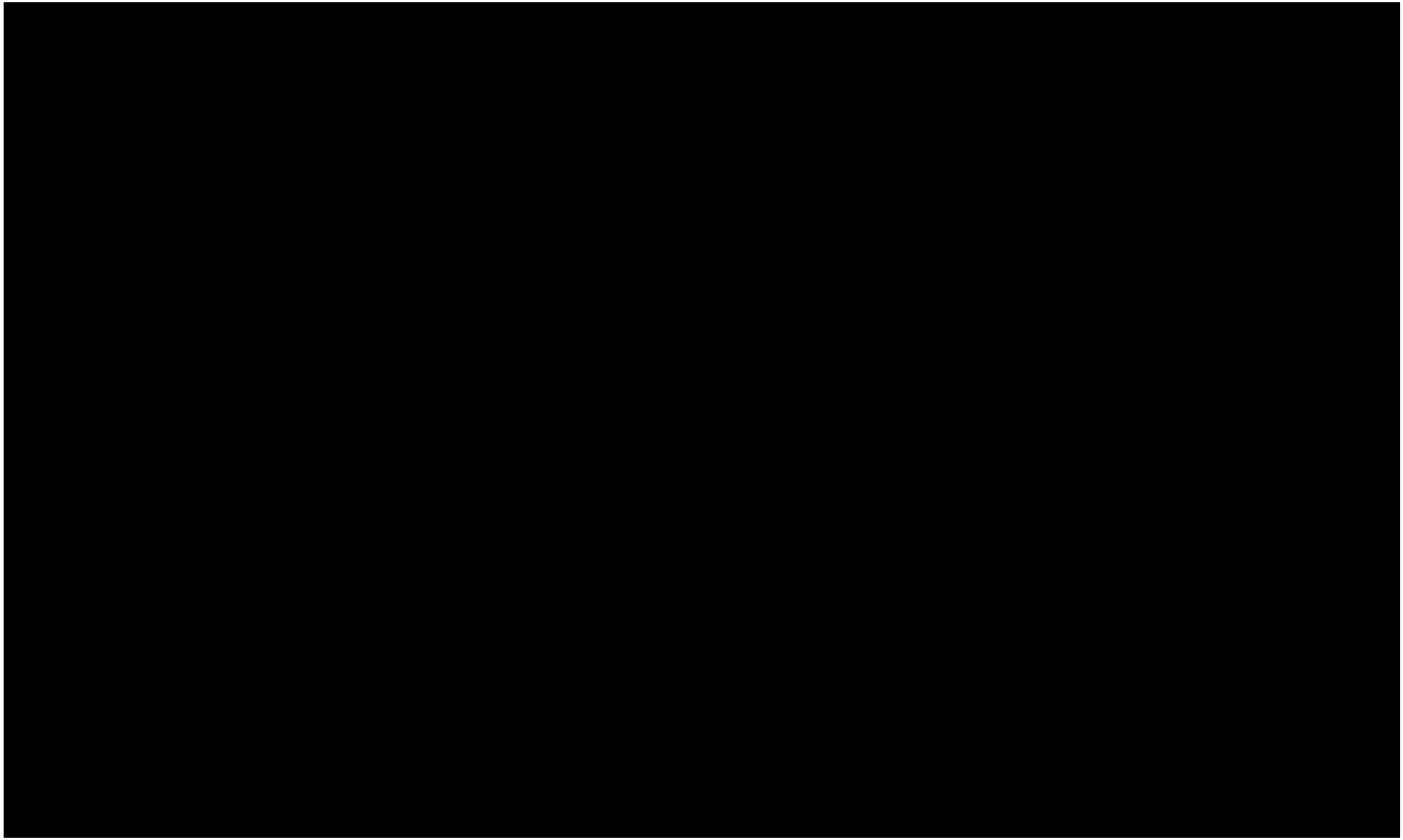
c15936970 Investigator's Brochure: BI 907828. Indication: Solid tumors 1403.P1. Current version.

10. APPENDICES





10.2 STATISTICAL DETAILS

10.2.1 Combination test approach

This appendix provides the technical details of the methodology used for the primary analysis of PFS, especially to control the familywise type I error rate. Familywise type I error rate will be strongly controlled under level of 2.5% (one-sided) using the following technique as described in [R14-2334; R15-5218; R20-0234; R21-0907].

Step 1: Get the stage-wise unadjusted p-value.

For each analysis, the relevant stage-wise p-value p_i will be derived from the data available at the time of analysis. Stage 1 (Phase II) is defined as the time period until 180 patients have been enrolled between the selected investigational arm and the control arm, and Stage 2 (Phase III) is defined as the time period after that (when 120 additional patients have been enrolled between the selected investigational arm and the control arm). Here, $i = 1, 2$ for the two stages. p_1 and p_2 are the stagewise one-sided p-values derived from the stratified log-rank test statistics for PFS based on patient enrolled in each stage until the planned follow up time, respectively.

Step 2: Get the adjusted p-value p_1^* for Stage 1 based on the Dunnett test.

The Dunnett test is a multiple comparison procedure for the comparison of multiple investigational treatments with a single control. This adjustment will avoid any potential type I error inflation due to dose selection.

Step 3: Combine stage-wise p-values for H_0 using inverse normal p-value combination function to generate the adjusted test statistics.

For the calculation of the final test statistics, an inverse-normal p-value combination approach will be used. The data of the two different stages will be combined to generate the adjusted test statistics z_2 at the end of Stage 2:

$$z_2 = w_1 \Phi^{-1}(1 - p_1^*) + w_2 \Phi^{-1}(1 - p_2)$$

based on patients enrolled at Stages 1 and 2

where w_i (i=1,2) are the predefined weights for Stages 1 and 2 with $\sum_{i=1}^{2} w_i^2 = 1$.

Φ denotes the standard normal distribution function and Φ^{-1} its inverse.

The weights are chosen to be proportional to the planned numbers of PFS events from

Stage 1 and Stage 2 patients. The planned number of PFS events from patients in Stage 1 is 120 and the planned number of PFS events from patients in Stage 2 is 65. Thus, the fraction of PFS events for the first stage patients will be around 0.64. Therefore, the weights are chosen as:

$w_1 = \sqrt{0.64}$ and $w_2 = \sqrt{0.36}$

To protect type I error, the weights are fixed and will not change.

Step 4: Hypothesis testing using a user-defined spending function.

In our two-stage setting, H_0 will be tested at the primary PFS analysis during Phase III ($\alpha_2 = 0.0245$ one-sided); a technical $\alpha_1 = 0.0005$ one-sided will be used at the end of Stage 1. The data available at the time of analysis will be used to calculate the test statistic based on Step 1 and Step 2. There is no plan to claim superior efficacy at the interim futility analysis despite setting one-sided alpha spending of 0.0005. This alpha spending will only make the trial planning more conservative in type one error control. The trial will be claimed a success if the selected investigational arm has p-value that crosses the efficacy boundary at the primary analysis, i.e.

$1 - \Phi(z_2) < \alpha_2$

All patients enrolled at Stage 1 and at Stage 2 will be included in the proposed combination test. The strong familywise type I error rate control has been established theoretically by [R14-1197].

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 Jan 2022
EudraCT number **EU number**		2021-002392-20
BI Trial number		1403-0008
BI Investigational Medicinal Product(s)		BI 907828
Title of protocol		Brightline-1: A Phase II/III, randomized, open-label, multi-center study of BI 907828 compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Synopsis**
Description of change		Instead of the likelihood ratio test based on logistic regression, the Cochran-Mantel-Haenszel test will be used as the primary analysis method for ORR.
Rationale for change		FDA request to use the Cochran-Mantel-Haenszel test as the primary analysis method for ORR.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, in the footnote starting with the text “A serum pregnancy test is mandatory (…)” the sentence “Pregnancy testing after EOT can be performed remotely or at the clinic.” was added.
Rationale for change		More flexibility for the patient.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, in the footnote starting with the text “Blood samples for biomarker analysis are mandatory. (…)”, “myeloid-deprived” was corrected to “myeloid-derived”.
Rationale for change		Typo corrected.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, the column “FU for survival” had a reference to a non-existing footnote 22; this was corrected to refer to the footnote starting with the text “During FU for survival, (…)”.
Rationale for change		Reference to a non-existing footnote.

Section to be changed		**Flowchart**
Description of change		[redacted]
[redacted]		
Section to be changed		**Flowchart**
Description of change		In all flowcharts, in the line "PROMs: QLQ-C30, items pain & fatigue" as well as in the footnote starting with the text "PROM = Patient Reported Outcome Measures; (…)", the frequency of the assessments was reduced.
Rationale for change		Less frequent assessments are sufficient.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, in the line "PRO-CTCAE" as well as in the footnote starting with the text "Patient assessments of pre-specified AEs (…)", the frequency of the assessments was reduced.
Rationale for change		Less frequent assessments are sufficient.
Section to be changed		**1.4.2**
Description of change		Update of numbers based on most recent data available with the new IB version 7.
Rationale for change		New IB version 7 is available.
Section to be changed		**3.3.4.1**
Description of change		Further details about the AEs that require treatment discontinuation is available in Section 4.1.4.2; a cross-reference to this section was added.
Rationale for change		FDA request to to further specify the AEs.
Section to be changed		**3.3.4.1**
Description of change		Specification that ongoing patients will be informed about the impact of the interim analysis before discussing the possibility to continue their assigned treatment.
Rationale for change		FDA request to specify that if the trial is stopped for futility, patients must be informed of this before being offered the opportunity to continue treatment with their assigned drug.
Section to be changed		**4.1.4.1**
Description of change		Deletion of the paragraph that allowed patients at 30 mg BI 907828 after confirmed PD to continue treatment at 45 mg BI 907828.

Rationale for change		FDA request to discontinue treatment at the time of progressive disease, also for patients randomized to 30 mg BI 907828.
Section to be changed		**4.1.4.2**
Description of change		Further details about the AEs that require treatment discontinuation were added.
Rationale for change		FDA request to to further specify the AEs.
Section to be changed		**4.1.4.2**, Figure 4.1.4.2: 1
Description of change		Modified instruction for dose delays of BI 907828 due to low platelet and/or neutrophil count for patients who do not recover within 14 days.
Rationale for change		FDA request to specify dose modifications for recurrent AEs and to shorten the maximum possible treatment delay.
Section to be changed		**4.1.4.2**
Description of change		Modified guidance for dose delays of BI 907828 due to other AEs.
Rationale for change		FDA request to specify dose modifications for recurrent AEs, to shorten the maximum possible treatment delay, and to remove investigator's considerations when re-exposure is clinically indicated.
Section to be changed		**5.1.1**
Description of change		For patients in the cross-over arm, the tumor assessment at EOT was removed ("At the EOT visit [if not performed within the previous 4 weeks]")
Rationale for change		The tumor assessment at EOT is not needed and was inconsistent with the flowchart.
Section to be changed		**5.4.4**
Description of change		"Myeloid-deprived" corrected to "myeloid-derived".
Rationale for change		Typo corrected.
Section to be changed		**5.6.1**
Description of change		Clarification on the information about the measurement of patient-reported outcomes was updated.
Rationale for change		Administrational change.
Section to be changed		**7.1**
Description of change		Instead of the likelihood ratio test based on logistic regression, the Cochran-Mantel-Haenszel test will be used as the primary analysis method for ORR.

Rationale for change		FDA request to use the Cochran-Mantel-Haenszel test as the primary analysis method for ORR.
Section to be changed		**7.2.1**
Description of change		"Key secondary endpoints" corrected to "selected secondary endpoints".
Rationale for change		Typo corrected.
Section to be changed		**7.2.4**
Description of change		Instead of the likelihood ratio test based on logistic regression, the Cochran-Mantel-Haenszel test will be used as the primary analysis method for ORR.
Rationale for change		FDA request to use the Cochran-Mantel-Haenszel test as the primary analysis method for ORR.
Section to be changed		**7.2.8**
Description of change		Inclusion of a definition of patients considered "evaluable" for the interim analysis for dosage selection.
Rationale for change		FDA request to further specify patients considered "evaluable" for the interim analysis for dosage selection.
Section to be changed		**8.7**
Description of change		Description of the DMC structure was modified.
Rationale for change		The details of the DMC composition will be described in the charter.
Section to be changed		**10.1**, Table 10.1: 1
Description of change		In the column "ECG", an "X" was added for Cycle 2, Day 1, 4:00 h assessment.
Rationale for change		The ECG assessment at Cycle 2 Day 1 is needed and is now consistent with the flowchart.
Section to be changed		**General**
Description of change		Minor grammar, typographical errors were corrected throughout the document.
Rationale for change		The corrections were made throughout the document to ensure that grammar and spellings were corrected.

11.2 GLOBAL AMENDMENT 2

Date of amendment		12 Sep 2022
EudraCT number **EU number**		2021-002392-20
BI Trial number		1403-0008
BI Investigational Medicinal Product(s)		BI 907828
Title of protocol		Brightline-1: A Phase II/III, randomized, open-label, multi-center study of BI 907828 compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Title Page and Synopsis**
Description of change		New phone number for one of the coordinating investigators was added.
Rationale for change		Update needed.
Section to be changed		**Synopsis and 2.1.1**
Description of change		Wording for HRQoL-related main objectives was modified to read “evaluate whether BI 907828 (…) has a favorable impact on quality of life, compared to doxorubicin”.
Rationale for change		Make it clearer that the evaluation covers both worsening and improvement.
Section to be changed		**Synopsis and 2.1.3**
Description of change		Wording of a secondary endpoints was updated to read “Health-Related Quality of Life (HRQoL), based on data collected through specific questionnaires (Patient Reported Outcome Measures, PROMs), analyzed from baseline to Week 6 and to Week 18. The HRQoL endpoints are defined as the scores calculated from data collected through selected EORTC QLQ-C30 domains (physical functioning, fatigue, pain, and global health status / quality of life), fatigue and pain based on items from the EORTC QLQ-C30 and the EORTC Item Library, and the EQ-5D5L.”
Rationale for change		Clarification of the HRQoL secondary endpoint.

Section to be changed		**Synopsis and 2.1.3**
Description of change		Safety was included as a secondary endpoint by adding "Occurrence of treatment-emergent adverse events (AEs)." and "Occurrence of treatment-emergent AEs leading to study drug discontinuation." to the secondary endpoints.
Rationale for change		Safety is a secondary objective for both parts of this trial, there need to be secondary safety endpoints.
Section to be changed		**Synopsis**
Description of change		Exclusion criterion was modified to read "Previous or concomitant malignancies other than DDLPS or WDLPS, treated within the previous 5 years, except effectively treated non-melanoma skin cancers, carcinoma *in situ* of the cervix, ductal carcinoma *in situ*, or other malignancy that is considered cured by local treatment."
Rationale for change		Allow for more exceptions from this exclusion criterion.
Section to be changed		**Synopsis and 3.1**
Description of change		Alignment of both sections to get a consistent description of the trial design and the statistical methods.
Rationale for change		The description was slightly inconsistent.
Section to be changed		**Flowchart**
Description of change		In Table 1, Cycles 1 and 2, Days 8 and 15, the entry for "Physical examination, vital signs, ECOG PS" was removed.
Rationale for change		These assessments are not needed.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, the PROM and the PRO-CTCAE schedule was modified from "until EOT" to "until "PD". The related footnote starting with the text "PROM = Patient Reported Outcome Measures; (…)" was corrected with the new text "Please note that the PGIC assessment is not required at C1D1." and the additional information that "Patients without PD who start subsequent anti-cancer treatment prior to Week 48, will switch to annual PROM assessment.". The related footnote starting with the text "Patient assessments of pre-specified AEs" was corrected with the additional information that "Patients without PD who start subsequent anti-

		cancer treatment prior to Week 48 do not need any further PRO-CTCAE assessments.”.
Rationale for change		Assessments until PD are sufficient. The PGIC assessment is not needed at C1D1. For patients without PD who start subsequent anti-cancer treatment, annual PROM assessments are sufficient, and no further PRO-CTCAE assessments are needed.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, in the footnote starting with the text “EOT = End Of Treatment.”, the following sentence was added: “An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment.”
Rationale for change		Explain a special situation where an EOT visit could happen more than 21 days after the last cycle Day 1.
Section to be changed		**Flowchart**
Description of change		In Table 1 and Table 2, in the footnote starting with the text “Tumor assessment will be performed according to RECIST version 1.1.”, brain MRI at screening was removed.
Rationale for change		Brain MRI at screening is not needed.
Section to be changed		**Flowchart**
Description of change		In all flowcharts, a new footnote was added: “Cycle 1 Day 1 assessments (physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done during screening within 72 h prior to treatment administration and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline. A window (+3 d) is acceptable for scheduling Cycle 2 Day 1.”
Rationale for change		Make logistics less complex for the clinical site.
Section to be changed		**Flowchart**
Description of change		In Table 2, in the footnote about “Safety laboratory assessments”, the text was corrected to now read “Hematology and serum biochemistry laboratory tests must be performed within 72 h prior to Day 1 of each cycle.”
Rationale for change		Error corrected.

Section to be changed		**Flowchart**
Description of change		[redacted]
Rationale for change		
Section to be changed		**Flowchart**
Description of change		In Tables 1 and 3, wording of the footnote related to PK sampling for BI 907828 was modified to read "A more detailed overview of the exact timing for PK sample collection can be found in Appendix 10.1.
Rationale for change		The old wording was difficult to understand for the investigators.
Section to be changed		**1.2**
Description of change		[redacted]
Rationale for change		New data in the IB available.
Section to be changed		**1.4.2**
Description of change		1) Myelosuppression: information about hematological AEs was updated; guidance text on treatment options was moved. 2) Gastrointestinal AEs: information about gastrointestinal AEs was updated; guidance text on treatment options was moved to Section 4.2.1.
Rationale for change		New data available. Wrong location for treatment options – now available in Section 4.2.1.
Section to be changed		**1.4.3**
Description of change		Information on COVID-19 vaccines was updated.
Rationale for change		New information available.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**3.3.1**
Description of change		Criteria to assist with the differentiation of locally advanced vs. metastatic DDLPS were added.
Rationale for change		Unclarity about locally advanced vs. metastatic DDLPS was resolved.

Section to be changed		**3.3.2**
Description of change		Inclusion criterion #2 was changed to state that birth control needs to be applied “until 6 months and 12 days after last dose.”.
Rationale for change		!"#$ %&'(&)*+)*,*&. /-.&0-*1 *1&2345 6+% 7+8+%(9-:-.*1,**1&7(%,*-+.+6:+.*%,:&;*-+.6+% 3,/& ;,*-&.*)3()* 9&<3+.*1) ,6*&%1&,)* 7+)&⇒1&-.:/()-+. :%-*&%-1;) 9&&(;7,*&7 *+)*,*& (.*-/ <3+.*1) ,.7 ?@ 7,A) ,6*&%,)* 7+)&,) *1-)-) *1&/+.B&)*3,.7,*&7 :+.*%,:&;*-+.;&%-+7 ,) 7&):%-9&7 2&:*-+.C=@=@=D=
Section to be changed		**>,9/& D=D=@E**
Description of change		F+%*1&,9+%,*+%GA,/(&HI%&,*-.-.&J*1&(.-* 0,) :+%%&:*&7HIKL3-. IIM *1& 6+%3(/, 0,) :+%%&:*&7NO PQ4RHI%&,*-.-.&&'(,*-+. II=
Rationale for change		Q%%)+0%&%&%%&:*&7=
Section to be changed		**D=D=D**
Description of change		Q8:/()-+. :%-*&%-S<Cwas modified: “Previous or concomitant malignancies other than DDLPS or WDLPS, treated within the previous 5 years, except effectively treated non-melanoma skin cancers, carcinoma *in situ* of the cervix, ductal carcinoma *in situ*, or other malignancy that is considered cured by local treatment.”= Q8:/()-+. :%-*&%-S?.TE +%%&:*-+. HH;-&)L3KII= Q8:/()-+. :%-*&%-S?.?E,77-*-+. +6HIHVWor not yet achieved sustained viral response (SVR)II= Q8:/()-+. :%-*&%-S?.C 0,) 3+7-6-&7EHIN.+0. 1A;&%)&.)-*-G+*%A+.*%,-.7-:,*-+. *+*1&*%-,/ 7%(BJUVWI= Q8:/()-+. :%-*&%-S?.<E;(/3+.,%A &39+/-)3 0-*1-. <3+.*1) ;%-+%+%,.7+3-X,*-+. 0,) %&3+G&)7 ,. &8:/()-+. :%-*&%-+.= Y&0 &8:/()-+. :%-*&%-S?.ZEHIS*-G&9/&&7-.BJ)-B.-6-:,.* %-)[+61,&3+%%1,BI&&=J%&G-+())&G&%B&*%+-.*&)*-.9//&&7-.BJ%&G-+() 1,&3+%%1,B):*%+[&* ,.A *-3&W-J%(%%&.* 9/&&7-.B 7-)+%7&% U&=B= 1,&3+;1-/-,J G+. \-//&9%,.7 7-)&,)&W= Y&0 &8:/()-+. :%-*&%-S@THIS1A 1-)*+%A6J+% :+.:+3-*,.* :+.7-*-+. *1,*J -. *1& +;-.-+. +6 *1& -.G&)*-B,*+0%J(/7 :+3;%+3-)& *1&,*-&.*I) ,9-/-*A*+:+3;/A 0-*1 *1&*%-,+%.*&%6&0%&

		1&&G,/(,-+. +6*1&),6&*A,7 &66-:,:A+6*1& *%-,7%(BH
Rationale for change		#4: Allow for more exceptions. S?TBQ%%0,% :+%%&:*&7= S??E"&;,*-*-) 5 *%&,*3&-)*:+.)-7&%&7)(::&))6(/ 9,)&7 +. 2]# M,(:1 ;,*-&.*) ,%& &/-B-9/& S?CE>1&-.G&)*-B,*+)%+(/7 ,/)+ :1&:[6+% :+.*%,-.7-:,*-+.= S?<E4,*-&.*)0-*1 ;(/3+.,%A &39+/-)3 0-*1-. <3+.*1) ;%-+%+%,.7+3-X,*-+. ,%&&/-B-9/&= S?ZEMyelosuppression, particularly thrombocytopenia and neutropenia, is the main toxicity associated with BI 907828. Patients with bleeding events are at risk. S@TS//+0 *1&.G&)*-B,*+% &8:/(7& ;,*-&.*) 9,)&7 +. [redacted] +;-.-+. =
Section to be changed		D=D=C=?
Description of change		New exception was added: “An individual patient will discontinue trial treatment if: (…) The patient has radiological documentation of progressive disease by central independent review on the current treatment (see Section 5.1) with the exception of patients receiving doxorubicin, who may be offered cross-over to treatment with BI 907828.”
Rationale for change		>1-) &8:&;*-+.-) ,;;/-:,9/&=
Section to be changed		**4.1.4.2**
Description of change		In the sentence “CTCAE Grade 4 AEs with the exception of myelosuppressive AEs of CTCAE Grade 4 (…) for which targeted treatment options (…) are available”, the word “targeted” was deleted.
Rationale for change		The term “targeted treatment” is misleading in this context.
Section to be changed		**4.1.4.2 and Figure 4.1.4.2: 1**
Description of change		Algorithm for treatment pauses was clarified in the figure and in the describing paragraph below the figure.
Rationale for change		The old wording was difficult to understand for the investigators.

Section to be changed		**4.2.1**
Description of change		In the guidance text on the use of colony-stimulating factors, the sentence "However, their use as primary prophylaxis during the first treatment cycle in the dose escalation phase is prohibited." was deleted. Recommendations for prevention and treatment of nausea and vomiting were modified. Blood transfusions are allowed at any time during the trial when clinically indicated. Further limitations were removed.
Rationale for change		Trial 1403-0008 is not a dose escalation trial, the restriction during Cycle 1 was incorrect. Colony-stimulating factors can be used throughout the trial (including Cycle 1) in accordance with the ASCO guidelines. Introduction of a 2-drug treatment for nausea and vomiting according to ACSO / ESMO / MASCC NCCN. Allow for more flexibility concerning blood transfusions.
Section to be changed		**4.2.2.1**
Description of change		A new paragraph on anti-viral treatments for COVID-19 infection was added. Herbal preparations / medications and nutritional supplements are now allowed throughout the trial at the discretion of the investigator. [redacted]
Rationale for change		New information on treatment of COVID-19 infection available. Allowing herbal preparations / medications and nutritional supplements follows the patient-centric approach. The additional table was added based on a request by the Swedish health authority.

Section to be changed		**Table 4.2.2.1: 1**
Description of change		Concerning concomitant ritonavir treatment, a footnote was added that it is allowed from 72 hours after the administration of BI 907828 until 72 hours prior to the next administration.
Rationale for change		[redacted]
Section to be changed		**Table 4.2.2.1: 2**
Description of change		[redacted]
Rationale for change		Cannabidiol is no longer a restricted comedication during treatment with doxorubicin.
Section to be changed		**4.2.2.3**
Description of change		Update to contraception requirements.
Rationale for change		!"#$ %&'(&)*+,77 , ;+*&.*-,/%-)[+6%&7(:&7 6&%*-/-*A+*13,/&) ,.7 6&3,/&;,%*-:-;,.*)J 01-:1 :+(/7 9&;&%3,.&.*J,.7 *+)*,*&. /-.& 0-*1 *1&2345 6+%7+8+%(9-:-.*1,**1&7(%,*-+. +6:+.*%,:&;*-+.6+%3,/& ;,*-&.*) 3()* 9& < 3+.*1) ,6*&%1&,)* 7+)&=
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Rationale for change		4,*-&.* :&.*%-: ,;;%+,:1 *1,* ,//+0) *+)*+; 6(%*1&,%3;/-.B -6)(66-:-&.*7,*, ,%&+//&:*&7=
Section to be changed		**5.6.1**
Description of change		The list of pre-defined AEs assessed by the PRO-CTCAE Item Library was corrected.
Rationale for change		Cough and fatigue were missing as pre-defined AEs, constipation and hair loss had to be deleted as pre-defined AEs.
Section to be changed		**5.6.2**
Description of change		Wording was changed to “The investigator (or a designee) will complete the AQA (…)”.
Rationale for change		Allow for more flexibility.

Section to be changed		**6.1 and 6.2.3.1**
Description of change		A new sentence was added: "An EOT visit beyond 21 days is possible for patients who delayed their next dose due to toxicity and only then decided to stop treatment.".
Rationale for change		Explain a special situation where an EOT visit could happen more than 21 days after the last cycle Day 1.
Section to be changed		**7.2.4**
Description of change		In the description of the planned analyses for HRQoL secondary endpoints, more details were added. A reference to Section 7.2.6 was added, where the analyses of secondary safety endpoints are described.
Rationale for change		Provide more information about the planned analyses. Make it easier to find the analyses for secondary safety endpoints.
Section to be changed		**Tables 10.1: 1 and 10.1: 2**
Description of change		Pre-dose ECG consistently added for all cycles, just before drug administration. Footnote was modified to make clear that pre-dose (planned time, PTM -0:05) is within 1 hour before drug administration.
Rationale for change		Some pre-dose ECG entries were missing. The old text about the timing of pre-dose was difficult to understand for the investigators.
Section to be changed		**10.3**
Description of change		[redacted]
Rationale for change		The additional section contains a table that was added based on a request by the Swedish health authority.
Section to be changed		**General**
Description of change		Wording throughout the document was harmonized: the interim futility analysis will happen around the end of Phase II; the sample size re-estimation will happen around the end of Phase II; all patients numbers in the CTP are estimates.
Rationale for change		The time points and numbers are approximations.

Section to be changed		**General**
Description of change		List of abbreviations was updated; list of references was updated; typos were removed, and grammar was corrected.
Rationale for change		Improve the readability of the document.

11.3 GLOBAL AMENDMENT 3

Date of amendment		26 Jan 2023
EudraCT number **EU number**		2021-002392-20
BI Trial number		1403-0008
BI Investigational Medicinal Product(s)		BI 907828
Title of protocol		Brightline-1: A Phase II/III, randomized, open-label, multi-center study of BI 907828 compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Synopsis**
Description of change		Trial design, number of patients, and statistical methods updated to reflect a higher overall sample size and PFS event rate.
Rationale for change		The trial is enrolling much faster than anticipated.
Section to be changed		**1.2**
Description of change		Changed “2” ongoing trials to “several” ongoing trials.
Rationale for change		New trials have started in the meantime.
Sections to be changed		**2.1.2, 3.3.4.1, 4.1.2, 7.1, 7.2.1, 7.3**
Description of change		Wording about the timing of the assessment of PFS at the interim futility analysis was modified to say that it will happen at **approximately the same time as the end of Phase II**.
Rationale for change		The trial is enrolling much faster than anticipated, this affects the timing of the analysis.
Section to be changed		**3.1, 7.1, 7.2.3, 7.2.4, 7.2.8, 7.4, 7.5, 10.2.1**
Description of change		Trial design, number of patients, and statistical methods updated to reflect a higher overall sample size and PFS event rate.
Rationale for change		The trial is enrolling much faster than anticipated.

Section to be changed		**4.2.2.1**
Description of change		[redacted]
Rationale for change		New information available.
Section to be changed		**4.2.2.3**
Description of change		Text modified to read: "WOCBP must use a highly effective method of birth control (as outlined in the patient information) per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation, and until 6 months and 12 days after the last dose of **BI 907828** (calculated as the period of relevant systemic exposure (5 half-lives plus 6 months) **or until 6 months after the last dose of doxorubicin**."
Rationale for change		Clarification.
Section to be changed		**5.2.3**
Description of change		New text added in Table 5.2.3: 1: "pH, glucose, erythrocytes **(hemoglobin / blood)**, leukocytes, protein, and nitrite analyzed by dipstick (semi-quantitative measurements)"
Rationale for change		Clarification.
Section to be changed		**7.2.4**
Description of change		Corrected text: "SD lasting less than 42 days and without evaluable response thereafter will be listed as "**Not evaluable"**.
Rationale for change		Correction.

11.4 GLOBAL AMENDMENT 4

Date of amendment		05 Dec 2023
EudraCT number **EU number**		2021-002392-20
BI Trial number		1403-0008

BI Investigational Medicinal Product(s)		BI 907828 (INN: brigimadlin)
Title of protocol		Brightline-1: A Phase II/III, randomized, open-label, multi-center study of brigimadlin (BI 907828) compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**All sections**
Description of change		Change from: BI 907828 To: Brigimadlin
Rationale for change		Introduction of the international nonpropietary name (INN) for BI 907828
Section to be changed		**Title page, Synopsis**
Description of change		The coordinating investigator information was updated
Rationale for change		The coordinating investigator changed from [redacted]
Section to be changed		**Flowchart (Table 1) footnote 11** **Flowchart (Table 2) footnote 11**
Description of change		The requirement to have an echocardiography or MUGA scan assessment within 7 days prior to treatment was removed
Rationale for change		Deleted to be consistent with Section 5.2.5.1, which stated that the assessment does not need to be repeated at the screening visit if there is a valid result with 28 days prior to treatment start.
Section to be changed		**Flowchart (Table 2)**
Description of change		Addition of ±3 d window for the EOT visit
Rationale for change		Allow flexibility
Section to be changed		**Flowchart (Table 3)**
Description of change		Addition of sample for “Blood GDF-15” at the EOT visit
Rationale for change		Added to be consistent with the assessment schedule in Table 10.1: 2
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		

Description of change		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		**3.3.3**
Description of change		Changed from: Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval (see also Section 4.2.1). To: Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval.
Rationale for change		The reference to Section 4.2.1 was irrelevant
Section to be changed		**3.3.4.1**
Description of change		Statement added: If the patient has radiological progression by investigator assessment while tolerating trial treatment, the treatment should be continued. The decision to withdraw treatment must be based on documentation of progressive disease according to RECIST version 1.1 based on central independent review.
Rationale for change		Clarification
Section to be changed		**4.1.3**
Description of change		Statement added: Palliative radiotherapy is permitted; however, the irradiated area cannot be used for further tumor response assessment.
Rationale for change		Clarification
Section to be changed		**4.1.4**
Description of change		Deletion of “pharmacy manual”
Rationale for change		Information is provided in the ‘Medication Handling Instruction’, not a pharmacy manual

Section to be changed		**4.1.4.1**
Description of change		Changed from: Doxorubicin will be administered according to institutional guidelines and the provided pharmacy manual as an intrvenous injection or as an infusion. To: Doxorubicin will be administered according to institutional guidelines and SmPC/US Package Insert as an intravenous injection or as an infusion.
Rationale for change		There is no pharmacy manual for this trial
Section to be changed		**4.1.4.2**
Description of change		Statement added: Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle.
Rationale for change		Clarification
Section to be changed		**4.1.6**
Description of change		Statement added for brigimadlin: Investigator information is omitted from the labels due to use of an IRT system. Statement added for doxorubicin: Investigator information is omitted from the labels due to use of an IRT system. The visit number is not relevant for the label of doxorubicin as the product will remain at the clinical site.
Rationale for change		Added to fulfill the requirements of Annex 6 becoming effective with the new CTR process
Section to be changed		**4.2.2.1 (Table 4.2.2.1: 1)**
Description of change		Footnote added: For fentanyl, transdermal patches are permitted
Rationale for change		Clarification
Section to be changed		**4.2.2.3**
Description of change		The contraception requirements for male patients on doxorubicin was changed from 6 months to 3 months and 10 days. For female patients it was changed from 6 months to 6 months and 10 days
Rationale for change		The change was made to reflect an update in the SmPC
Section to be changed		**5.3.1**
Description of change		Statement added: Plasma samples from the trial may be used for the measurement of unbound brigimadlin

		concentrations. For this purpose, pooled plasma samples may be used. Results may be included in a separate report.
Rationale for change		Clarification
Section to be changed		**6.2.3.2**
Description of change		Statement added: In cases where the EOT may be after the EOR period, the EOT and EOR can be done as a single visit.
Rationale for change		Clarification
Section to be changed		**6.2.3.3**
Description of change		***Changed from:*** Data will be collected every 12 weeks (±7 days) and may also be collected at additional timepoints when a snapshot of data is required (e.g. at the time of analysis). ***To:*** ***Survival*** data will be collected every 12 weeks (±7 days) starting from last contact (EOT and/or EOR) and may also be collected at additional timepoints when a snapshot of data is required (e.g. at the time of analysis).
Rationale for change		Clarification
Section to be changed		**Synopsis, 7.1**
Description of change		Statement added: If statistical significance is obtained for PFS but not for ORR, then OS will continue to be followed up until the pre-specified numbers of OS events are met at the end of Phase III and then analyzed without being formally tested.
Rationale for change		Clarification
Section to be changed		**Synopsis**, **7.2.3**, **7.2.8**, **7.5**
Description of change		[redacted]
Rationale for change		The primary analysis of PFS will only be analyzed when the number of events has been reached.
Section to be changed		**7.2.4**
Description of change		Statement added: Any assessments done in compliance with the pre-specified (-)7-day assessment window will also be accounted for as within the 42-day duration.
Rationale for change		Clarification
Section to be changed		**7.3 (Table 7.3: 1)**
Description of change		Changed from:

		Patient without death or patient with death after second performed radiological assessment To: Patient without death or patient with death after second planned radiological assessment
Rationale for change		Correction
Section to be changed		**7.3 (Table 7.3: 1)**
Description of change		Changed from: Date of last radiological assessment prior to missed assessments To: Date of last radiological assessment prior to missed radiological assessments
Rationale for change		Correction
Section to be changed		**8.7**
Description of change		Statement added: In EU/EEA countries, the trial is sponsored by Boehringer Ingelheim International GmbH, [redacted]
Rationale for change		The clinical trial regulation requires trial protocol to state trial sponsor name and address, but the current protocol template does not include the information.
Section to be changed		**General**
Description of change		List of abbreviations was updated; typos were removed, and grammar was corrected.
Rationale for change		Improve the readability of the document.

11.5 GLOBAL AMENDMENT 5

Date of amendment		02 May 2024
EudraCT number **EU number**		2021-002392-20
BI Trial number		1403-0008
BI Investigational Medicinal Product(s)		BI 907828 (INN: brigimadlin)
Title of protocol		Brightline-1: A Phase II/III, randomized, open-label, multi-center study of brigimadlin (BI 907828) compared to doxorubicin as first line treatment of patients with advanced dedifferentiated liposarcoma
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Flowcharts (Tables 1, 2, and 3)**
Description of change		Addition of (± 7 d) window for FU for PD
Rationale for change		Allow flexibility
Section to be changed		**Flowcharts (Tables 1, 2, and 3)**
Description of change		Addition of (± 7 d) window for FU for survival
Rationale for change		Visibility and consistency; the window was in place, but it was not in the column header of flowcharts.
Section to be changed		**1.4.2**
Description of change		[redacted]
Rationale for change		
Section to be changed		**4.1.4.1**
Description of change		Addition of: (in case of platelet transfusion after the last drug administration, this criterion must be met in a measurement taken at least 72 hours after the last platelet transfusion)
Rationale for change		Update of guidance
Section to be changed		**4.2.1**
Description of change		Removed: In case of long-lasting thrombocytopenia (i.e. no recovery to $\geq 75.0 \times 10^9$/L after at least 4 weeks from the nadir), a hematology workup should be considered at the investigator's discretion including bone marrow cytology, platelet volume, and hematologist advice for appropriate therapy and follow-up.

Rationale for change		Update of guidance
Section to be changed		**4.2.1**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**4.2.1**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**4.2.2.1**
Description of change		[redacted]

Rationale for change		Update of guidance
Section to be changed		**4.2.2.1**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**4.2.2.3**
Description of change		Addition of: The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives and experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.
Rationale for change		Update of guidance
Section to be changed		**Table 5.2.3: 1**
Description of change		Change from: (if CK is elevated, then *CK-MB [cardiac], Troponin I or T, and myoglobin should be reactively tested).* To: CK (if CK is elevated, then *patient should be further evaluated according to local standard of care).*
Rationale for change		Update of guidance
Section to be changed		**General**
Description of change		List of abbreviations and references was updated; typos were removed, and grammar was corrected.
Rationale for change		Improve the readability of the document.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial [redacted]	[redacted]	03 May 2024 17:25 CEST
Approval-Clinical Program [redacted]		03 May 2024 17:47 CEST
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