

Clinical Trial Protocol

Phase I/II trial of meclofenamate in progressive MGMT-methylated glioblastoma under temozolomide second-line therapy (MecMeth/ NOA-24)

Version 2.0, 02.07.2021

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Document History

Version Number	Date of Issue	Summary of Changes
2.0	02.07.2021	Revision of the following sections 1 and 2: revision according to the main text 9: revision of exclusion criterion 4, 6, 8, 14, and 17; deletion of oral contraceptives for birth control 11: addition of section 11.1.1 – 11.1.3 and definition of permitted anticoagulants and their dosage 12: addition of a mandatory HIV Test and a whole skin examination; correction of inconsistencies regarding pregnancy testing and hepatitis B and C serology 13: addition of a trial termination criterion and definition of the regular end of trial as LPLV 14: Definition of the IB as RSI and addition of Sponsor reporting requirements (all SAR are reported as SUSAR)

Protocol Approval Signatures

Sponsor/ Sponsor Delegated Person (SDP)

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Date

Signature

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Date

Signature

Investigator Agreement Page

Please provide institution's / clinic's
stamp here

By my signature below, I confirm that I have read, understood and agree to adhere to all conditions, instructions and restrictions as specified in this Clinical Trial Protocol.

I will discuss the Clinical Trial Protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the clinical trial.

I confirm that I and my colleagues will conduct this clinical trial in compliance with the Declaration of Helsinki, the ICH-GCP guidelines, and that I will abide by the national laws and regulations.

Furthermore, I and my colleagues commit ourselves not to commence subject enrollment before the authorization of the authorities, the acceptance by the relevant and responsible Ethics Committee and the legally valid conclusion of contract by the authorized representation of my institution concerning this clinical trial.

I recognize that any changes in the protocol must be approved by the Sponsor/Sponsor Delegated Person (SDP), the Ethics Committee and, if applicable, the respective authority before implementation except when necessary to eliminate hazards to the subjects or when changes involve only logistical or administrative aspects of the clinical trial.

Under my supervision I will allocate copies of this Clinical Trial Protocol and possible updates as well as access to all information regarding the carrying out of this clinical trial at the disposal of my colleagues; in particular, I will promptly forward all information from the Sponsor/Sponsor Delegated Person (SDP) in relation to pharmaceutical safety (SUSAR) to my colleagues.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without prior written consent of the Sponsor/Sponsor Delegated Person (SDP).

The investigational medicinal products will be used only for the purpose of the clinical trial.

Principle investigator:

Name, first name (print)

Signature

Date

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1 Synopsis

Clinical trial title	Phase I/II trial of meclofenamate in progressive MGMT-methylated glioblastoma under temozolomide second-line therapy
Trial short title	MecMeth/ NOA-24
Trial Code	NEU-201901
EudraCT No.	2021-000708-39
Phase of trial	I/II
Indication	Adult patients with IDHwt, MGMT promotor methylated glioblastoma at first relapse
Trial Design	Prospective, open-label, randomized, multicenter phase I/II study
Summary	<p>Glioblastoma (GBM) is the most frequent and malignant primary brain tumor. Even in the prognostically favourable MGMT-methylated subgroup treated with temozolomide (TMZ), survival after relapse is short (12 months). Thus, there is a high medical need for improved survival-prolonging second-line therapies. Preclinical results show that meclofenamate (MFA), originally developed as a nonsteroidal anti-inflammatory drug (NSAID), sensitizes GBM cells to TMZ-induced toxicity via inhibition of connexin43 and reduction of tumor microtubes. The MecMeth/NOA-24 trial brings the concept of combined MFA/TMZ therapy to clinical application. Phase I (6-14 patients, 2 dose levels of MFA + standard dose TMZ) evaluates safety and feasibility and determines the dose for the randomized phase II (2 x 30 patients) with primary endpoint progression-free survival. If results of phase II provide indications for efficacy, further exploration in phase III and integration into medical practice could be envisioned.</p>
Investigational medicinal product	<p>Trade Name: Meclofenamate</p> <p>Substance: Meclofenamate sodium (MFA)</p> <p>Manufacturer: Mylan Pharmaceuticals Inc.</p>
Dose and Mode of Application	<p>Mode of Application: Oral</p> <p>Dose (in addition to standard TMZ (150-200 mg/m²/d days 1-5/28))</p> <p>Phase I:</p> <ul style="list-style-type: none"> • Level 1: 2 x 100 mg qd • Level 2: 2 x 50 mg daily or 2 x 200 daily depending on the incidence of dose-limiting toxicities in level 1 <p>Phase II: daily MFA at the dose determined in phase I (in addition to standard TMZ)</p> <p>In phase I and II, MFA treatment starts within 7 days of inclusion in the trial and not later than the start of the first course of the standard TMZ therapy.</p>
Control intervention Phase II	Standard oral TMZ 150-200 mg/m ² /d applied in each 28 day course on day 1-5

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<p>Duration of therapy and follow-up for an individual patient</p>	<p><u>Duration of intervention per patient (Phase I and II):</u> 224 days at maximum (in case of postponement of the following TMZ cycle due to hematotoxicity, MFA treatment will be continued and expanded to a maximum of 250 days) OR until tumor progression OR until unacceptable toxicity attributable to MFA (CTCAE5 grade 4 seizures; grade 3 for any other organ toxicity, grade 4 myelotoxicity for >14 days) OR until definitive termination of standard TMZ, whatever comes first.</p> <p><u>Follow-up per patient phase I:</u></p> <ul style="list-style-type: none"> • for determining DLT: 8 weeks after the first intake of MFA • for AE recording: at least 8 weeks, if MFA is taken longer than 8 weeks until day 3 after the last intake of MFA (maximum: 224 days + 3 days = 227 days) • for recording of survival parameters: <ul style="list-style-type: none"> <i>if phase II starts:</i> until end of the entire study (phase I + phase II) which will be reached when the following 2 requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days). <i>In case phase II is never started,</i> survival parameter recording is concluded when the following 2 requirements are fulfilled for phase I patients: (1) at least 6 months after inclusion of the last patient AND (2) at least 3 days after definite termination of MFA intake in all phase I patients <p><u>Follow-up per patient phase II:</u></p> <ul style="list-style-type: none"> • End of study and of follow-up in the entire trial will be reached when BOTH of the following requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in all patients receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).
Objectives	Endpoints
Phase I	
Primary	
<p>The primary objective is to determine toxicity of MFA therapy in addition to standard TMZ and, on this base, determine the daily MFA dose to be recommended for phase II.</p>	<ul style="list-style-type: none"> • Incidence of dose-limiting toxicities (DLTs) during the first 8 weeks/56 days of MFA treatment.
Secondary	
<p>To determine the efficacy of MFA therapy in addition to standard TMZ throughout the trial.</p>	<ul style="list-style-type: none"> • Progression-free survival (PFS) as measured from the inclusion into the trial until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center.

	<ul style="list-style-type: none"> Analysis of PFS according to post hoc central reference neuroradiological assessment. Overall survival as measured from the day of inclusion into the trial
To assess the safety and tolerability of MFA therapy in addition to standard TMZ throughout the trial.	<ul style="list-style-type: none"> Assessment of safety beyond 8 weeks MFA treatment: Toxicity, i.e. continuous monitoring of AE/SAE/SUSARs
To evaluate the clinical effect of MFA therapy in addition to TMZ and the development of quality of life throughout the trial.	<ul style="list-style-type: none"> Karnofsky performance score (KPS), Quality of life (QoL) throughout the trial and Mini Mental state examination (MMSE).
Phase II	
Primary	
Efficacy of MFA therapy in addition to standard TMZ therapy	<ul style="list-style-type: none"> Progression-free survival (PFS) as measured from the day of randomization until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center. In a sensitivity analysis, the PFS analysis does also include patients from phase I who received MFA at the same dose as applied in phase II (PFS measured from day of trial inclusion)
Secondary	
To evaluate the efficacy throughout the trial.	<ul style="list-style-type: none"> Analysis of PFS according to post hoc central reference neuroradiological assessment. PFS analysis including both patients from phase II and patients from phase I who received MFA at the same dose as applied in phase II (PFS measured from day of trial inclusion). Overall survival (OS) as measured from the day of randomization in phase II. A further sensitivity analysis, will also include patients from phase I who received MFA at the same dose as applied in phase II. In these patients, OS starts from day of inclusion into the trial.
To assess the safety and tolerability of MFA therapy in addition to standard TMZ throughout the trial.	<ul style="list-style-type: none"> Assessment of safety: Toxicity, i.e. continuous monitoring of AE/SAE/SUSARs until 3 days after end of therapy
To evaluate the clinical effect of MFA therapy in addition to TMZ and the development of quality of life throughout the trial.	<ul style="list-style-type: none"> Karnofsky performance score (KPS), Quality of life (QoL) throughout the trial and Mini Mental state examination (MMSE).
Subject Number	To be allocated to trial (up to n=74); Phase I up to n=14 (6-12+2 dropouts) Phase II n=60
Inclusion Criteria	For Phase I and II 1. First relapse after first-line therapy with radiotherapy (RT) and alkylating chemotherapy, > 3 months after last chemotherapy application and >6 months after end of RT. Drug therapy and/or radiotherapy for first relapse

	<p>treatment not yet started.</p> <ol style="list-style-type: none"> 2. Tumor progression according to RANO criteria 3. Written informed consent 4. Cognitive state to understand rationale and necessity of study therapy and procedures 5. MGMT promotor-methylated (MGMTmeth), IDH wildtype glioblastoma (GBM) or gliosarcoma confirmed with histology of the primary resection 6. Age > 18 years 7. Karnofsky performance score (KPS) ≥60%; 8. Life expectancy > 6 months 9. Adequate bone marrow reserve (WBC >3 G/nl, platelets >100 G/nl) 10. Adequate liver function (bilirubin <1.5 x ULN; ASAT /ALAT <3 x ULN, creatinine < 1.5 x ULN) 11. Patient compliance and geographic proximity that allow adequate follow up 12. Male and female patients with reproductive potential must use an approved contraceptive method during and for 3 months after the trial (Pearl index <1%) 13. Pre-menopausal female patients with childbearing potential: a negative serum pregnancy test (beta-HCG) must be obtained prior to treatment start <p>Additional criterion ONLY for phase I:</p> <ol style="list-style-type: none"> 14. Resection at first relapse not yet performed; according to the local treating neurosurgeon and the documented decision of local neurooncological tumor board, resection of the tumor is clinically indicated and can be safely deferred until day 7-10 after initiation of MFA/TMZ therapy.
<p>Exclusion Criteria</p>	<p>For Phase I and II</p> <ol style="list-style-type: none"> 1. Indication for hematotoxicity in first-line therapy not allowing TMZ starting dose 150 mg/m²/d 2. Skin or liver toxicity >CTCAE5 grade 1 in first-line therapy 3. History of gastrointestinal bleeding or gastroduodenal ulcer, active gastritis 4. History of asthma, urticaria or allergic-type skin reactions to NSAID 5. Prior malignancy other than glioma 6. History of confirmed or suspected hypersensitivity (delayed type and immediate type, inclusive of anaphylactic reaction) to any background/standard TMZ drug product or one of its ingredients of the chosen product, or to cyclooxygenase inhibitors (“NSAIDs”), or to any ingredient of meclufenamate drug product 7. History of disease with poor prognosis 8. Severe coronary heart disease (esp. after coronary artery bypass graft or history of myocardial infarction), severe heart failure 9. Known HIV infection, active hepatitis B or C 10. Breastfeeding or pregnant 11. Unable to undergo contrast-enhanced MRI (i.e. contrast allergy, implants, etc). 12. Treatment in another clinical trial with therapeutic medical intervention

	<p>or use of any other investigational agent during the trial or within the 30 days before enrollment</p> <p>13. Medication with a drug that is not allowed in conjunction with MFA intake and cannot be discontinued: i.e. lithium, methotrexate, etc.</p> <p>14. Patients with active bleeding, bleeding diathesis, antiplatelet therapy or anticoagulant therapy except for the following anticoagulants which are permitted for low-dose thrombosis prophylaxis up to the dosage specified here: unfractionated heparin 7,500 IU BID or 5,000 IU TID; low molecular weight heparin e. g. enoxa-parin 40 mg/d; fondaparinux 2.5 mg/d; danaparoid sodium 750 IU BID; argatroban IV route thrombin time < 70 s; vitamin-K-antagonist INR < 1.8; dabigatran 150 mg BID; rivaroxaban 10 mg/d; edoxaban 30 mg/d; epixaban 2.5 mg BID This restriction is due to a potentially increased risk of GI ulcers with subsequent bleeding under MFA therapy.</p> <p>15. Patients with medically diagnosed hereditary Galactose Intolerance, complete lactase deficiency or confirmed Glucose-Galactose-Malabsorption</p> <p>16. Medical History of gastrointestinal Resection of any kind that may potentially alter the absorption of the investigational study drug, according to investigators judgement</p> <p>17. The presence of any other concomitant severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac (including coronary artery bypass graft), or psychiatric disease, or signs and symptoms thereof, that may affect the subjects participation in the study, according to investigators judgement</p>
<p>Discontinuation rules for study treatment (see also section 13.3)</p>	<p>For the individual patient, MFA therapy within the trial will be stopped if one of the following criteria applies</p> <ol style="list-style-type: none"> 1. Unequivocal MRI signs of disease progression according to RANO criteria 2. CTCAE5 grade 4 myelotoxicity/hematotoxicity for >14 days in courses 1 and 2 related to MFA treatment 3. CTCAE5 grade 3+ for any other organ toxicity related to MFA treatment except for asymptomatic laboratory changes CTCAE5 grade 3 4. Definitive termination of standard TMZ therapy 5. Any event that leads to a delay in TMZ dosing lasting > 8 weeks from the beginning of the previous course of TMZ 6. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued meclofenamate application. 7. Pregnancy 8. Lack of compliance of the subject (e.g. taking prohibited medication) 9. Significant protocol violations <p>1. events probably related to the tumor resection/perioperative treatment or the underlying disease will not lead to discontinuation</p>
<p>Discontinuation rules Phase I (see also section 13.2)</p>	<p>The recommended MFA dose for phase II is the highest MFA dose that does not lead to DLT in more than 1/6 patients during the first 8 weeks of MFA therapy. If even the lowest dose level of 2 x 50 mg daily MFA leads to DLT in more than 1/6 patients, phase II of the trial cannot be performed.</p>

<p>Trial Procedures (see also section 2 and section 12)</p>	<p>The screening visit must be completed within 5 days to baseline visit. Study-specific treatment has to start within 7 days after completion of Baseline visit. MFA treatment start coincides with the beginning of TMZ standard therapy. In Phase II, tumor re-resection (OP visit day 7-10) is optional. If resection is performed under MFA therapy, the last dose of MFA prior to resection is applied on the morning of the resection day and the resection has to be planned in a way that ensures that tumor material for determination of MFA levels can be obtained within 2-4h after last MFA intake. End of treatment is reached three days after last MFA intake (phase I and experimental arm of phase II) or on day 31 of the last TMZ cycle (standard arm of phase II) or in case of MFA discontinuation. Until end of study is reached, patients are followed-up every eight weeks.</p>
<p>Investigational trial sites</p>	<p>Phase I: n=10 Phase II: n=15</p>
<p>Statistical Rationale</p>	<p>Phase I: Analysis of the primary endpoint toxicity</p> <ul style="list-style-type: none"> • Toxicity according to CTCAE 5 in all patients of phase I • DLT for each dose level is defined as any CTCAE5 grade 3/4 organ toxicity or grade 4 hematotoxicity > 2 weeks during the first 8 weeks of MFA; events probably related to the tumor resection and/or perioperative treatment or to the underlying disease are not regarded as DLT. • 2 dose levels are explored: starting level of 100 mg twice daily, second level 200 mg twice daily is explored if at starting level 1/6 patient or less experienced DLT, second level 50 mg twice daily is explored if at starting level more than 1/6 patients experienced DLT. The recommended dose for phase II is the highest dose explored with a DLT rate not higher than 1/6 patients • Dropout patients not being evaluable for DLT will be replaced. Patients experiencing DLT will be removed from MFA but not from the trial; also, TMZ therapy can go on <p>Phase II: Analysis of the primary endpoint PFS</p> <ul style="list-style-type: none"> • Progression-free survival (PFS) as measured from the day of randomization until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center. PFS is analyzed using a two-sided logrank test and a Cox regression analysis to estimate the hazard ratios in the ITT population • Patients in phase I receiving the MFA at the same dose as it is used in phase II will be included (in addition to the 60 randomized patients) in the intention-to-treat analysis of phase II <p>Analyses of secondary endpoints common in both phase I and II</p> <ul style="list-style-type: none"> • PFS analysis including both patients from phase II and patients from phase I who received MFA at the same dose as applied in phase II (PFS measured from day of trial inclusion). • Post hoc analysis of the primary endpoint PFS as reviewed centrally by a neuroradiologist (Department of Neuroradiology, Univ. Hospital Bonn) blinded to the treatment protocol (two-sided logrank test and Cox regression analysis to estimate the hazard ratios in ITT population of phase II + all patients receiving MFA at the phase II dose in phase I.

	<ul style="list-style-type: none"> • Determination of intratumoral levels of MFA and one metabolite. MFA levels are determined in tumor samples resected on day 7-10 after start of MFA medication (resection under MFA treatment obligatory in phase I, optional in phase II). The resection has to take place within 2-4 hours of intake of the last MFA dose. • Overall survival calculated from inclusion into the trial. Comparison between groups using a two-sided logrank test, Kaplan-Meier plots and a Cox regression analysis for estimated hazard ratios. Target population: ITT of phase II + all patients receiving MFA at the phase II dose in phase I. • Cox regression analyses for common prognostic factors (Age, KPS) in both arms and subgroup analyses for categorized common prognostic factors are also included. • Descriptive statistics of AEs, dose reductions of TMZ, delay of TMZ therapy ins subsequent courses and premature withdrawal od study therapy (incl. reason for it) will be performed • Analysis of QoL and KPS over time until the end of the trial.
Trial Duration	<p>Phase I</p> <ul style="list-style-type: none"> • Recruitment period: 10 months • First patient in to last patient out: 12 months for determination of DLT; MFA treatment continues for a maximum of 224 days and follow-up continues until the conclusion of the entire trial, i.e. after a maximum of 30 months + 3 days, see “Duration of therapy and follow-up”)) <p>Phase II</p> <ul style="list-style-type: none"> • Recruitment period: 10 months • First patient in to last patient out: 18 months + 3 days <p><u>Duration of the entire trial (first patient in phase I to last patient out phase II: 30 months + 3 days</u></p>
Accompanying scientific program	<ul style="list-style-type: none"> • To evaluate the bioavailability of MFA, the intratumoral levels of MFA and metabolite I is measured in the tumor resected after the start of MFA treatment. • MFA and metabolite I levels are measured in serum taken on day 1 2h after first MFA intake and in the morning of the resection day and 2h, 4h, 6h, 8h thereafter. Serum sampling 2h after morning intake between day 1 and resection day is optional. • Histological, immunohistochemical, molecular and electrophysiological assessments of fresh frozen, PFA-fixed, and FFPE tumor tissue samples obtained during the trial for effects of MFA/TMZ vs. TMZ mono, for example number of TMs per cell, number of TM-based cell-cell connections per cell, TM-length, 3D-reconstruction of TM-based network architecture, intercellular gap-junction-mediated cytosolic traffic (calcein dye single cell injections), MEA und Calcium imaging, connectivity score

	<ul style="list-style-type: none">• Analysis of blood samples acquired at all MRI timepoints for factors potentially correlating with tumor progression. Analysis of extracellular vesicles is planned, biobanking of residual material for further analyses such as proteomic and miRNA profile.• Histological, immunohistological and molecular assessments of FFPE and fresh frozen tumor tissue samples obtained from resections prior, during and or after the end of trial therapy: analyses for factors related with prognosis, response to therapy (MFA/MTZ or TMZ), immunological reaction against the tumor.• Exploratory neuroradiological analysis with all MRIs documenting the course of the disease of the study patients: analysis of MRI parameters that could be associated with prognosis or response to therapy. This does also include the use of artificial intelligence (AI) algorithms.• If available, EEG or MEG analysis at baseline, on day 28 after first MFA or TMZ intake (in phase II both arms) and at the first follow-up visit after discontinuation of MFA (MFA arm only)
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2 Summary of Study Procedures

	Screening Visit	Baseline Visit	Treatment phase						End of Therapy	Follow-up	End of Study	Un-scheduled Visit
			MFA start Day 1	Day 7-10	Day 28 (±3)	Day 56 (±3) *	Start of Cycle 3 (±7) *	Start of Cycle 4-8 (±7)				
Time Points (accepted deviation)	within 5 days prior to visit 1	within 7 days prior to treatment start							** (+3)	every 8 weeks (±3)	***	
Visit Number	0	1	2.1	OP	2.2	DLT	2.3	2.4 - 2.8	3	4.1 - 4.X	5	UV
Study eligibility												
Informed consent for trial participation	x											
Assessment of Inclusion / Exclusion criteria	x	x										
demographics, medical history	x											
Clinical examination												
Vital signs	x	x	x				x		x	x	x	x
Physical and neurological examination, and whole skin examination including adjacent transitional mucosal and oropharyngeal	x	x	x				x		x	x	x	x
Concomitant medication	x	x	x				x		x	x	x	x
Steroid need	x	x					x		x	x	x	x
Daily TMZ dose in the last 4 weeks							x		x			
Karnofsky score		x	x		x	x		x ¹	x	x		x
QoL: EORTC C30 and BN20		x	x				x	x ¹	x	x	x	
Further tumor therapy										x	x	x
MMSE		x							x			

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	Screening Visit	Baseline Visit	Treatment phase						End of Therapy	Follow-up	End of Study	Un-scheduled Visit
Time Points (accepted deviation)	within 5 days prior to visit 1	within 7 days prior to treatment start	MFA start Day 1	Day 7-10	Day 28 (±3)	Day 56 (±3) *	Start of Cycle 3 (±7) *	Start of Cycle 4-8 (±7)	** (+3)	every 8 weeks (±3)	***	
Visit Number	0	1	2.1	OP	2.2	DLT	2.3	2.4 - 2.8	3	4.1 - 4.X	5	UV
Laboratory tests												
Pregnancy test (beta-HCG in serum)		x			x				x			
HIV, Hepatitis B and C serology		x										
Differential hematology		x			x				x	x		x
Chemistry2		x			x				x	x		x
CRP		x			x				x	x		x
Safety												
Evaluation of preexisting conditions in analogy to CTCAE V5		x										
(S)AE evaluation		x			x				x	x	x	x ⁷
MRI and response assessment												
Gd-MRI		x ³			x ¹					x		x ⁸
Phase I												
DLT evaluation					x	x						
Phase II												
Randomization		x										
Accompanying scientific program												
Asservation of tumor material				x ⁴								
Blood samples for PK			x ⁵	x ⁵								
Blood samples biochemistry		x			x ¹					x		
optional EEG or MEG analysis		x			x					x ⁶		

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* DLT visit will only be performed in Phase I. In Phase I visit 2.3 is only performed additionally, if the start of cycle 3 is prolonged for more than 3 days after the DLT visit. All patients in phase II have visit 2.3

** EoT: End of treatment is reached 3 days after last MFA intake (phase I and experimental arm of phase II) or on day 31 of the last TMZ cycle (standard arm of phase II)

*** End of study and of follow-up in the entire trial will be reached when BOTH of the following requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days)

¹every 8 weeks: progression assessment, Karnofsky score and Quality of Life, blood samples

²Na, K, creatinine, ASAT, ALAT, bilirubin

³gadolinium-enhanced MRI obtained prior to inclusion/randomization can be used as baseline MRI if the interval between this MRI and start of study therapy is shorter than 21 days. In patients who have undergone re-resection prior to randomization (only possible in phase II) the MRI used as baseline MRI has to be a postoperative MRI.

⁴Relapse tumor resection 7-10 days after initiation of study therapy, tissue asservation should take place 2-4h after last intake of MFA/TMZ : (1) fresh frozen, (2) 4% PFA, (3) FFPE tumor material for MFA/MFA metabolite level determination and for analysis of MFA-dependent tissue effects. The exact timepoint of last MFA intake prior to resection and the exact timepoint of asservation of the tumor material has to be documented.

⁵Timepoints (to be documented): (a) 2h after first intake, (b) on the days between MFA start and resection daily blood sampling 2h after morning application of MFA (optional), (c) on the day of resection 5 blood samples at an interval of 2h (0h (prior to last preOP MFA dose) 2h, 4h, 6h, 8h later);

⁶only at the first follow-up visit after discontinuation of MFA

⁷only during ongoing MFA treatment + 3 days

⁸only if clinically indicated

3 Abbreviations

AR	Adverse (Drug) Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz
BID	bis in die (twice a day)
BOB	Bundesoberbehörde
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CA	Competent Authority
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
FPFV	First Subject First Visit
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IB	Investigator's Brochure
ISF	Trial site File
LPLV	Last Subject Last Visit
PEI	Paul Ehrlich Institute
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDP	Sponsor Delegated Person
SUSAR	Suspected Unexpected Serious Adverse Reaction
SZB	Study Center Bonn (Studienzentrum Bonn)
UAR	Unexpected Adverse Reaction
TMZ	Temozolomide
MFA	Meclofenamate
IDHwt	Isocitrate dehydrogenase wildtype
MGMT	O ⁶ -methylguanine DNA methyltransferase
MGMTmeth	MGMT promoter methylated
GBM	Glioblastoma
NSAID	Nonsteroidal anti-inflammatory drug
RSI	reference safety information

RT	Radiotherapy
PFS	Progression-free survival
Gd-MRI	Gadolinium enhanced - Magnetic resonance imaging
mOS	median overall survival
mPFS	median progression-free survival
TM	tumor microtube
DLT	Dose-limiting toxicity
qd	quaque die (every day)
PK	Pharmacokinetics
SmPC	Summary of Product Characteristics
MMSE	Mini Mental State examination

4 Trial Administration Structure

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Participating trial site(s):	10 German sites for phase I, additional 5 German sites for phase II
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5 Introduction

Glioblastoma (GBM) is the most frequent and malignant primary brain tumor. Even in the prognostically favourable MGMT-methylated subgroup treated with temozolomide (TMZ), survival after relapse is short (12 months). Thus, there is a high medical need for improved survival-prolonging second-line therapies. Preclinical results show that meclofenamate (MFA), originally developed as a nonsteroidal anti-inflammatory drug (NSAID), sensitizes GBM cells to TMZ-induced toxicity via inhibition of connexin43 and reduction of tumor microtubules. The MecMeth/NOA-24 trial brings the concept of combined MFA/TMZ therapy to clinical application. Phase I (6-14 patients, 2 dose levels of MFA + standard dose TMZ) evaluates safety and feasibility and determines the dose for the randomized phase II (2 x 30 patients) with primary endpoint progression-free survival. If results of phase II provide indications for efficacy, further exploration in phase III and integration into medical practice could be envisioned.

5.1 Background

Glioblastoma (GBM) is the most frequent (3000 new cases/year in Germany) and most malignant (median overall survival (mOS) 17 months) primary brain tumor in adults.^{7,8} The subgroup of patients with an MGMT-meth tumor (35% of patients) responds particularly well to alkylating chemotherapy with TMZ, has a longer mOS (26-48 months), nevertheless relapses after a median of 16 months (Herrlinger et al., 2019) with a strong need for second-line chemotherapy. Here a re-exposure to alkylating therapy with TMZ or CCNU is standard, but survival is short with a median progression-free survival (mPFS) of 3-3.2 months and a mOS of 10.4-12.5 months after relapse (Perry et al., 2010; Weller et al., 2015). Thus, there is a high unmet medical need for improved therapies for relapsed GBM.

Previous work by the group of Frank Winkler (Heidelberg) has shown that GBM cells exhibit ultra-long and thin membrane protrusions - so-called tumor microtubules (TMs) - that extend into the surrounding brain and tumor tissue in order to interconnect tumor cells over long distances (Osswald et al., 2015). TMs also interact with neurons through AMPAergic synapses which integrate the tumor cells into neural circuits and foster the malignant growth of these tumors by synaptic activity (Venkataramani et al., 2019; Venkatesh et al., 2019). On a molecular level, the intercellular contact points of these tumor syncytia are composed of connexin-43 (Cx43)-based gap junctions that enable GBM cells to assemble to a multicellular functional network. As a consequence, Cx43-knockdown reduces communication between astrocytoma cells via intercellular calcium waves and additionally reduces the number of glioblastoma cells with TM formation. Functional TMs, in turn, were associated with resistance to cytotoxic treatment through formation of a self-repairing syncytial network which is markedly disturbed when Cx43 is down-regulated. If the ability to establish TM networks is compromised, both TMZ chemotherapy and radiotherapy are much more efficient in preclinical glioblastoma models (Osswald et al., 2015; Weil et al., 2017). Previous experiments of one of the trial coordinators of MecMeth/NOA-24 (Matthias Schneider, Bonn) demonstrated that pharmacological inhibition of gap junctions via INI-0602 – a novel experimental gap junction inhibitor – profoundly sensitized primary MGMTmeth human GBM cell populations to TMZ-mediated toxicity (Potthoff et al., 2019). Together with other *in vitro* studies that suggested gap junction inhibition to significantly increase the tumor cells' susceptibility to standard TMZ therapy (Munoz et al., 2013; Murphy et al., 2016), these findings raise hope for novel therapeutic applications for GBM patients. However, a direct transfer into a clinical application has not been possible since none of the previously discussed gap junction inhibitors are suitable and available for clinical application. The MecMeth/NOA-24 trial proposes meclofenamate (MFA) – a nonsteroidal anti-inflammatory drug (NSAID) with clinical use in the US – as a gap junction inhibitor for GBM therapy. MFA is known to profoundly block Cx43/gap junction-mediated intercellular communication in various physiological cell types (Harks et al., 2001; Manjarrez-Marmolejo et al., 2016; Ning et al., 2013). Also, formation of tumor-promoting glioblastoma-neuron synapses is inhibited by MFA (Venkatesh et al., 2019). Based on this knowledge, in our very recently published mwork (Schneider et al., 2021) we aimed to investigate to what extent MFA might affect gap junction-mediated intercellular cytosolic traffic as well as electrical coupling in preformed GBM networks. For this purpose, we quantified gap junction-mediated cytosolic traffic within tumor networks by realtime imaging of fluorescence guided cell-to-cell transfer

of calcein – a fluorescent molecule that is only able to spread from cell-to-cell through intercellular gap junctions, workflow is depicted in Figure 1A. For MFA treatment, we observed a significant reduction of calcein receiver cells after up to 150 minutes, Figure 1B,C. In line with these findings of a MFA-mediated functional inhibition of intercellular cytosolic exchange via gap junctions, MFA yielded a complete block of functional network connectivity which was reflected by electrophysiologically isolated tumor cells that were no longer responsive to glutamate stimulation (Figure 1D,E).

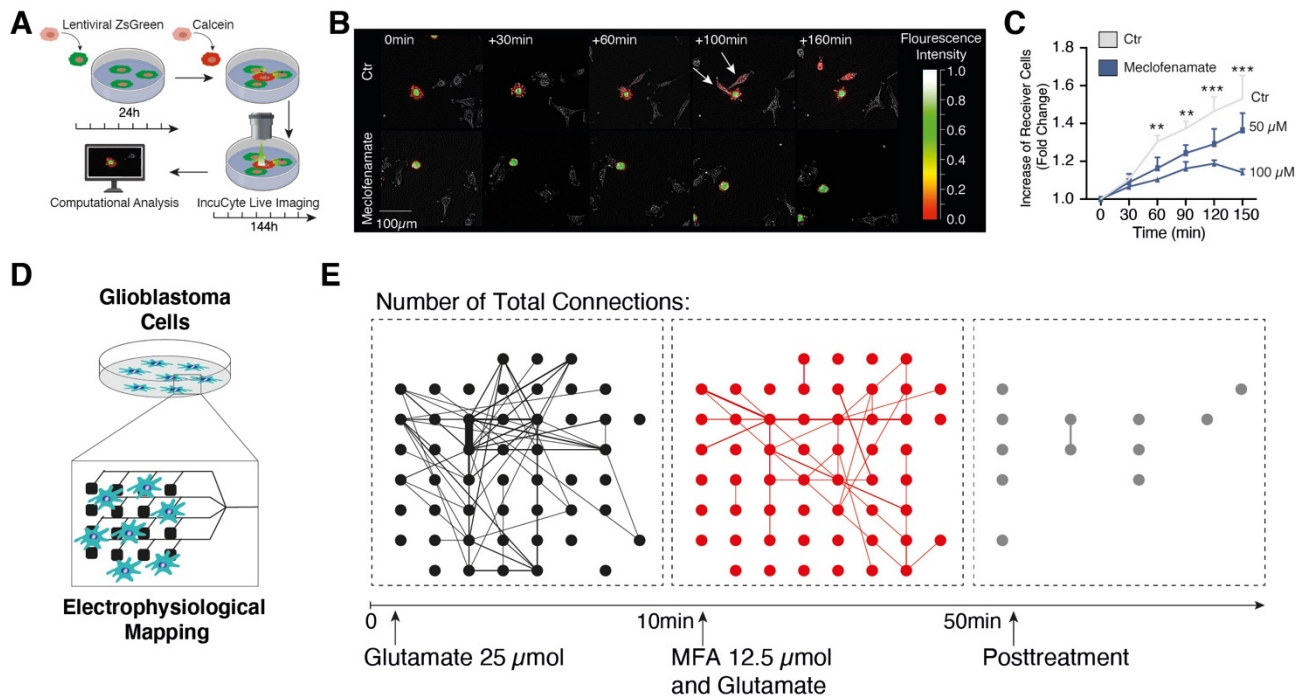


Figure 1: Meclofenamate causes functional decoupling of glioblastoma cells.

(A) Workflow illustration. Donor cells contain calcein, a fluorescent dye that passes only through connexin-43 connected cells. (B) Fluorescence images of BTSC#G35 acquired by the IncuCyte® S3 Live-Cell Analysis System. Fluorescence intensity enables to decide between donor cells (green in the center) and receiver cells (whole red). (C) Quantification of the increase of receiver cells after MFA treatment compared to the control. Experiments were performed in triplicate with BTSC#G35. Data is given as mean \pm SEM. P-values are determined by Wilcoxon matched-pairs signed rank test. (D) Schematic illustration of the experimental procedure (MEA-plates). (E) Profound reduction in intercellular electrophysiological activity by MFA. Cell (G40) communication computed from MEA data based on glutamate-induced extracellular Ca^{2+} flux. Dots indicate an active electrode, lines indicate the number of connections.

Based on the fact that MFA inhibits functional coupling of glioblastoma cells, we next analyzed gene expression changes caused by MFA treatment. We identified 301 differentially expressed genes in the BTSC#168 cell populations ($p\text{-adj} < 0.01$), 452 differentially expressed genes in BTSC#233 and 361 differentially expressed genes in the BTSC#G35 cell populations of which 163 genes are commonly differentially expressed, Figure 2A. A gene-set enrichment analysis identified a significant reduction of two pathways that are involved in neural development and cell-cell connections: the neural cell adhesion molecule (NCAM) pathway (MSigDM REACTOME NCAM1_INTERACTIONS) and the NETRIN-signaling pathway that is involved in axon guidance (MSigDB REACTOME_NETRIN_1_SIGNALING), Figure 2B.

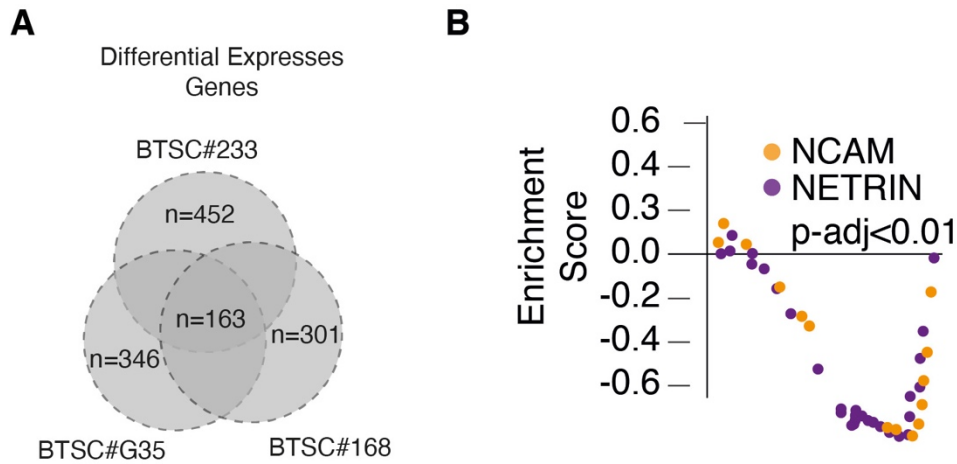


Figure 2: Meclofenamate causes downregulation of NCAM and axon guidance molecule signaling.

(A) Venn diagram shows the number of differentially expressed genes (DEGs) of each cell population separately and the number of shared DEGs. (B) Gene set enrichment analysis (GSEA) of downregulated pathways after MFA treatment.

In the development of the central nervous system axon guidance molecules are known to mediate directed migration of neurons as well as spatial configuration of astrocytes. Osswald and colleagues therefore assumed that axon guidance molecules might be involved in the regulation of TMs; we hypothesized whether MFA - via its downregulating effects on axon guidance molecule signaling, see Figure 2B - might also exert a morphological impact on glioblastoma network architectures. In order to address these questions, we injected primary GBM cell populations into human cortical brain slices and treated the slices with MFA. After seven days of coculturing, 3D reconstruction of tumor cell networks was performed based on two-photon imaging data, workflow is depicted in Figure 3A. MFA treatment resulted in a breakdown of intercellular network architectures, Figure 3B,C, which was reflected by a reduction in the number of TM-based intercellular connections per cell, Figure 3D, as well as a reduction in TM length, data not shown.

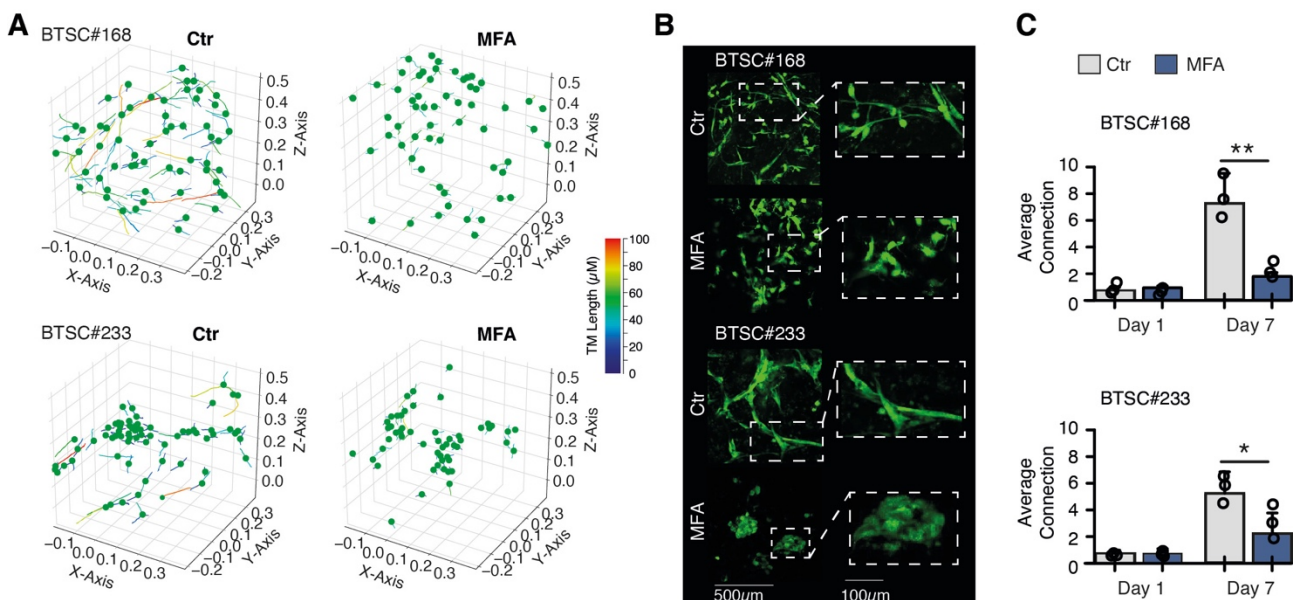


Figure 3: Meclofenamate demolishes tumor microtube-based intercellular network morphology.

(A) 3D-reconstruction of TM formations in human slice cultures for BTSC#168 and BTSC#233 for MFA and control. TM length is color-coded as depicted in the heatmap. (B) Stacked fluorescence multiphoton images of the slice cultures. (C) Quantitative statistics show the number of cellular connections for MFA treatment and

control. P-values are determined by one-way ANOVA. Mean \pm SD is depicted. P-values are determined by one-way ANOVA. *, ** and **** denote $p < 0.05$, $p < 0.01$ and $p < 0.0001$.

With regard to our findings of MFA to functionally, Figure 1, and morphologically, Figure 3, demolish GBM networks, we next asked for the effects of TMZ in such an impaired intercellular malignant connectivity. For MFA-TMZ combination treatment, we observed a failure in the upregulation of genes that are required to overcome TMZ-induced cell death, Figure 4A, which culminated in significantly increased cell death rates for the MGMTmeth BTSC#35 and BTSC#40 cell populations, Figure 4B,C. In case of MGMTnonmeth GBM cell population BTSC#233 with absent cell death induction in case of TMZ single application, MFA-TMZ combination treatment expectably did not reveal any sensitizing effects, Figure 4C. Applying a murine orthotopic *in vivo* setting with MGMTmeth BTSC#35 cells, workflow depicted in Figure 4D, combination treatment of MFA and TMZ exhibited profoundly reduced tumor volumes and tracer uptake in cranial 11C-MET PET scans of mice, Figure 4E, and revealed a tendency for a survival benefit for the chosen observation time period of 8 weeks after treatment onset, Figure 4F, indicating MFA to exert sensitizing effects beyond the murine blood brain barrier.

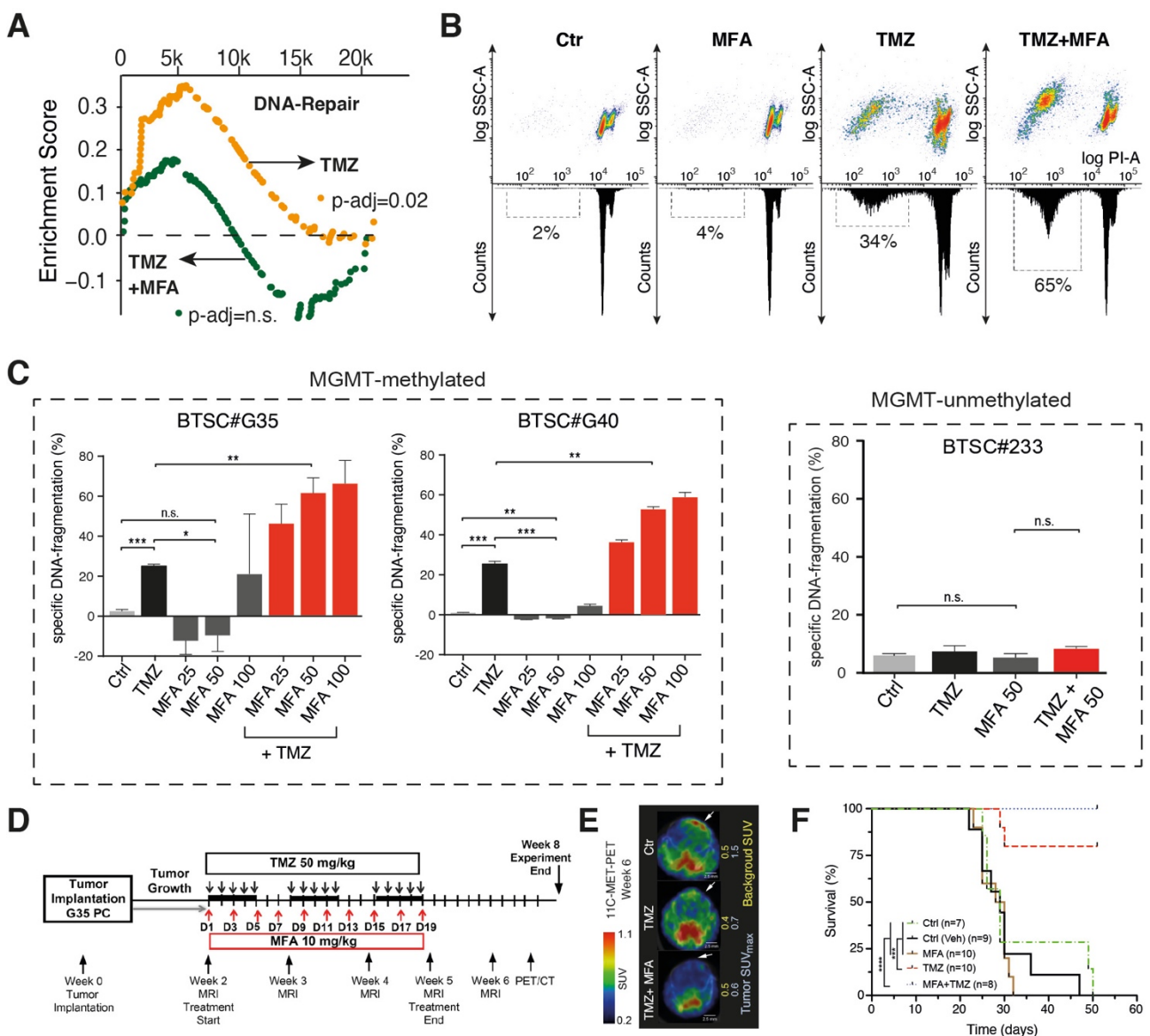


Figure 4: Reduced connectivity due to meclufenamate treatment results in profound temozolomide sensitivity. (caption see next page)

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(A) Gene set enrichment analysis (GSEA) of DNA damage pathway (MSigDB). TMZ mono-treatment is marked in yellow and TMZ+MFA combination treatment in green. For statistical analysis see methods section. (B) Representative scatter plots from flow cytometric analysis of MGMTmeth BTSC#G35 cel populations. The SubG1 peak is accentuated within the corresponding histograms and the mean percentage of DNA-fragmentation is depicted below. (C) Barplots show the percentage of specific DNA-fragmentation of PI-stained nuclei as surrogate readout for cell death for MGMTmeth BTSC#G35, MGMTmeth BTSC#168 and MGMTnon-meth BTSC#233 under indicated treatment conditions. Data is given as mean \pm SEM. P-values are determined by Mann-Whitney test. (D) Schematic illustration depicting tumor implantation and treatment schedule for the *in vivo* experiments (E) Representative 11C-MET PET scans of mice brains illustrate the uptake of this tracer following treatment with TMZ and TMZ+MFA compared to the controls. Scale bar 2.5 mm. Scale for SUV shown in the left side and background/tumor SUV is shown next to the PET images. (F) Kaplan–Meier curves showing percentage survival in days. MGMTmeth BTSC#G35 cells were orthotopically implanted into NOD-SCID mice. One-way ANOVA with Bonferroni correction for multiple testing, ***P < 0.001 and ****P < 0.0001.

In summary, our results show MFA to lead to both a morphological and a functional breakdown within GBM network arrangements and that this breakdown is driven by MFA-mediated inhibition of TM outgrowth and intercellular communication via two mechanisms: on the one hand a direct connexin-43-inhibition resulting in significantly reduced intercellular gap junction-mediated cytosolic traffic, on the other hand a downregulation of adhesion as well as axon guidance molecules which spawns a reduction in tumor microtubule length and reduces the ability of forming cell-cell contacts. Loss of tumor microtubule-based network arrangements was accompanied by a failure in the upregulation of genes that are required for DNA repair in response to TMZ treatment and culminated in a profound sensitivity to TMZ-mediated cell death. Our murine experiments support the notion that MFA achieves effective CNS drug levels. These findings are also corroborated by further studies that have evaluated MFA in *in vivo* settings: systemic administration of MFA yielded CNS-mediated anticonvulsive effects in murine epilepsy models (Wallenstein et al., 1984). Furthermore, in mouse models for induction of metastatic breast or lung cancer, systemic treatment with MFA was associated with a prevention of CNS metastasis while lung metastasis could not be prevented (Chen et al., 2016). The latter finding is the background for an already ongoing US pilot trial for brain metastasis (not GBM) using MFA (NCT02429570).

5.2 Trial Rationale

Improving efficacy of second-line therapy for patients with GBM is of utmost importance. With promising preclinical data for combined MFA/TMZ treatment in MGMTmeth GBM (see section 5.1) there is a clear chance to improve the course of the relapsed GBM with MFA treatment in addition to standard TMZ therapy. Since this combination has not been used so far in other trials, the MecMeth/NOA-24 trial explores the dose of MFA in combination with standard dose TMZ in the phase I part of the trial and generates first survival data within the randomized phase II part of the trial. Ultimately, the phase II part will explore whether it is promising to pursue the combined MFA/TMZ treatment strategy in subsequent larger randomized trials with confirmatory intention.

6 Side Effects and Risk Benefit Assessment

6.1 Benefit for study participants and patient population

With MFA application in the MecMeth/NOA-24 trial, each patient in phase I and in the experimental arm of phase II has the chance to receive a more effective treatment of their progressive glioblastoma. Patients in the standard arm of the phase II trial do not have an additional therapeutic benefit beyond the one conveyed by standard TMZ therapy regularly applied off-study.

6.2 Risk for study participant

The risk for the individual patient to participate in the trial is additional toxicity brought in by addition of MFA to standard TMZ therapy in phase I (all patients) and in phase II (experimental arm only). The risk of toxicity is considered low since the investigational drug has an acceptable safety profile (MFA: US drug label) and the dose used within this trial does not exceed recommendations in the US registration. There is no additional risk by the tissue sample collection performed to phase I participants 7 to 10 days after MFA therapy since only patients who have a clinical indication of tumor resection are included in the trial and the resection is performed using standard procedures which are not changed in any way by the asservation of tumor tissue for study purposes. Thus, no extra risks for the surgical procedure or anesthesia are expected. The 7-10 days delay for tumor resection appears to be acceptable due to the following reasons: (1) it is well balanced with the perspective that a new drug combination with the potential of enhanced efficacy is applied and an optimal dose for all patients with relapsed MGMTmeth GBM will be found, (2) a delay of resection for this length of time is not supposed to have an influence on survival as shown for the delay of radiotherapy for weeks in first-line treatment of GBM (Blumenthal et al., 2018), (3) patients with an indication of urgent resection will not be included in the study (e.g. large space-occupying tumors with risk of increased intracranial pressure and herniation), (4) It is common and safe practice in neurosurgery to schedule a planned non-emergency re-resection within 5-20 days after detection of progression on MRI. The trial does not extend this time interval and the resection is only postponed if there is no additional risk coming with the planned delay.

In phase II, patients who have an indication for re-resection will be asked whether they would allow the resection to be performed 7-10 days after TMZ/MFA (experimental arm) or TMZ initiation, provided that a re-resection 2-3 weeks after diagnosis of relapse would not impose any additional clinical risks to the patient in comparison to a resection within few days after MRI-based diagnosis, according to investigator's medical judgement. This, however, would not be a prerequisite for participation in the phase II part of the trial; patients with an indication for re-resection can have their resection before inclusion in the study and in a second step be included, randomized and treated in the phase II trial.

6.3 Risk Benefit Assessment

Adverse events (AEs) under MFA are the ones common to NSAIDs: >10% gastrointestinal problems including diarrhea, nausea and abdominal pain; MFA may cause gastrointestinal ulcers, asthmatic/anaphylactoid reactions, or may worsen cardiovascular diseases. Therefore, patients with a history of gastrointestinal ulcers, asthma, anaphylactic reaction to NSAIDs or severe coronary heart disease or heart failure are excluded. Also, rash, dizziness and headache may occur frequently. In rarer cases, AEs include acute skin reaction, impaired liver or renal function. To determine the optimal MFA dose for combined GBM therapy, the proposed trial contains a phase I dose finding part. The dose will be selected according to the observed frequency of Dose-limiting toxicities (DLTs) during the first 56 days of MFA treatment. Of note, the MFA starting dose used for this trial (2 x 100 gd) is well below the maximum dose (see above) and even in case of further dose escalation in the second step, the maximum dose will not be exceeded. Since the risk of gastrointestinal ulcers/bleedings is increased, patients with a history of ulcer will be excluded and trial patients will be treated prophylactically with proton pump inhibitors according to local standard.

The risk-benefit for participants will be continuously re-assessed throughout the conduct of the trial (see 13.2).

7 Trial Objectives and Endpoints

7.1 Phase I

Objectives	Endpoints
Primary	
The primary objective is to determine toxicity of MFA therapy in addition to standard TMZ and, on this base, determine the daily MFA dose to be recommended for phase II.	<ul style="list-style-type: none"> Incidence of dose-limiting toxicities (DLTs) during the first 8 weeks/56 days of MFA treatment.
Secondary	
To determine the efficacy of MFA therapy in addition to standard TMZ throughout the trial.	<ul style="list-style-type: none"> Progression-free survival (PFS) as measured from the inclusion into the trial until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center. Analysis of PFS according to post hoc central reference neuroradiological assessment. Overall survival as measured from the day of inclusion into the trial
To assess the safety and tolerability of MFA therapy in addition to standard TMZ throughout the trial.	<ul style="list-style-type: none"> Assessment of safety beyond 8 weeks MFA treatment: Toxicity, i.e. continuous monitoring of AE/SAE/SUSARs
To evaluate the clinical effect of MFA therapy in addition to TMZ and the development of quality of life throughout the trial.	<ul style="list-style-type: none"> Karnofsky performance score (KPS), Quality of life (QoL) throughout the trial and Mini-Mental-status examination (MMSE).

7.2 Phase II

Objectives	Endpoints
Primary	
Efficacy of MFA therapy in addition to standard TMZ therapy	<ul style="list-style-type: none"> Progression-free survival (PFS) as measured from the day of randomization until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center. In a sensitivity analysis, the PFS analysis will also include patients from phase I who received MFA at the same dose as applied in phase II (PFS measured from day of trial inclusion)
Secondary	
To evaluate the efficacy throughout the trial.	<ul style="list-style-type: none"> Analysis of PFS according to post hoc central reference neuroradiological assessment. PFS analysis including both patients from phase II and patients from phase I who received MFA at the same dose as applied in phase II (PFS measured from day of trial inclusion). Overall survival (OS) as measured from the day of randomization in phase II. A further sensitivity analysis, will also include patients from phase I who received MFA at the same dose as applied in phase II. In these patients, OS starts from day of inclusion into the trial.
To assess the safety and tolerability of MFA therapy in addition to standard TMZ throughout the trial.	<ul style="list-style-type: none"> Assessment of safety: Toxicity, i.e. continuous monitoring of AE/SAE/SUSARs until 3 days after end of therapy
To evaluate the clinical effect of MFA therapy in addition to TMZ and the development of quality of life throughout the trial.	<ul style="list-style-type: none"> Karnofsky performance score (KPS), Quality of life (QoL) throughout the trial and Mini-Mental-status examination (MMSE).

8 Trial Design

This is a multicenter phase I/II trial that determines the recommended MFA dose in addition to standard TMZ in the single-arm phase I part and explores efficacy in a randomized, unblinded phase II part. The trial flow chart is shown in Figure 5.

Prior to the start of phase II a substantial amendment application presenting the final dose and the underlying clinical data will be submitted to the EC and the BfArM. This amendment will also include an updated assessment of benefit/risk for this trial.

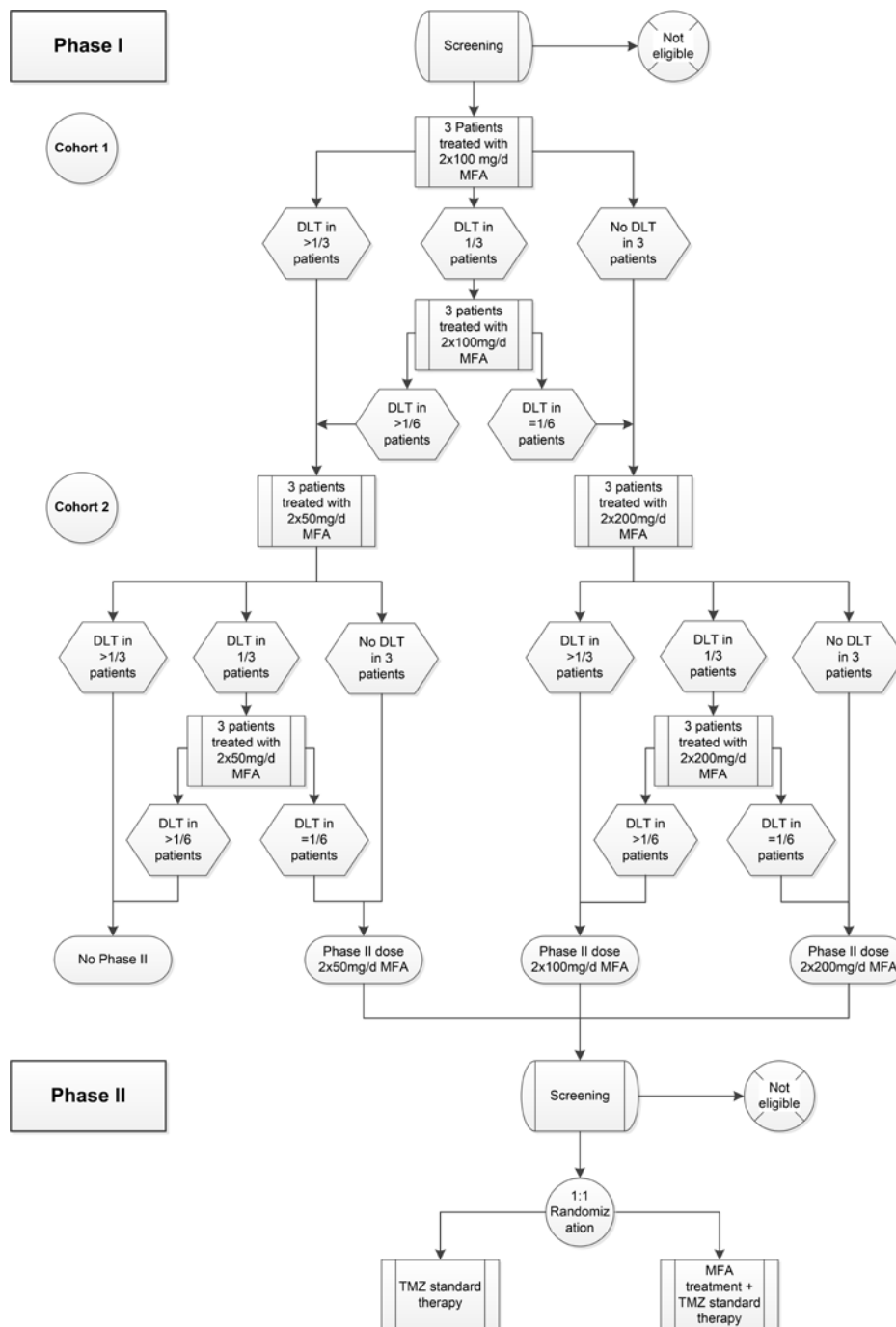


Figure 5: Trial design chart of the MecMeth/NOA-24 trial.

8.1 Phase I

8.1.1 Treatment groups

Patients with first relapse of a MGMT-methylated glioblastoma (MGMT promotor methylation status determined on tumor material from first-line resection; RANO criteria fulfilled; >3 months after end of first-line therapy, >6 months after end of primary radiotherapy) are screened for the trial. Patients can be accrued, if the inclusion/exclusion criteria are fulfilled and if, according to the local treating neurosurgeon, re-resection of the tumor is clinically indicated and can be safely deferred until day 7-10 after initiation of MFA/TMZ therapy. After inclusion, patients are treated with MFA in addition to standard TMZ (according to Figure 6) and tumor resection is performed 7-10 days after initiation of therapy. MFA tissue level measurements and translational analyses are performed on the tumor material obtained from resection. AEs are documented throughout the whole MFA/TMZ treatment (and 3 days later). Each patient is particularly screened for DLTs during the first 8 weeks of his/her MFA treatment.

8.1.2 Recruitment of Phase I cohorts

Recruitment breaks will be provided between cohort expansion to evaluate DLT incidence. To control for patient inclusion, sites will be encouraged to announce pre-screenings. Details of the procedure can be found in the Recruitment Manual, which will be filed in the Investigator Site File.

8.1.3 DLT Definition

All toxicities will be graded using the CTCAE version 5.0.

DLT is determined in the first 2 courses of MFA (within 8 weeks/56 (+/-3) days after first study treatment administration) in subjects with a compliance rate of 90% (i.e. 50 days of treatment) and no overdose.

If judged to be related to the administration of Meclofenamate, the following toxicities will be considered a DLT:

- grade ≥ 4 hematotoxicity for >14 days in courses 1 and 2
- grade ≥ 3 for any other organ toxicity,

The following events will not be considered a DLT:

- events probably related to the tumor resection/perioperative treatment, temozolomide treatment or to the underlying disease or to any other concurrent disease
- asymptomatic grade 3 laboratory abnormality deemed clinically not significant.

The assessment of the relatedness of potential DLTs and MFA medication is performed as follows (also refer to section 14.8):

1. the local physician files a DLT report if he/she thinks that the AE is probably related to MFA (refer to section 14.8);
2. a representative of the sponsor assesses the relatedness;
3. the DSMB convening when decisions are to be made regarding the next dose level or start of phase II reviews all DLT assessments and gives a recommendation regarding the classification of an adverse event as DLT.

DLT definition criteria will also apply for definition of "inacceptable toxicity" during the Phase II Trial In Phase II, this will be applied throughout the whole MFA treatment phase, i.e. until day 3 after last MFA intake (refer to section 13.3.2).

8.1.4 Trial Sites

The trial will be conducted in 10 centers in Germany, which must meet the structural and personnel requirements for performing the planned regular trial-related investigations. If necessary, additional qualified centers may be included in the implementation of the trial.

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8.1.5 Number of subjects

Patients are recruited in two cohorts of three to six patients. Dose adaptation in between cohorts depends on the occurrence of DLTs. The first three patients of cohort 1 start with a MFA dose of 2 x 100 mg qd. After all three patients have completed 8 weeks of MFA therapy, the rate of DLTs in the first 8 weeks of each patient's therapy is determined. If no DLT occurs, the second cohort will be treated with the highest dose of 2 x 200 mg qd. If 1 of 3 patients experiences a DLT, another three patients will be recruited in cohort 1 and treated with MFA (in addition to standard TMZ) for 8 weeks. Again, the DLT rate in the first 8 weeks of MFA therapy will be determined in these three additional patients. If more than 1 of 6 patients experiences a DLT, the MFA dose of 2 x 100 mg qd is not regarded as suitable for phase II and the lower dose of 50 mg qd MFA is explored in the same way (Figure 5). In case of DLT during the first 8 weeks 2 x 100 mg qd MFA therapy in 0/3 or $\leq 1/6$ patients, the higher dose of 200 mg twice daily MFA is explored. The higher dose of 2 x 200 mg qd MFA is chosen for phase II, if DLT at this level occurs in 0/3 and not more than 1/6 patients. In any other case, MFA 2 x 100 mg qd will be chosen for phase II (Figure 5).

DLT is only measured in the first 8 weeks of MFA treatment, but MFA treatment using the MFA dose applied in the first 8 weeks is continued beyond the first 8 weeks for a maximum of 224 days (32 weeks), or until discontinuation rules for MFA therapy apply (refer to Section 13.3.2). In case MFA therapy is terminated, standard TMZ therapy can be continued at the discretion of the treating physician.

Between day 7 and 10 consecutive analysis of tumor MFA levels (for exploratory analyses) is performed. After one dose level has been closed with 3-6 patients, the dose of the next dose level is determined according to the schedule in figure 4. At this time point, the DSMB is asked to give a recommendation regarding the next dose step and, after phase I is concluded, the DSMB gives a recommendation regarding the dose for phase II (refer to section 14.9).

All patients of phase I are followed for toxicity and efficacy until the end of the whole trial (incl. phase II).

The histology of the re-resected tumor is analyzed by the local (neuro)pathologist.

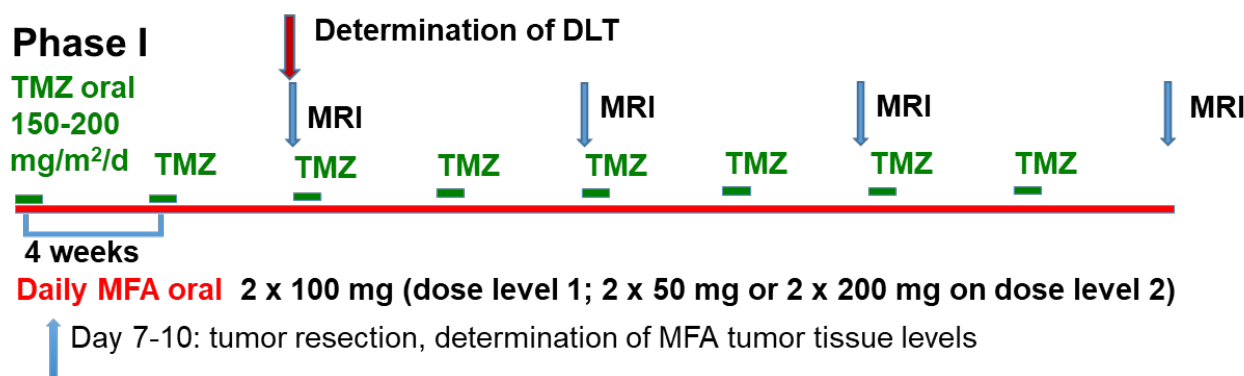


Figure 6: Interventions and control points for safety and efficacy in phase I. TMZ will be adapted in course 2 according to toxicity in course 1 (standard procedure), without toxicity, escalation up to 200 mg/m².

8.1.6 Time Schedule

Per Subject:

Duration of intervention per patient: 224 days at maximum (in case of postponement of the following TMZ cycle due to hematotoxicity, MFA treatment will be continued and expanded to a maximum of 250 days) OR

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until tumor progression OR until unacceptable toxicity attributable to MFA (CTCAE5 grade 4 seizures; grade 3 for any other organ toxicity, grade 4 myelotoxicity for >14 days) OR until definitive termination of standard TMZ, whatever comes first

Follow-up per patient phase I:

- for determining DLT: 8 weeks after the first intake of MFA
- for AE recording: at least 8 weeks, if MFA is taken longer than 8 weeks until day 3 after the last intake of MFA (maximum: 224 days + 3 days = 227 days)
- for recording of survival parameters:

if phase II starts: until end of the entire study (phase I + phase II) which will be reached when the following 2 requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).

In case phase II is never started, survival parameter recording is concluded when the following 2 requirements are fulfilled for phase I patients: (1) at least 6 months after inclusion of the last patient AND (2) at least 3 days after definite termination of MFA intake in all phase I patients

Trial duration:

- Recruitment period: 10 months
- First patient in to last patient out: 12 months for determination of DLT; MFA treatment continues for a maximum of 224 days and follow-up continues until the conclusion of the entire trial, i.e. after a maximum of 30 months + 3 days (if phase II takes place) or until the following 2 requirements are fulfilled (in case phase II is never started): (1) at least 6 months after inclusion of the last patient AND (2) at least 3 days after definite termination of MFA intake in all phase I patients, i.e. a maximum of 224 + 3 days after treatment start of the last patient of phase I.

8.2 Phase II

8.2.1 Treatment Groups

Patients with first relapse (RANO criteria fulfilled; >3 months after end of primary therapy, >6 months after end of primary radiotherapy) are screened for the trial. Patients can be included in the study, if the inclusion/exclusion criteria are fulfilled. After inclusion, patients are randomized in the experimental or standard treatment arm. The experimental treatment is defined as the MFA dose determined in phase I in addition to standard TMZ (according to Figure 5). The standard treatment arm is TMZ monotherapy according to SmPC. If tumor resection for the relapsed tumor is clinically indicated, the local treating neurosurgeon can decide whether the resection can be safely postponed until day 7-10 after initiation of therapy (optional, not a prerequisite for study participation) and tumor material for determination of MFA levels can be obtained.

MFA is taken at the dose determined in phase I. Daily MFA treatment is continued for 8 four-week courses (i.e. 224 days), OR until tumor progression OR until occurrence of a DLT attributable to MFA OR until definitive discontinuation of standard TMZ, whatever comes first (also refer to Section 13.3.2). In case MFA therapy is terminated, standard TMZ therapy can be continued at the discretion of the treating physician.

All patients are followed for toxicity and efficacy until the end of the whole trial, i.e. the day when both of the following requirements are fulfilled: (1) *at least* 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).

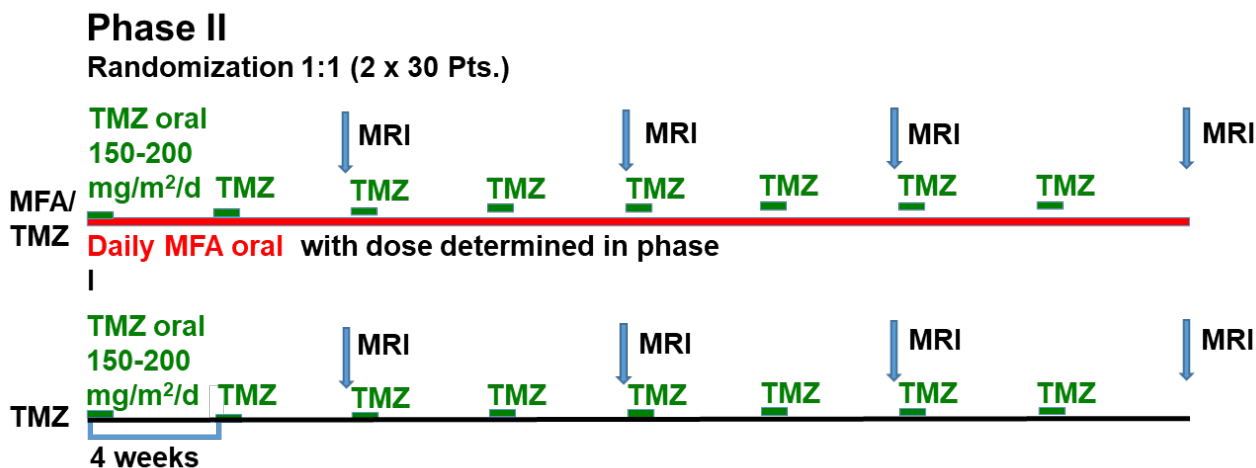


Figure 7: Interventions and control points for safety and efficacy in the MecMeth/NOA-24 trial Phase II. Standard TMZ will be adapted in course 2 according to toxicity in course 1 (standard procedure), without toxicity, escalation up to 200 mg/m².

8.2.2 Trial sites

The trial will be conducted in approximately 15 centers in Germany, which must meet the structural and personnel requirements for performing the planned regular trial-related investigations. If necessary, additional qualified centers may be included in the implementation of the trial.

8.2.3 Number of subjects

It is planned to enroll a total a number of 60 subjects in phase II of this trial. Subjects will be randomized as follows: 30 subjects will be randomized in the experimental treatment arm (MFA/TMZ) and 30 subjects in the standard treatment arm (TMZ monotherapy).

8.2.4 Time Schedule

Per Subject:

Duration of intervention per patient: 224 days at maximum OR until tumor progression OR until unacceptable toxicity attributable to MFA (CTCAE5 grade 4 seizures; grade 3 for any other organ toxicity, grade 4 myelotoxicity for >14 days) OR until definitive termination of standard TMZ, whatever comes first

Follow-up per patient phase II: End of study and of follow-up in the entire trial will be reached when BOTH of the following requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in all patients receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).

Trial duration:

- Recruitment period: 10 months
- First patient in to last patient out: 18 months + 3 days

9 Trial Population and Selection Criteria

This trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

9.1 General considerations

Patients with histologically proven IDHwt and MGMT promotor methylated glioblastoma or gliosarcoma at first progression can be recruited for this trial if tumor progression according to RANO criteria occurred later than 6 months after the end of primary radiotherapy and >3 months after last administration of primary chemotherapy. This rule is in place to minimize the recruitment of patients with pseudoprogression which can occur late and in a prolonged fashion in patients with methylated glioblastoma (Stuplich et al., 2012). This population will not be included in the trial to avoid bias during the efficacy analysis.

9.2 Gender Distribution

No gender ratio has been stipulated in this trial as the results of preclinical and / or clinical studies or medical literature did not indicate any difference in the effect of the trial treatment in terms of efficacy and safety.

In the previous CeTeG/NOA-09 trial with MGMT methylated GBM patients (Herrlinger et al., 2019; EudraCT No. 2009-011252-22), 60% male and 40% female patients had been included. Since the present MecMeth/NOA-24 trial uses similar inclusion criteria and thus addresses the same population, a similar distribution of gender can be expected. Gender is not a prognostically significant marker in glioblastoma (incl. the previous CeTeG/NOA-09 trial) thus, neither stratification nor subgroup analysis based on gender is planned.

There is no evidence in the literature to support any clinically relevant differences between gender groups regarding tolerability or efficacy of MFA.

9.3 Inclusion Criteria

Only patients meeting **all** of the following criteria will be enrolled in the study:

Inclusion criteria for Phase I and II

1. First relapse after first-line therapy with radiotherapy (RT) and alkylating chemotherapy, > 3 months after last chemotherapy application and >6 months after end of RT. Drug therapy and/or radiotherapy for first relapse treatment not yet started.
2. Tumor progression according to RANO criteria
3. Written informed consent
4. Cognitive state to understand rationale and necessity of study therapy and procedures
5. MGMT promotor-methylated (MGMTmeth), IDH wildtype glioblastoma (GBM) or gliosarcoma confirmed with histology of the primary resection
6. Age > 18 years
7. Karnofsky performance score (KPS) ≥60%;
8. Life expectancy > 6 months
9. Adequate bone marrow reserve (WBC >3 G/nl, platelets >100 G/nl)
10. Adequate liver function (bilirubin <1.5 x ULN; ASAT /ALAT <3 x ULN, creatinine < 1.5 x ULN)
11. Patient compliance and geographic proximity that allow adequate follow up
12. Male and female patients with reproductive potential must use an approved contraceptive method during and for 16 weeks after the end of trial medication (Pearl index <1%)
13. Pre-menopausal female patients with childbearing potential: a negative serum pregnancy test (beta-HCG) must be obtained prior to treatment start

Additional inclusion criterion ONLY for phase I:

14. Resection at first relapse not yet performed; according to the local treating neurosurgeon and the documented decision of the local neurooncological tumor board, resection of the tumor is clinically

indicated and can be safely deferred until day 7-10 after initiation of MFA/TMZ therapy.

9.4 Exclusion Criteria

Patients meeting **any** of the following criteria **cannot** be enrolled:

1. Indication for hematotoxicity in first-line therapy not allowing TMZ starting dose 150 mg/m²/d
2. Skin or liver toxicity >CTCAE5 grade 1 in first-line therapy
3. History of gastrointestinal bleeding or gastroduodenal ulcer, active gastritis
4. History of asthma, urticaria or allergic-type skin reactions to NSAID
5. Prior malignancy other than glioma
6. History of confirmed or suspected hypersensitivity (delayed type and immediate type, inclusive of anaphylactic reaction) to any background/ standard TMZ drug product or one of its ingredients of the chosen product, or to cyclooxygenase inhibitors ("NSAIDs"), or to any ingredient of meclufenamate drug product
7. History of disease with poor prognosis
8. Severe coronary heart disease (esp. after coronary artery bypass graft or history of myocardial infarction), severe heart failure
9. Known HIV infection, active hepatitis B or C
10. Breastfeeding or pregnant
11. Unable to undergo contrast-enhanced MRI (i.e. contrast allergy, implants, etc).
12. Treatment in another clinical trial with therapeutic medical intervention or use of any other investigational agent during the trial or within the 30 days before enrollment
13. Medication with a drug that is not allowed in conjunction with MFA intake and cannot be discontinued: i.e. lithium, methotrexate, etc.
14. Patients with active bleeding, bleeding diathesis, antiplatelet therapy or anticoagulant therapy except for the following anticoagulants which are permitted for low-dose thrombosis prophylaxis up to the dosage specified here: unfractionated heparin 7,500 IU BID or 5,000 IU TID; low molecular weight heparin e. g. enoxa-parin 40 mg/d; fondaparinux 2.5 mg/d; danaparoid sodium 750 IU BID; argatroban IV route thrombin time < 70 s; vitamin-K-antagonist INR < 1.8; dabigatran 150 mg BID; rivaroxaban 10 mg/d; edoxaban 30 mg/d; epixaban 2.5 mg BID This restriction is due to a potentially increased risk of GI ulcers with subsequent bleeding under MFA therapy.
15. Patients with medically diagnosed hereditary Galactose Intolerance, complete lactase deficiency or confirmed Glucose-Galactose-Malabsorption
16. Medical History of gastrointestinal Resection of any kind that may potentially alter the absorption of the investigational study drug, according to investigators judgement
17. The presence of any other concomitant severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac (including coronary artery bypass graft), or psychiatric disease, or signs and symptoms thereof, that may affect the subjects participation in the study, according to investigators judgement

9.5 Contraception Requirements

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Therefore, these women must have a negative serum pregnancy test (beta-HCG) at screening, and agree to one of the following:

Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent. Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

OR

Consistent and correct use of one of the following acceptable methods of birth control for one month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:

- Injectable progestogen

- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

A man who is sexually active with a woman of child bearing potential (WOCBP) or a pregnant woman and has not had a vasectomy must agree to use a barrier method of contraception (condom) from start of treatment until 16 weeks after last dose. Contraception of WOCBP partner is recommended. Sperm Donation should be avoided during the same time period.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Women of non-childbearing potential who do not require contraception during the study are defined as:

- postmenopausal (defined as no menses for 12 months without an alternative medical cause)
- permanently sterile (hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy)

All study participants should comply additionally with the required contraception measures corresponding to the use of the TMZ standard therapy as stated in the SmPc of the product.

9.6 Subject Information and Recruitment

If a subject appears to be eligible for the trial, the investigator will inform the subject about the trial and ask the subject for his/her written consent (see also section 18.7).

Before the subject's participation in the study, the investigator will thoroughly inform the patient about all trial-specific aims, methods, anticipated benefits, and potential hazards. An informed consent form will be signed and dated by the patient and her/his physician, in accordance to ICH-GCP and local applicable regulations. The patient's decision to participate in the study, as well as the consent process, will be documented in the patient's records. It is a requirement that written consent is obtained prior to any trial-specific procedures. The study subjects will be assigned a unique identifier, all the data collected for the purpose of the study will be recorded under this identifier in the eCRF in order to comply with data protection laws.

9.7 Time of inclusion into clinical study

Patients are included into the clinical study after informed consent has been obtained. Subjects dropping out before starting study treatment (phase I) or randomization (phase II) will be listed as screening failures.

9.8 Patients Replacement

Phase I: Patients not evaluable for DLT will be replaced (conservative estimate: 1/6 patients; thus maximal patient number in phase I: 12+2=14).

Phase II: The noncompliance/early dropout rate is low in GBM trials (9%; Herrlinger et al., 2019). Since phase II is searching for indications of efficacy but is not a confirmatory trial, drop-outs will not to be replaced. Screening failures (i.e. patients not randomized after informed consent is obtained) are replaced.

10 Investigational Medicinal Product (IMP)

10.1 General

MFA is not registered in Germany/the EU. In the USA, MFA is approved for marketing authorization indicated as an NSAID for the treatment (pain relief) of bone/joint diseases (such as rheumatoid arthritis, osteoarthritis, acute pain shoulder), dysmenorrhoea and fever since 1986 for a maximal daily dose of 400 mg.

10.2 Specification of IMP

Product name	Meclofenamate Sodium
Name of manufacturer	Mylan Pharmaceuticals Inc.
Substance name	Meclofenamate Sodium
Name and dose of active ingredient per unit	Meclofenamate sodium capsules, USP contain 50 mg or 100 mg meclofenamic acid as the sodium salt
Other ingredients	Colloidal silicon dioxide, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 3, gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), sodium lauryl sulfate and titanium dioxide. In addition, the imprinting ink contains black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.
Pharmaceutical form	Capsule
Mode of administration	Oral
Batch number/ Expiry date	Will be provided with the investigational medicinal product
Storage conditions	20° to 25°C
Mode of action	The mode of action of the anti-inflammatory activity is a dual COX-1/COX-2 inhibition. In animal studies, meclofenamate sodium was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor site. In vitro, meclofenamate sodium was found to be an inhibitor of human leukocyte 5-lipoxygenase activity. In the present study MFA's known action as a gap junction inhibitor through blockage of Cx43-mediated intercellular communication will be exploited.
Interactions	Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors. When meclofenamate sodium is administered with aspirin, its protein binding is reduced, although the clearance of free meclofenamate sodium is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of meclofenamate sodium capsules and aspirin is not generally recommended because of the potential of increased adverse effects. Clinical studies, as well as post-marketing observations, have shown that meclofenamate sodium can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

	<p>NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.</p> <p>NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.</p> <p>The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.</p>
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10.3 Pharmacodynamics

Meclofenamate sodium is a nonsteroidal agent which has demonstrated anti-inflammatory, analgesic, and antipyretic activity in laboratory animals. The mode of action, like that of other nonsteroidal anti-inflammatory agents, is a dual COX-1/COX-2 inhibition. Therapeutic action does not result from pituitary-adrenal stimulation. In animal studies, meclofenamate sodium was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor site. *In vitro*, meclofenamate sodium was found to be an inhibitor of human leukocyte 5-lipoxygenase activity. These properties may be responsible for the anti-inflammatory action of meclofenamate sodium. There is no evidence that meclofenamate sodium alters the course of the underlying disease. In several human isotope studies, meclofenamate sodium, at a dosage of 300 mg/day, produced a fecal blood loss of 1 to 2 mL per day, and 2 to 3 mL per day at 400 mg/day. Aspirin, at a dosage of 3.6 g/day, caused a fecal blood loss of 6 mL per day. In a multiple-dose, 1-week study in normal human volunteers, meclofenamate sodium had little or no effect on collagen-induced platelet aggregation, platelet count, or bleeding time. In comparison, aspirin suppressed collagen-induced platelet aggregation and increased bleeding time. The concomitant administration of antacids (aluminum and magnesium hydroxides) does not interfere with absorption of meclofenamate sodium. MFA has anticonvulsive effects in murine epilepsy models (Wallenstein and Mauss, 1984).

10.4 Pharmacokinetics

Meclofenamate sodium is rapidly absorbed in man following single and multiple oral doses with peak plasma concentrations occurring in 0.5 to 2 hours (see Table 1). Based on a comparison to a suspension of meclofenamic acid, meclofenamate sodium is completely bioavailable. The plasma concentrations of meclofenamic acid decline monoexponentially following oral administration. In a study in ten healthy subjects following a single oral dose the apparent elimination half-life ranged from 0.8 to 5.3 hours. After the administration of meclofenamate sodium for 14 days every 8 hours, the apparent elimination half-life ranged from 0.8 to 2.1 hours with no evidence of accumulation of meclofenamic acid in plasma

Table 1: Pharmacokinetics of meclofenamate

Mean (Range) Parameter Values (n = 10)		
	Meclofenamic Acid 100 mg*	Metabolite I†
C_{max} mcg/mL‡	4.8 (1.8 to 7.2)	1 (0.5 to 1.5)
t_{max} hr§	0.9 (0.5 to 1.5)	2.4 (0.5 to 4)
C_{min} mcg/mL¶	0.2 (0.5 to 1.5)	0.4 (0.2 to 1.1)
Cl/F mL/min#	206 (126 to 342)	---
Vd/F liters ^p	23.3 (9.1 to 43.2)	---
$t_{1/2}$ hr ^β	1.3 (0.8 to 2.1)	15.3 ^à
% of Dose in Urine Unconjugated	0 ---	0.5 (0 to 1.2)
Total	2.7 (0 to 4.5)	21.6 (7.5 to 32.6)

* Administered every 8 hours for 14 days

† 3-Hydroxymethyl metabolite of meclofenamic acid with 20% activity of meclofenamate sodium *in vitro*

‡ Peak plasma concentration

§ Time to peak plasma concentration

¶ Trough plasma concentration

Oral clearance

Meclofenamic acid is extensively metabolized to an active metabolite (Metabolite I; 3-hydroxymethyl metabolite of meclofenamic acid) and at least six other less well characterized minor metabolites. Only this Metabolite I has been shown *in vitro* to inhibit cyclooxygenase activity with approximately one fifth the activity of meclofenamate sodium. Metabolite I (3-hydroxymethyl metabolite of meclofenamic acid) with a mean half-life of approximately 15 hours did accumulate following multiple dosing. After the administration of 100 mg meclofenamate sodium for 14 days every 8 hours, Metabolite I reached a peak plasma concentration of only 1 mcg/mL. By contrast, the peak concentration was 4.8 mcg/mL for the parent compound on both days 1 and 14. Therefore, the accumulation of Metabolite I is probably not clinically significant. Approximately 70% of the administered dose is excreted by the kidneys with 8% to 35% excreted as predominantly conjugated species of meclofenamic acid and Metabolite I (see Table 1). Other metabolites, whose excretion rates are unknown, account for the remaining 35% to 62% of the dose excreted in the urine. The remainder of the administered dose (approximately 30%) is eliminated in the feces (apparently through biliary excretion). There is insufficient experience to know if meclofenamate sodium or its metabolites accumulate in patients with compromised renal or hepatic function. Therefore, meclofenamate sodium should be used with caution in these patients. Trace amounts of meclofenamate sodium are excreted in human breast milk.

Meclofenamic acid is greater than 99% bound to plasma proteins over a wide drug concentration range. Unlike most NSAIDs, which when administered with food have a decrease in rate but not in extent of absorption, meclofenamic acid is decreased in both. It has been reported that following the administration of meclofenamate sodium capsules one-half hour after a meal, the average extent of bioavailability decreased by 26%, the average peak concentration (C_{max}) decreased 4-fold and the time to C_{max} was delayed by 3 hours.

10.5 Side Effects

The following adverse reactions with an incidence greater than 1% were observed in clinical trials and included observations from more than 2,700 patients, 594 of whom were treated for one year and 248 for at least 2 years. The adverse reactions with an incidence less than 1% were reported during controlled clinical trials and through voluntary reports since marketing. The probability of a causal relationship exists between the drug and these adverse reactions.

Very frequent (> 10%) side effects:

- diarrhea (10% to 33%)
- nausea with or without vomiting (11%)

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Frequent (1-10%) side effects:

- other gastrointestinal disorders (10%)
- abdominal pain, pyrosis, flatulence, rash, headache, dizziness (3-9%)
- severe diarrhea (4%)
- anorexia, constipation, stomatitis, peptic ulcer, edema, urticaria, pruritus, tinnitus (1-3%)

Occasionally (< 1%) side effects:

- Gastrointestinal: bleeding and/or perforation with or without obvious ulcer formation, colitis, cholestatic jaundice
- Renal: renal failure
- Hematologic: neutropenia, thrombocytopenic purpura, leukopenia, agranulocytosis, hemolytic anemia, eosinophilia, decrease in hemoglobin and/or hematocrit
- Dermatologic: erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitis
- Hepatic: alteration of liver function tests
- Allergic: lupus and serum sickness-like symptoms

For further information, refer to the summary of product characteristics.

10.6 Packaging and Labelling of IMP

The central pharmacy is responsible for the import, packaging, labelling and distribution of the IMP to the trial sites. For details of packaging, refer to the IMP Manual, which will be filed in the Trial Master File (TMF) and the ISF. Sample of label according to GCP-V §5 will be provided separately. Subject identification number will be filled in manually on the label by the study staff at trial site.

10.7 Transport of IMP

All further details concerning ordering and transport of the IMP to the trial sites are described in further detail in the IMP Manual of this study, which will be filed in the TMF and the ISF.

10.8 Storage requirements

Until dispense to the patients, study medication will be stored in a securely locked area, accessible to authorized personnel only. Personnel who have access to the trial drug need to be listed (name and responsibilities) on the Authorization and Delegation Log in the trial specific Investigator Site File (ISF). The investigator should ensure that the IMP is only used according to the protocol.

Meclofenamate has to be stored at 20°C to 25°C. Temperature logging at the site is required to account for compliance to storage temperature.

10.9 Handling of IMP at the site and drug accountability

The study sites will be supplied by the central pharmacy with sufficient study medication. Study medication must be received by a designated person (site delegation log) at the trial site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel has access.

The trial site maintains records to document receipt of the IMP, the stocks of IMP at the trial centre, the dispense and use by the individual subject (drug accountability), the reconciliation, and the return of unused investigational medicinal products and their disposal on appropriate forms.

Verification of drug accountability will be part of on-site monitoring activity. It is the responsibility for the investigator or the monitor (whoever first discovers it) to inform the sponsor delegated person or the coordinating investigator in case of deficiency regarding e.g. storage or accountability of the IMP.

Copies of all forms completed at the trial site will be returned to the sponsor delegated person or the coordinating investigator at the end of the trial or will be collected by the monitor during the close out visit or have to be sent to the sponsor delegated person or the coordinating investigator on request.

The investigator may only dispense the investigational medicinal product to subjects who have signed the informed consent and who have been enrolled in the trial. The dispensing of the investigational medicinal product to subjects outside of this clinical trial is not permitted. The investigator, or an individual who is designated by the investigator, should explain the correct use of the investigational medicinal product to each subject and check at regular intervals that each subject is following the instructions correctly.

10.10 Subject/ Treatment Compliance

At the beginning of the treatment each patient will receive a patient diary to document treatment compliance, co-medication and the occurrence of AEs.

10.11 Return and Disposal of IMP

The subject has to return the unused IMP at Visit 2.9 or at the “end of treatment” visit. All unused IMP should be destroyed in the clinic pharmacy on behalf of the site but only after release of the Sponsor. In case of destruction of IMP, a destruction form has to be completed with the information about date and location of destruction, sort and amount of IMP, and contact details of the person who will destroy the IMP.

Copies of relevant forms completed at the trial site will be returned to the sponsor delegated person or the coordinating investigator at the end of the trial and will be collected by the monitor during the close out visit or have to be sent to the sponsor delegated person or the coordinating investigator on request.

Unused IMP stored at the central pharmacy will be destroyed according to local requirements and documented on appropriate forms including information about date and location of destruction, sort and amount of IMP, and contact details of the person who will destroy the IMP.

11 Therapeutic Regimens, Dose Modifications, Concomitant Medication

11.1 Meclofenamate Dosage, Mode of Application and Dose Schedule

In the USA, MFA is registered and indicated as an NSAID for the treatment (pain relief) of bone/joint diseases (such as rheumatoid arthritis, osteoarthritis, acute pain shoulder), dysmenorrhoea and fever since 1986 for a maximal daily dose of 400 mg qd. AEs under MFA are the ones common to NSAIDs: >10% gastrointestinal problems incl. diarrhea, nausea and abdominal pain; MFA may cause gastrointestinal ulcers, asthmatic/anaphylactoid reactions, or may worsen cardiovascular diseases. Therefore, patients with a history of gastrointestinal ulcers, asthma, anaphylactic reaction to NSAID or severe coronary heart disease or heart failure are excluded. Also, rash, dizziness and headache may occur frequently. In rarer cases, AEs include acute skin reaction, impaired liver or renal function.

11.1.1 Justification for the selected dosage and its regime in phase I

The starting dose of MFA 200 mg/d (100 mg BID) is justified by the fact that it is a standard dose for the use as an NSAID in the USA. This allows that the bulk of existing safety data from the US SmPC is also pertinent for the patients treated in the MecMeth trial, making MFA treatment in the trial particularly predictable and thus safe. The twice daily application of MFA is justified by the fact that this is the regimen applied also in the US trial for recurrent or progressive brain metastases from solid primary tumors (NCT02429570).

11.1.2 Justification for the dose reductions and its steps in phase I

Depending on the DLT rate found in the first dose step, the dose for the second cohort in phase I will be either elevated to 400 mg/d or (200 mg BID), in case DLT has been observed in more than 1/6 patients in cohort 1, lowered to 100 mg/d (50 mg BID). The higher dose of 400 mg/d is justified by the fact that this dose is still within the dose range covered by the US SmPC and can be regarded as safe according to the SmPC data. Further escalation beyond 400 mg/d would be highly experimental and not be easily justified. Therefore, MecMeth/NOA-24 renounces on further escalation. The dose of 100 mg daily is still substantially lower than 200 mg/d but still within a range where efficacy can be expected. Thus, this dose is adequate in case 200 mg/d leads to DLT in more than 1/6 patients. Further de-escalation would not be reasonable since doses below 100 mg/d may have a negative effect on the expected efficacy.

Beyond the potential dose reduction in phase I cohort 2 to 100 mg/d there is no further dose reduction. During the max. 224 days of MFA treatment in phase I, the MFA dose will not be individually reduced since dose reduction would potentially impair the efficacy to MFA treatment. In case of intolerable toxicity (for definition, see below 11.1.5) MFA therapy will be terminated and standard TMZ treatment can be continued at the discretion of the treating physician.

11.1.3 Dosage in phase II

To determine the tolerable MFA dose in the context of glioblastoma and standard TMZ therapy, phase I determines the MFA dose that will be applied in phase II. The dose for phase II is the highest one that leads to DLT (see section 8.1.3 DLT Definition) in less than 2 patients of a 6 patient cohort. The MFA dose in phase II is therefore justified by the low toxicity found in phase I. During the max. 224 days of MFA treatment in phase II, the MFA dose will not be reduced since dose reduction would potentially impair the efficacy to MFA treatment. In case of intolerable toxicity (for definition, see below 11.2.5) MFA therapy will be terminated and standard TMZ treatment can be continued at the discretion of the treating physician.

11.1.4 Instruction for MFA intake

Since the resorption of MFA taken 30 minutes after a meal decreases the bioavailability by 26%, the average peak concentration by factor of 4 and delayed the time to peak concentration by 3 hours, MFA should be taken with a substantial time interval to meals, e.g. in the morning before the first meal which follows at least 1 hour

later and in the evening at least 1 hour prior to or 3h after the last meal. These are also the ideal timepoints for the intake of TMZ, which has a 10% resorption deficit if taken in conjunction with meals.

11.1.5 Termination of MFA treatment

MFA therapy will be terminated in case of tumor progression OR unacceptable toxicity attributable to MFA (CTCAE grade 3 for any other organ toxicity except for asymptomatic laboratory value changes, grade 4 myelotoxicity for >14 days) OR definitive termination of standard TMZ, whatever comes first.

In case of postponement of the following TMZ cycle due to hematotoxicity, MFA treatment will be continued and expanded to a maximum of 250 days.

In case of termination of standard TMZ therapy, MFA treatment will be discontinued at day 28 of the current TMZ cycle.

In case MFA therapy is terminated, standard TMZ therapy can be continued at the discretion of the treating physician.

In case of recurrent disease, salvage therapy is chosen at the discretion of the treating physician.

11.2 Prior and Concomitant Therapy/Medication

11.2.1 Previous therapy / medication

All concomitant medications, received from 30 days prior to study entry until completion/early withdrawal, will be recorded in the CRF at each visit. The information should include the name of the drug, indication for use in this patient, daily dose, and the start and stop date(s) of administration. Patients may receive, at the discretion of the investigator, any other appropriate medical and surgical treatment. Treatment with steroids in the further course of the disease has to be documented on CRF (dose, day).

11.2.2 Concomitant therapy / medication for trial-specific illness

All concomitant therapy or medication needs to be documented in the subjects' medical record and in the appropriate CRF.

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed (except the prohibited medication described in 11.2.4), provided their use is documented in the patient records and on the appropriate CRF.

Standard TMZ therapy

TMZ is a commercially available drug approved for marketing authorization in Germany and used here to treat patients with relapsed glioblastoma as a standard therapy according to SmPc. TMZ is therefore prescribed by the treating physician and provided by the local pharmacy.

Standard TMZ is applied as specified by the currently valid SmPC: TMZ is given on day 1-5 of 28 day courses. The daily dose (d1-5) is 150 mg/m² in course 1; this can be escalated to 200 mg/m² in further courses if no myelotoxicity (neutrophils \geq 1500/ μ l, thrombocytes \geq 100000/ μ l) has occurred in course 1. Temozolomide has to be reduced by one dose stage (dose steps are: 75 mg/m², 100 mg/m², 125 mg/m², 150 mg/m² and 200 mg/m²) in case of neutrophils < 1000/ μ l or thrombocytes < 50000/ μ l.

A prophylactic standard antiemetic regimen using a serotonin antagonist (e.g. ondansetron, tropisetron) prior to administration of standard TMZ is strongly advised. If vomiting occurs during the course of TMZ treatment, no redosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore 2 hour before or a minimum of 3 hours after a meal.

Prophylaxis and treatment of cytopenic side effects of TMZ is performed according to local standard at the discretion of the local investigator.

Gastrointestinal ulcers and/or bleeding

All trial patients receiving MFA should be treated prophylactically with a proton-pump-inhibitor. Patients with a history of ulcer will be excluded. In case signs or symptoms of a GI ulcer the MFA medication has to be stopped immediately.

Steroid medication

Steroid medication is performed at the discretion of the local investigator and documented at each visit. Steroid comedication should be kept as low as possible and as high as needed for adequate symptom control.

The investigators should be aware of the fact that combined NSAR/steroid therapy leads to an even higher risk of gastrointestinal side effects (including ulcer). However, since trial patients will be treated prophylactically with proton pump inhibitors according to local standard, this risk should be minimal.

11.2.3 Concomitant therapy / medication for other indications

All concomitant therapies/medications other than the trial therapy/investigational medicinal product applied during the trial at the discretion of the investigator will be documented in the subject's medical record and in the appropriate CRF.

11.2.4 Prohibited therapy / Concomitant medication

The administration of any other anticancer substance or other anticancer intervention is not permitted. This also applies to agents with hypothetical anticancer effects such as St John's wort extracts, high-dose vitamin therapy, Boswellia acids, any sort of immunotherapy. Similarly, the use of other investigational drugs, experimental radiotherapy beyond standard radiotherapy (stereotactic boost, hyperfractionated radiotherapy) or hyperthermia is not allowed. This also applies to the application of tumor-treating fields.

Furthermore, lithium and methotrexate are not allowed. Considering the risk of potentially bleeding gastric ulcers under MFA, anti-platelet (acetylsalicylic acid, clopidogrel) or anticoagulant therapy are not permitted except for the following anticoagulants which are permitted for low-dose prophylaxis up to the dosage specified here:

	Agent	Dosage
Parenteral anticoagulant	unfractionated heparin	7,500 IU BID or 5,000 IU TID
	low molecular weight heparin	e. g. enoxaparin 40 mg/d
	fondaparinux	2.5 mg/d
	danaparoid sodium	750 IU BID
	argatroban	IV route, thrombin time < 70 s
Oral anticoagulant	vitamin-K-antagonist	INR < 1.8
	dabigatran	150 mg BID
	rivaroxaban	10 mg/d
	edoxaban	30 mg/d
	epixaban	2.5 mg BID

Table 2. Anticoagulants which are permitted in the MecMeth/NOA24 trial for low-dose prophylaxis up to the dosage specified here.

12 Trial Procedures

12.1 Methods of Assessment

The following section will give an overview and adequate explanations to the examinations and procedures to be performed in this trial and will be determined according to the time schedule given in section 2.

12.1.1 Determination of DLTs

For DLT definition refer to section 8.1.3. The assessment of the relatedness of (S)AEs and MFA medication is performed as follows:

- the local physician files a DLT report if he/she thinks that the AE is probably related to MFA (refer to section 14.8);
- a representative of the sponsor assesses the relatedness;
- the DSMB convening when decisions are to be made regarding the next dose level or start of phase II reviews all DLT assessments and gives a recommendation regarding the classification of an adverse event as DLT.

12.1.2 Asservation of tumor material

Patients receiving MFA and relapse tumor resection 7-10 days after initiation of study therapy will provide tumor material for determination of MFA/ MFA metabolite tumor levels according to SOPs for tumor tissue acquisition and processing. The resection should take place within 2-4 hours of intake of the last MFA dose. MFA and metabolite measurements are performed under GLP conditions.

12.1.3 Asservation of blood samples

Patients receiving MFA and relapse tumor resection 7-10 days after initiation of study therapy will provide blood for determination of MFA/ MFA metabolite levels during the first days of treatment until the day (10 ml/day) of resection according to SOPs for blood sample acquisition and processing. MFA and metabolite measurements are performed under GLP conditions.

The total amount of blood per subject drawn for the scientific accompanying program during the entire trial will be maximally 300 ml. This calculation takes into account all optional blood draws as well as a maximum follow-up period of 22 months, which is achievable only for the first patient. Considering a median follow-up time of 10 months, an average blood volume of 200 ml is to be expected.

Time points:

- 2h after first MFA intake
- on the days between MFA start and resection: daily blood sampling 2h after morning application of MFA (optional)
- on the day of resection five blood samples at an interval of 2h: 0h prior to last preOP MFA dose and 2h, 4h, 6h, and 8h later;
- every 8 weeks from visit DLT/ 2.3 throughout follow-up period

12.1.4 Clinical examination

Vital Signs

Vital signs include blood pressure, pulse rate and body temperature.

Blood pressure and pulse rate will be measured in a supine position after the subject has rested for minimum of 5 minutes with an automated or manual instrument. If blood draw is scheduled for the same timepoint this should be performed preferably at the nominal time point, but vital signs should be measure before the blood sample collection.

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Temperature will be measured oral or tympanic in degrees Celsius (°C), pulse rate will be counted for a full minute and recorded in beats per minute.

Physical and neurological examination

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Neurological examination will be documented according to the NANO score.

Physical examination: examination of heart (auscultation), lung (auscultation, percussion), abdomen (auscultation, palpation); palpation of lymphnodes; whole skin examination including adjacent transitional mucosal and oropharyngeal surfaces.

Recording of concomitant medication

The following information will be collected on the patient's records:

- Steroid need: Current dose and highest dose in the last 4 weeks
- Daily TMZ (in mg/m²/d) dose in the last 4 weeks, application performed as specified in the treatment plan
- Further tumor therapy after progression under study treatment (follow-up period)

Karnofsky score

KPS (Karnofsky Performance Score) is an attempt to quantify cancer patients' general well-being and activities of daily life. The Karnofsky Performance Score (KPS) ranking runs from 100 to 0, where 100 is "perfect" health and 0 is death.

- 100 - Normal; no complaints; no evidence of disease.
- 90 - Able to carry on normal activity; minor signs or symptoms of disease.
- 80 - Normal activity with effort; some signs or symptoms of disease.
- 70 - Cares for self; unable to carry on normal activity or to do active work.
- 60 - Requires occasional assistance, but is able to care for most of their personal needs.
- 50 - Requires considerable assistance and frequent medical care.
- 40 - Disabled; requires special care and assistance.
- 30 - Severely disabled; hospital admission is indicated although death not imminent.
- 20 - Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 - Moribund; fatal processes progressing rapidly.
- 0 - Dead

QoL: EORTC C30 and BN20

Quality of Life: The EORTC QoL questionnaire modules QLQ-C30 and BN20 will be used to assess the quality of life. These assessments will be performed on the visits specified in the Time and Events Schedule. Patients will be given these questionnaires to complete by a study center staff member. The staff member will collect each completed assessment and check it for completeness before giving the patient the next assessment to complete.

The European Organization for Research and Treatment of Cancer (EORTC) QoL (Quality of Life Questionnaire) – BN20 is a well validated and internationally recognized questionnaire designed to reflect the core dimensions of patients' QoL. The 30 item questionnaire incorporates five functional scales: general physical symptoms, physical functioning, psychological distress, social functioning, and fatigue/malaise. Most items are rated on a 4 point Likert scale ranging from "not at all" to "very much". Seven questions regarding physical functioning/evaluation of activities of daily living are in a simple dichotomous yes/no format. Two global QoL questions complete the questionnaire and are arranged in visual analogue format with superimposed numbers ranging from 1-7. The questionnaire is designed to be self-administered following a brief explanation of its purpose and format. It takes approximately 10 minutes to complete the questionnaire both in the pretreatment setting as well as while the patients are on treatment. The questionnaire has demonstrated validity in different cancer populations as well as in different disease stages and their associated treatments. Test-retest reliability of the core questionnaire tested within a four day period ranged from good to excellent for all functional scales with Pearson's r values ranging from 0.72 to 0.91. The EORTC QoL-BN20 has been used successfully in several clinical trials.

QoL results are summarized in 26 domains. As proposed in previous trials (Chinot et al., 2014; Schäfer et al., 2016; Weller et al., 2019) domains of particular interest for brain tumor patients are preselected for particular consideration (global health status, physical functioning, social functioning, cognitive functioning, communication deficit and motor dysfunction).

Mini-Mental-state examination (MMSE)

The Mini Mental state examination (MMSE, first described by Folstein et al in 1975) is a widely used test of cognitive functions. It includes tests of orientation, attention, memory, language and visual-spatial skills.

In this test, the patient can reach up to 30 points (no cognitive impairments). If the result is <27 but >25, it is assessed as mild cognitive impairment. The next steps are <24 but >18: mild dementia; <17 but >10: moderate dementia; <10: severe dementia.

In this study, it will be measured to evaluate cognitive deficits and associated reduction in quality of life throughout the trial.

12.1.5 MRI and response assessment

Contrast-enhanced MRI scans are analyzed for progression locally at the trial site and study-relevant decisions are made on the base of the local evaluation. Additionally, all MRIs are collected at the Neuroradiology reference center at the Department of Neuroradiology, University of Bonn (blinded scans) and will receive post-hoc reanalysis at the end of the trial. The MRIs should be sent as electronic files online or on CD/DVD. The MRIs have to be sent blinded (only labelled with Pat.-ID and visit number) to ensure unbiased progression assessment.

The following MRI protocol is suggested:

- Pre-contrast injection: T1-w (e.g. spin echo, SE); T2-w (e.g. turbo-spin-echo, TSE); T2- fluid-attenuated inversion recovery (FLAIR); Diffusion-weighted imaging (DWI); Susceptibility-weighted imaging (SWI); 3D T1-w (e.g. gradient-echo, GRE)
- Post-contrast injection: T1-w Spin-Echo (e.g. spin echo, SE); 3D T1-w (e.g. gradient-echo GRE)

Progression-free survival: The progression-free survival is defined as the time from randomization to the first documented evidence of progression of disease according to the RANO criteria. PFS is measured from randomization (phase II)/inclusion (phase I) until progression or death.

Progression-free survival (PFS, Primary endpoint in phase II) builds on the RANO criteria (Wen et al., 2010) that include the following criteria for complete and partial response, stable disease and progression:

- **Complete Response (CR):** Disappearance of all measurable contrast enhancing lesions in magnetic resonance imaging at least 4 weeks apart, T2/FLAIR lesions stable or decreasing, without steroids and neurologically stable or improved.
- **Partial Response (PR):** At least 50% reduction in the size of all measurable contrast enhancing lesions in magnetic resonance imaging at least 4 weeks apart, T2/FLAIR lesions stable or decreasing, steroids stable or reduced, and neurologically stable or improved.
- **Stable disease:** Less than 50% reduction or less than 25% increase in the size of a solid mass or all contrast enhancing lesions in magnetic resonance imaging, with no escalation of steroid treatment and no neurological deterioration.
- **Progression:** At least 25% increase in the size of measurable contrast enhancing lesions in magnetic resonance imaging OR clear increase of a non-measurable lesion or the appearance of a new lesion OR significantly increasing T2/FLAIR hyperintensities (only if other causes for increased T2/FLAIR hyperintensities are unlikely such as radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects) OR clear and significant worsening of the neurological status not attributable to other causes apart from the tumor (see above)

Overall survival is measured from randomization (phase II)/inclusion (phase I) to death or last seen alive (censored observation).

12.1.6 Laboratory testing

Clinical Laboratory Tests: Laboratory tests at each visit will be performed at the Laboratory of the treating University Medical Center. Laboratory tests taken between the visits outside the center will be reviewed by the investigator. Any clinically relevant changes occurring during the study must be reassessed in the University Medical Center Laboratory, assessed for identification of AEs by the investigator and recorded, if applicable, in the adverse event section of the CRF.

12.2 Time schedule of Measurements

A deviation of more than 3 days regarding the defined time points for each visit is regarded as a protocol deviation. This does not apply to the delay of chemotherapy courses due to prolonged toxicity in the previous course.

12.2.1 Screening Visit (V0)

All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the trial.

Clinically significant findings at Screening visit (visit 0) which describe the baseline status of the subjects will be documented as concomitant disease under medical history.

This requires the unequivocal demonstration of first progression according to RANO criteria and a time interval of >3 months after last first-line chemotherapy and >6 months after last day of first-line radiotherapy.

Procedures:

- Informed consent,
- medical history and demographics.
- I/E criteria
- Documentation of concomitant medication
- Steroid need
- Physical and neurological examination
- Vital signs

12.2.2 Baseline Visit (V1)

Baseline visit (the day of inclusion (phase I) or randomization (phase II)) is determined as day 1 ONLY for survival analyses.

The following study-related procedures are included in the baseline visit which is concluded with inclusion (phase I) or randomization (phase II) of the patient:

- I/E criteria,
- documentation of preexisting conditions in analogy to CTCAE5,
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication
- steroid need
- Karnofsky Score
- Mini Mental State examination
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires
- (S)AE evaluation prior to MFA therapy
- Gd-enhanced MRI: a maximum of 14 days between MRI acquisition and start of therapy is allowed.
- Pregnancy test: beta HCG in serum
- HIV, Hepatitis B and C serology
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- EEG or MEG analysis (optional)

12.2.3 Treatment period (V2)

The treatment period will include a maximum of 9 visits from day 1 after MFA treatment start until 3 days after the last intake of MFA (end of therapy).

V 2.1: Day 1 of MFA treatment (only patients receiving MFA, no delay allowed)

MFA treatment starts within 7 days of inclusion (phase I) or randomization (phase II) in the trial and not later than the start of the first course of the standard TMZ therapy.

- Phase I: On day 1, MFA has to be taken in the center (may not be administered together with a meal), followed by blood sampling 2h later for MFA blood concentrations: 10 ml serum, stored and processed according to SOP "Blood sampling for determination of MFA levels"
- In phase II only patients undergoing tumor resection on day7-10 after initiation of MFA therapy will have blood sampling as described above
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication
- steroid need
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Pregnancy test: beta HCG in serum
- Blood sampling for analysis of factors potentially correlating with tumor progression or MFA effects in tumors and for biobanking: 10 ml blood, processed according to SOP "Blood sampling for biobanking".

V OP: Day of resection of the tumor 7-10 days after initiation of therapy (no delay allowed)

- Asservation, processing and storage of fresh frozen tumor material for analysis of MFA-dependent tissue effects, following SOP "Tissue asservation and processing". Tumor tissue has to be obtained 2-4h after last MFA intake
- Asservation, processing and storage of 4% PFA-fixed tumor material and paraffin-embedded tumor

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material (one block or 20 slices) for analysis of MFA-dependent tissue effects, following SOP "Tissue asservation and processing"

- Asservation of blood samples (10 ml serum) for determination of MFA serum levels prior to the last MFA intake in the morning of the resection and 2h, 4h, 6h and 8h later. Asservation and storage according to SOP "Blood sampling for determination of MFA levels"

If in phase II, patients in the standard TMZ arm are resected under ongoing TMZ therapy, fresh frozen, 4% PFA-fixed and paraffin-embedded tissue can also be asserved and stored, bloods samples will not be taken

V 2.2: Four weeks (day 28) after start of MFA or standard TMZ therapy (tolerance of +/-3 days)

- Determination of DLT (ONLY phase I)
- documentation of AEs according to CTCAE5,
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication and steroid need (mg dexamethasone) and temozolomide dose (in mg/m²) in the last 4 weeks
- survival and progression status
- Karnofsky Score
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Pregnancy test: beta HCG in serum
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires

Phase I V DLT: Eight weeks (day 56) after start of MFA or standard TMZ therapy (tolerance of +/-3 days)

Phase II (to be performed in Phase I only if the beginning of cycle 3 is prolonged by more than 3 days) V 2.3: Eight weeks (day 56) after start of MFA or standard TMZ therapy (tolerance of +/-7 days)

- Determination of DLT (ONLY phase I)
- documentation of AEs according to CTCAE5,
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication and steroid need (mg dexamethasone) and temozolomide dose (in mg/m²) in the last 4 weeks
- survival and progression status
- Karnofsky Score
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Pregnancy test: beta HCG in serum
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires
- Gd-enhanced MRI for determination of tumor progression.
- Blood sampling for analysis of factors potentially correlating with tumor progression or MFA effects in tumors and for biobanking: 10 ml blood, processed according to SOP "Blood sampling for biobanking"

V 2.4 – 2.8: Every 4 weeks during MFA therapy (maximum 224 days = 32 weeks = 8 4 weeks courses, tolerance of +/-7 days))

- documentation of AEs according to CTCAE5,
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication, steroid need (mg dexamethasone) and temozolomide dose (in mg/m²) in the last 4 weeks
- Survival and progression status
- Blood count with differential and CRP

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- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Pregnancy test: beta HCG in serum

Additional examinations for V 2.5, 2.7

- Survival and progression status
- Karnofsky Score
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires
- Gd-enhanced MRI for determination of tumor progression.
- Blood sampling for analysis of factors potentially correlating with tumor progression or MFA effects in tumors and for biobanking: 10 ml blood, processed according to SOP "Blood sampling for biobanking"

12.2.4 End of Treatment (V3 or premature termination)

End of therapy 3 days after last MFA intake (phase I and experimental arm of phase II) or day 26 after last TMZ intake (standard arm of phase II)

- documentation of AEs according to CTCAE5,
- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of concomitant medication and steroid need (mg dexamethasone) and temozolomide dose (in mg/m²) in the last 4 weeks
- Survival and progression status
- Karnofsky Score
- Mini Mental State examination
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Pregnancy test: beta HCG in serum

12.2.5 Follow-up period (V4)

Follow-up after end of therapy, every 8 weeks, beginning 8 weeks after the last evaluation with Gd-enhanced MRI

- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of medication incl. further anti-tumor therapies and steroid need (mg dexamethasone)
- Survival and progression status
- Karnofsky Score
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires
- Gd-enhanced MRI for determination of tumor progression.
- Blood sampling for analysis of factors potentially correlating with tumor progression or MFA effects in tumors and for biobanking: 10 ml blood, processed according to SOP "Blood sampling for biobanking"

12.2.6 End of Study (V5)

The following procedures will be performed at the final visit or in case for subjects who withdraw from the trial and will terminate the trial prematurely:

End of study and end of follow-up in the entire trial will be reached when BOTH of the following requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).

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- vital signs (blood pressure, pulse rate, temperature),
- physical examination,
- neurological examination (documented according to the NANO score),
- documentation of medication incl. further anti-tumor therapies and steroid need (mg dexamethasone)
- Survival and progression status
- Karnofsky Score
- Blood count with differential and CRP
- Serum chemistry (Na, K, creatinine, ASAT, ALAT, bilirubine) and urine analysis
- Health-related quality of life (QoL) determined by the EORTC-QLQ C30 and BN20 questionnaires

12.2.7 Unscheduled Visit

- vital signs,
- physical and neurological examination,
- concomitant medication,
- steroid need,
- further tumor therapy
- KPS,
- Differential blood count, serum chemistry and urine analysis,
- CTCAE evaluation (only during ongoing MFA treatment + 3 days),
- contrast-enhanced MRI scan and progression assessment (only if clinically indicated)

13 Definition of End of Trial

13.1 Regular End

13.1.1 Phase I

The regular end of trial is as Last Patient Last Visit:

- *if phase II starts*: until end of the entire study (phase I + phase II) which will be reached when the following 2 requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving therapy (i.e. all patients have concluded study-related MFA intake for more than 3 .days).
- *in case phase II is never started*, survival parameter recording is concluded when the following 2 requirements are fulfilled for phase I patients: (1) at least 6 months after inclusion of the last patient AND (2) at least 3 days after definite termination of MFA intake in all phase I patients

13.1.2 Phase II

Follow-up per patient phase II: End of study and of follow-up in the entire trial will be reached when BOTH of the following requirements are fulfilled: (1) at least 6 months after randomization of the last patient in phase II AND (2) at least 3 days after definite termination of MFA intake in the last patient receiving MFA therapy (i.e. all patients have concluded study-related MFA intake for more than 3 days).

The regular end of trial is defined as Last Patient Last Visit.

13.2 Premature Termination

13.2.1 Termination of Phase I

The sponsor/coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of the entire clinical trial. The sponsor/coordinating investigator will be supported in this responsibility by a data and safety monitoring board (DSMB) meeting at least after conclusion of each dose level. The reasons for such a decision should be documented in written form. The recommended MFA dose for phase II is the highest MFA dose that does not lead to DLT in more than 1/6 patients during the first 8 weeks of MFA therapy. If even the lowest dose level of 2 x 50 mg gd MFA leads to DLT in more than 1/6 patients, phase II of the trial cannot be performed. Furthermore, the trial can be terminated prematurely in case of withdrawal of the import or manufacturing licence of the IMP.

13.2.2 Termination of Phase II

In phase II, the DSMB and/or the sponsor-delegated person can stop the trial transiently or permanently for any safety reason. In this small phase I/II trial there is not stopping rule based on efficacy parameters

The entire clinical trial must be stopped prematurely if:

- New toxicological or pharmacological or SAEs invalidate the earlier benefit-to-risk ratio for the subject.
- Adverse events occurring in such severity and frequency that the proposed schedule can no longer be adhered to.
- The sponsor/coordinating investigator (German LKP) considers that the termination of the trial is necessary.
- Indications arise that the subjects' safety is no longer guaranteed,
- The question(s) addressed in the trial can be clearly answered on the basis of an interim analysis,
- An insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible.
- The import or manufacturing licence of the IMP is withdrawn.

13.2.3 Termination of the Trial in Individual Sites

Both the investigator and the sponsor/sponsor delegated person have the right to terminate the trial at one of the centers at any time under the following conditions:

Unforeseeable circumstances have arisen at the trial center that preclude the continuation of the clinical trial.

- The investigator considers that the resources for continuation are no longer available.
- The investigator considers that the continuation of the trial is no longer ethically or medically justifiable.
- Subject recruitment is inadequate.
- Serious problems arise with regard to the quality of the collected data which cannot be resolved.
- Withdrawal of the opinion of the EC and/or regulatory authority.

Premature termination at one of the trial centers does not automatically mean a termination of already enrolled trial subjects. A separate decision on further treatment must be made for each subject, depending on the overall situation. So, it has to be clarified that:

- An adequate further treatment and follow-up of already enrolled subject subjects must be ensured.
- The documentation of already enrolled subject subjects will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the centre is closed. These queries must be answered properly by the centre.
- The competent authority(ies) and ethics committee(s) must be duly notified of the centre's closure, including reasons, within the specified period(s).
- The trial centre concerned will be closed in stages by the clinical monitor when a decision has been made on the further treatment of the subjects concerned.

13.3 Discontinuation Rules for Study Treatment

13.3.1 Discontinuation by Patient

Subjects may withdraw from the trial at any time at their own request without stating the reason(s) for withdrawal. They will experience no disadvantage as a result of this decision and no alternative therapy will be withheld by the investigator. The investigator should inquire about the reason for withdrawal. Patients retracting their consent for study treatment will be asked to stay in the follow up for their own safety and to obtain follow up data. If they are not willing to do so, the investigator is urged to ask the subject to return for an early termination visit and to document subject outcome, if possible. The subject has to be requested to return all unused investigational product. Any clinically significant abnormalities persisting at withdrawal will be followed by the investigator until resolution or until reaching a clinically stable endpoint. If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

13.3.2 Discontinuation by Investigator

Subjects may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Whenever a subject is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the CRF. All patients who are discontinued from study therapy for any reason have to be followed according to the study protocol with clinical and MRI investigations (see section 12.2.5 Follow-up period (V4)) until the end of the follow-up-time of the whole trial.

Discontinuation rules for study treatment

For the individual patient, MFA therapy within the trial will be stopped if one of the following criteria applies

1. Unequivocal MRI signs of disease progression according to RANO criteria
2. CTCAE5 grade 4 myelotoxicity/hematotoxicity for >14 days in courses 1 and 2 related to MFA treatment

3. CTCAE5 grade 3+ for any other organ toxicity related to MFA treatment except for asymptomatic laboratory changes CTCAE5 grade 3
4. Definitive termination of standard TMZ therapy
5. Any event that leads to a delay in TMZ dosing lasting > 8 weeks from the beginning of the previous course of TMZ
6. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued meclofenamate application.
7. Pregnancy
8. Lack of compliance of the subject (e.g. taking prohibited medication)
9. Significant protocol violations
10. events probably related to the tumor resection/perioperative treatment or the underlying disease will not lead to discontinuation

13.4 Further treatment after termination of the clinical trial

The specialists at the neuro-oncology center where the study treatment (and usually also the pre-treatment) was carried out will care for the patient. In case of progression under or after MFA therapy or standard TMZ therapy alone, a proposal for the type of further treatment is decided in the Neurooncology Tumor Board of the treating Center for Neurooncology. It should be noted that

- In case of termination of standard TMZ therapy, MFA treatment will be discontinued at day 28 of the current TMZ cycle.
- In case MFA therapy is terminated, standard TMZ therapy can be continued at the discretion of the treating physician.
- In case of recurrent disease, salvage therapy is chosen at the discretion of the treating physician.

14 Safety Data Collection, Recording and Reporting

Safety data collection, documentation and reporting of adverse events will be performed according to the applicable laws and regulations (AMG, GCP-V, Regulation EU No 536/2014, once it comes into effect).

Details regarding safety data documentation and reporting are specified in the Safety Management Plan (SMP) of this trial. The Investigator's Brochure (IB) for Meclofenmate will be used as reference document referring to safety specifications.

The investigator will be provided with AE and SAE reporting forms by SZB and will receive training for AE/SAE definition, documentation and reporting. The AE/SAE documentation and reporting will be monitored on site.

14.1 Definitions

14.1.1 Adverse Event (AE)

An Adverse Event is defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse. Any findings that have improved compared to the status at baseline are not adverse events.

14.1.2 Adverse (Drug) Reaction (AR)

An adverse reaction is any adverse and unintended reaction to an investigational product, regardless of the dosage. Any adverse event for which the investigator and/or sponsor have assessed the causal relationship with the investigational product as possible is considered a suspected adverse reaction.

14.1.3 Unexpected Adverse (Drug) Reaction (UAR)

An adverse reaction, in which the nature or severity of the event is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

14.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

A serious adverse event or reaction is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Leads to permanent or serious disability or to invalidity, or
- leads to congenital malformations or birth defects
- is another, according to medical assessment, clinically relevant event.
 - 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it has been more severe
 - In general, 'hospitalization' signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious
 - In-patient stays without an underlying adverse event are not SAE (e.g.: elective in-patient

treatment due to a pre-existing condition; inpatient admission for social reasons; admission to a rehabilitation clinic or hospice)

- The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm that do not result in hospitalisation, other examples include the development of drug dependency, drug abuse or overdose.

14.1.5 Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)

A SUSAR is an adverse reaction, which is suspected, serious and unexpected. Serious Adverse Reactions (SARs) are considered "unexpected" if they are not consistent with the information provided in the currently valid reference document (IB) in terms of their nature, severity, manifestation, and outcome.

14.2 Criteria to be evaluated by the investigator (1st assessment)

By including the patient in the clinical trial, all adverse events (AEs), including intercurrent diseases, must be documented in the patient file and subsequently in the CRF. Disease signs, symptoms and laboratory changes should, as far as possible, be combined **into one single diagnosis**. The documentation of the event shall include the following criteria: "type", "beginning and end" and "outcome of the event" (recovered, improved, unchanged, recovered with sequelae, worsened, death, unknown). The event is then evaluated according to the following criteria:

14.2.1 Assessment of Intensity

An assessment of intensity grade will be made using the general categorical descriptors outlined in the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e. g, laboratory abnormalities).

14.2.2 Assessment of Seriousness (AE vs. SAE)

Determination of the seriousness of the adverse event according to the definitions for a serious adverse event (SAE) given in section 14.1.

14.2.3 Assessment of Causality

Determination of the relationship of the adverse events to the medicinal product being studied after having evaluated all accessible data according to the following classification:

Suspected relationship (related):

The temporal relationship between the event and the administration of the IMP makes a **causal relationship possible, probable, or definite**, or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No suspected relationship (not related):

The temporal relationship between the event and the administration of the IMP makes a **causal relationship unlikely or impossible (i.e. not related)**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

When the final causality assessment is unknown and it is **uncertain** whether or not the investigational product caused the event, then the event should be handled as an SAE **related** (suspected) to the investigational product for reporting purposes.

The evaluation should consider nature and pattern of the reaction, temporal relationship to study medication, the clinical status of the patient, the concomitant medication and other relevant parameters. If the investigator believes that the SAE is not related to the investigational product but is potentially related to the conditions of the study the relationship should be specified in the narrative section of the SAE report form.

14.3 Criteria to be evaluated by the Sponsor (2nd assessment)

To take into account safety data available to the sponsor but not to the investigator at the time the SAE was detected, in addition to the initial assessment of a serious adverse event by the investigator, a second assessment of the event by the sponsor in terms of causality and probability of occurrence ("expectedness") and a continuous benefit-risk assessment are performed.

- **Causality:** If no information on causality is available from the investigator, the sponsor should consult the investigator and ask him to comment on this aspect. The sponsor cannot not downgrade the investigator's assessment of causality. If the sponsor disagrees with the investigator on the causal link, the report should include the opinion of both the investigator and the sponsor.
- **Expectedness:** Whether a serious adverse reaction is to be expected is assessed using the currently valid reference information on safety (RSI). If the investigator has provided information on whether an event is expected, the sponsor should take this into account.

14.4 Documentation and Reporting of AEs

Any AE defined in Trial protocol as relevant for the evaluation and analysis of the clinical trial has to be documented in the CRF on the respective Adverse Event Report Form. Documentation and evaluation of each AE occurring between:

- the baseline visit
- the visit at least 3 days (>5 MFA half-life times) after the termination of MFA administration

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0)

According to the GCP-V, only adverse events and unexpected clinical diagnostic findings that are identified in the protocol as critical for clinical trial evaluation must be documented/transmitted to the sponsor.

All medical conditions prevalent prior to study enrolment and all Adverse Events (AE) that occur during the screening period and within 3 days of discontinuation of dosing will be collected throughout the study and documented in the subject's medical record using medical terminology and transferred to the CRF. If applicable, AEs and SAEs that relate to any later protocol-specified procedure will be recorded. Furthermore, the investigator should report any SAE that occurs after these time periods and that is believed to be related to the study drug. An SAE report should be completed for any event where doubt exists regarding its seriousness. To ensure comparability of the safety data of the two study arms any adverse medical incident in patients of

the control arm will also be recorded although no study drug will be administered. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. All measures required for adverse event management must be recorded in the source document and reported according to sponsor's instructions. The investigator evaluates all Adverse Events regarding severity, causality as well as seriousness.

14.5 Reporting of SAEs

Every SAE has to be reported immediately to Study Coordinating Center of the SZB except those SAEs the protocol mentions in 14.5.1

The documentation of the SAEs for a patient is carried out as described under 14.4, the reporting of SAEs for study patients is carried out within the following time periods:

- after the subject has been randomized and has received trial drug for the first time up to 3 days after the subject has received the last dose of trial drug

14.5.1 Serious Adverse Events exempted from reporting

The following adverse events are documented but do not need to be reported, even if the investigator considers the events to be serious:

- Progression of the glioblastoma: Since progression-free survival is one of the endpoints of this study, each progression of the underlying disease is documented.
- Events probably related to the tumor resection/perioperative treatment, temozolomide treatment or to the underlying disease as long as the severity of the event is to be expected and not aggravated.
- Asymptomatic grade 3 laboratory abnormality deemed clinically not significant.

14.5.2 Reporting of Serious adverse events

Reporting of SAEs to Studienzentrale Studienzentrum Bonn (SZB)

IMMEDIATELY

upon becoming aware of the event

(at the latest within 24 hours)

FAX: +49 (0)228 287 9080110

E-MAIL: safety-szb@ukbonn.de

Reporting should occur by fax on the **SAE report form** provided for this purpose. Symptoms, signs and laboratory changes should, as far as possible, be combined **into one single diagnosis**. The investigator is responsible for assessing the event (seriousness, intensity, causality). If necessary information is not fully available at this time, follow-up reports should be sent as soon as possible. Questions must be answered promptly. Further information and details how to report are described in the **Safety Management Plan**.

14.5.3 Reporting of Serious adverse events to authorities and ethics committees

AEs

The sponsor shall submit the documentation of AEs to the responsible higher federal authority (BfArM) upon request.

SAR

All SAR will be reported by the sponsor as SUSAR.

SUSARs

The sponsor has to inform the responsible ethics committee, the competent higher federal authority (BfArM) and the investigators involved in the clinical trial **immediately**, but **not later than 15 days** after becoming aware of any suspected unexpected serious adverse reaction (SUSAR).

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For each suspected unexpected serious adverse reaction (SUSAR) that has led to **death** or is **life-threatening** and of which the sponsor becomes aware, the sponsor should immediately, but **no later than 7 days** after becoming aware, provide all information relevant for the assessment to the responsible ethics committee, the competent higher federal authority (BfArM) and the investigators involved in the clinical trial and **within a further maximum of 8 days** the sponsor should provide the follow up information.

Re-examination of the risk-benefit assessment

The sponsor shall immediately, but **no later than 15 days** after notification, inform the competent ethics committee and the competent higher federal authority (BfArM) of any matter requiring a reassessment of the risk-benefit assessment of the investigational product. This includes in particular:

- individual case reports of expected serious adverse reactions with an unexpected outcome
- Raise in frequencies of expected serious adverse reactions that are considered clinically relevant
- suspected cases of serious unexpected side effects arising after the trial participant has completed the clinical trial
- Events related to the conduct of the trial or the development of the investigational product that may affect the safety of subjects.

Development Safety Update Report (DSUR)

The sponsor provides a report on the safety of the trial participants to the responsible ethics committee and the responsible higher federal authority (BfArM) at least once a year during the clinical trial or upon request. The safety report is prepared in accordance with the ICH Guideline E2F "Development Safety Update Report - DSUR".

The data-lock point of the patient data included and analyzed in the report refers to the date of approval of the clinical trial by the higher federal authority. The sponsor will provide the report within 60 days of the data-lock point annually.

For further details please see section 19.1.

Arrangements to protect trial participants against imminent danger

Whenever the safety of subjects is compromised and the sponsor and investigator are taking measures to protect subjects from imminent danger, the sponsor has to inform the responsible Ethics Committee and the BfArM of such arrangements and their underlying circumstances, as soon as possible.

14.6 Pregnancy

Women of childbearing potential are required to have a negative serum β -hCG pregnancy test to exclude a pregnancy before being enrolled in the clinical trial. Pregnancy testing will be conducted within 7 days prior to the first dose of trial drug and during treatment if clinically indicated. Furthermore, females of childbearing potential have to use medically reliable methods of contraception for the entire study duration.

Any pregnancy that occurs during study participation must be reported to the Sponsor. To ensure subject safety, each pregnancy must be reported immediately after awareness of learning of its occurrence. For this purpose, the investigator documents and reports the pregnancy on the registration form provided for this purpose and remits this immediately (at the latest after 24 hours) to the Study Center Bonn.

The pregnant subject has to discontinue the treatment with the IMP permanently and has to be excluded from the trial and has to be instructed to return any unused portion of the study drug to the investigator.

The pregnancy itself is not classified as an AE or an SAE, but must be followed up to determine outcome (including premature termination) and status of mother and child. The investigator will request this information after the scheduled date of birth and provide it in writing to the (sponsor/sponsor's representative).

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be reported.

In addition to this information, the examiner will also ask about the planned date of birth and inform the (sponsor/representative of the sponsor) in writing.

If the outcome of the pregnancy corresponds to one of the following cases

- spontaneous or therapeutic abortion or voluntary abortion
- stillbirth
- the presence of birth defects, or
- congenital anomalies (also in miscarriages, stillbirths or premature death)

the auditor reports this case as SAE. In the case of stillbirth, the (presumed) causality is documented.

14.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 14.1.4 for reporting details).

14.8 DLT Reports

For DLT definition refer to Section 8.1.3. The assessment of the relatedness of (S)AEs and MFA medication is performed as follows:

1. the local physician files a DLT report if he/she thinks that the AE is probably related to MFA;
2. a representative of the sponsor determines the relatedness;
3. the DSMB reviews all DLT assessments and gives a recommendation regarding the classification of an adverse event as DLT when decisions are to be made regarding the next dose level or start of phase II.

14.9 Data and Safety Monitoring Board (DSMB)

The independent DSMB consists of 4 members: a neurooncologist, a neurosurgeon, a medical oncologist and a statistician. A DSMB charta details the task of the DSMB. In summary, the DSMB reviews safety data and recruitment data and provides a recommendation for the further proceeding of the trial to the sponsor. In phase I, the DSMB convenes (1) after a maximum of 6 patients per dose step are evaluable for DLT with the purpose to give a recommendation regarding the dose for step 2, (2) after a maximum of 6 patients per dose step are evaluable for DLT with the purpose to give a recommendation regarding the dose for phase II, (3) about 6 months after recruitment of the first patient of phase II to oversee adverse events in phase II and (4) after all patients have concluded MFA therapy. The sponsor or the DSMB itself can schedule additional meetings at any timepoint.

15 Statistics and Analysis

15.1 Trial Design

See also section 8.

15.2 Randomization (Phase II)

The allocation to the treatment group in the phase II part will be performed via the validated randomization tool of the eCRF system in the Study Center Bonn (SZB) (MARVIN). The randomization will be performed using permuted blocks with a variable block size.

Phase II is randomized to allow a more reliable comparison with standard treatment. Considering that survival times in trial populations of patients with MGMT-methylated glioblastoma is constantly increasing over the last 15 years (from 21.7 months to 31.4; Herrlinger et al., 2019) without changing the standard of therapy, the implementation of a standard arm appears to be superior to the use of historical controls.

Low sample sizes generally do not allow a meaningful stratification for common prognostic factors. Instead we will perform subgroup analyses to evaluate the influence of such factors.

15.3 Target Variables/Endpoints and their Analyzes

15.3.1 Primary Target Variable

Phase I

Primary endpoint toxicity: Incidence of DLTs and subsequent determination of the optimal dose for phase II does not require extensive statistical analysis. To have robust results and the required number of patients with all necessary data for determining the phase II dose, early drop-out patients/patients with insufficient data for 8-weeks DLT will be replaced. For DLT definition refer to section 8.1.3.

Phase II

Primary endpoint PFS: PFS is analyzed using a two-sided logrank test and a Cox regression analysis to estimate the hazard ratios in the ITT population of the Phase II part. Progression-free survival (PFS) is measured from the day of randomization until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center.

Additional sensitivity analysis will be performed including also the patients of the Phase I part who received the dose of MFA planned for the phase II part.

15.3.2 Secondary Target Variables

Secondary endpoints: Additional analyses will include a post hoc analysis of the primary endpoint PFS as reviewed centrally by a neuroradiologist (Department of Neuroradiology, Univ. Hospital Bonn) blinded to the treatment protocol. This analysis will also be performed on the two populations specified for the primary endpoint.

Overall survival (OS) is analyzed using a two-sided logrank test and a Cox regression analysis to estimate the hazard ratios in the ITT population. OS is measured from the day of randomization until diagnosis of progressive disease determined by MRI (RANO criteria) in the local center. This analysis will also be performed on the two populations specified for the primary endpoint.

Descriptive Cox regression analyses for common prognostic factors (Age, KPS) and subgroup analyses for categorized common prognostic factors are also included.

Phase II also includes descriptive statistics of all AEs (with reference to number of patients and number of MFA/TMZ courses applied) during therapy. Dose reductions of TMZ, delay of TMZ therapy in subsequent courses and premature withdrawals and development of KPS throughout the trial will also be described.

MFA/MFA metabolite tumor tissue and serum levels in patients resected after the start of MFA therapy are described.

Quality of life (QoL) is recorded through the standardized and validated EORTC QLQ-C30 and BN20 questionnaires (Osoba et al., 1996). The scores for the different dimensions will be compared between repeated assessments throughout the trial and between the two arms of the trial. As proposed in previous trials (Chinot et al., 2014; Schäfer et al., 2016; Weller et al., 2019) domains of particular interest for brain tumor patients are preselected for particular consideration (global health status, physical functioning, social functioning, cognitive functioning, communication deficit and motor dysfunction).

More details of the statistical analysis will be specified in the SAP of the trial.

15.3.3 Sample Size Calculation

Phase I

Phase I uses an adaptive design based of DLT. Starting with 3(-6) patients per dose level is standard for dose finding in phase I. Starting with a middle level MFA dose of 2 x 100 mg /d ensures that only 2 dose levels have to be explored (n= 6-12 patients). Patients not evaluable for DLT or MFA tumor levels will be replaced (conservative estimate: 1/6 patients; thus maximal patient number in phase I: 12+2=14).

A patient is evaluable for DLT

- if the DMSB has determined that a DLT has occurred in this patient (independent of the duration of MFA intake)
- if until DLT visit (day 56 +/- 3 days after start of MFA treatment) the patient has taken at least 100 doses of MFA (i.e. 89.3% of the maximally positive cumulative dose in 56 days) as documented by the patient's diary and the documented return of 1 empty container of Meclofenamate (containing 100 capsules) (for dose step 2 x 100 mg daily or 2 x 50 mg daily) or of 2 empty containers of Meclofenamate (for dose step 2 x 200 mg daily).

Phase II

The randomized phase II part accrues 30 patients per arm. For the evaluation of PFS, the experimental arm also includes the 3-6 patients of phase I which have been treated with the same dose of MFA as in phase II for an additional analysis. Since phase II is searching for indications of efficacy but is not primarily a confirmatory trial, drop-outs will not to be replaced. In GBM trials, the drop-out rate is relatively low (9% in CeTeG/NOA-09).⁹ Therefore, and since data from drop-out patients are included as censored observation, the results may be expected to be robust regarding patients with short follow-up/early drop-outs.

With 30 subjects per arm and a two-sided alpha-level of 10% we can detect a hazard ratio of approximately 0.44 if we assume a PFS-6 of 40% for the reference treatment and use a power of 80%.

15.3.4 Definition of Populations Included in the Analysis

This clinical trial will be analyzed according to the intention-to-treat (ITT) principle. This means that the subjects will be analyzed in the treatment arms to which they were randomized, irrespective of whether they refused or discontinued the treatment or whether other protocol violations are revealed.

The per-protocol (PP) population is a subset of the ITT population and is defined as the group of subjects who had no major protocol violations, received two 4-week courses of MFA and underwent the examinations required for the assessment of the endpoints at relevant, predefined times. The analysis of the PP group will be performed for the purpose of a sensitivity analysis.

15.3.5 Phase I Interim Analyses

An interim analysis is planned for the point of time when the first and second cohort has been treated for 56 days with MFA. The interim analysis and interim report will describe subject recruitment, treatment compliance as well as safety and tolerability and the occurrence of any DLT for the subjects in this period. Efficacy parameters will not be analyzed. After data cleaning and analysis, the interim report will be submitted to the data and safety monitoring board (DSMB) to obtain its advice.

15.3.6 Protocol Violations

Protocol violations are major deviations from the procedures outlined in this document like:

- missed relevant evaluations
- incorrect timing of evaluations
- non-compliance with investigational medicinal product, if applicable
- the intake of medications not allowed
- any non-adherence to the protocol that would have an impact to the subject's rights, safety or welfare or on the primary aim of the trial.

After a subject has been enrolled, it is the investigator's responsibility to make a reasonable effort to correct any protocol violations and to continue the subject's participation in the trial, if possible.

Protocol violations do not per se constitute a justification for withdrawal of a subject from the trial.

Protocol violations will be reported to the sponsor/sponsor delegated person during the course of the trial in the monitoring reports.

All protocol violations will be listed and the impact on the evaluation of the subjects concerned will be discussed prior to statistical analysis.

15.3.7 Handling of Drop-outs, Withdrawal, and Missing Data

Phase I

Patients not evaluable for DLT will be replaced.

Phase II

- Subjects dropping out of the trial prior to randomization will be listed as screening failures including the reason of drop-out.
- Subjects dropping out of the trial after randomization will be analysed using all available data and will not be replaced.

Subjects prematurely discontinuing the trial will be censored regarding the analysis of PFS or OS at the time of discontinuation. The technique for the analysis of missing values will be defined in the statistical analysis plan. A check of a possible treatment effect on the frequency of missing values will be done.

16 Data Collection, Handling and Record Keeping

16.1 Data Management

Data management of the study will be carried out by the SZB (section IMBIE). The study data is recorded and stored in a suitable, validated CDMS (Clinical Data Management System). Details on data management (procedures, responsibilities, data corrections, if any, which may be made by Data Management staff themselves, etc.) will be described in a **data management plan** prior to the trial. During the trial, the performance of data management and any deviations from the data management plan will be documented in a data management report. Queries and edit checks will be specified in a **data validation plan**. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented in an specific item list.

The study data is entered into the study database directly at the centre by trained staff. The access and processing rights in the study database are defined by predetermined roles. An audit trail is kept to track changes. Queries are generated by the CDMS itself, displayed to the testing personnel and answered in the system. The data management personnel systematically monitor the correctness and completeness of the data input. For more complex queries or checks, external programs created with the SAS software can be used.

16.2 Data Coding

The following clinical data are to be recorded using a standardized coding system:

- The description of AEs with MedDRA

The versions of the coding systems to be used are defined in the Data Management Plan.

16.3 Documentation of Trial Data

16.3.1 Documentation of Trial Data in the Medical Record

The investigator will record the participation in the trial, the frequency of the trial visits, the relevant medical data, the concomitant treatment and the occurrence of adverse events in the medical record of each subject subject.

Data collected on the CRFs must match the sources data. These may include but are not limited to the hospitals' or the physician's medical files, laboratory and pharmacy records, diaries etc.

16.3.2 Case Report Form (CRF)

The investigator has ultimate responsibility for the accuracy, authenticity, timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs. All these data may only be entered into the CRF by authorized trial personnel as promptly as possible.

An Electronic Data Capture (EDC) System will be used in this trial (eCRF called hereinafter) using the Software Marvin by XClinical. All data collected during the trial will be documented electronically on the trial-specific CRF pages by the responsible investigator, or an individual who is designated by the investigator, as timely as possible. Entry and corrections on eCRF pages are automatically documented in an audit trail (user, date, reason) created by the program. The investigator signs completed data electronically.

The monitor is responsible to verify the eCRF at regular intervals throughout the trial to verify the adherence to the protocol, completeness, accuracy, and consistency of the data. Therefore, the monitor should have access to subject medical records and other trial-related records needed to verify the entries on the eCRF.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRF are resolved.

A clinical data management review will be performed on subject data entered in the eCRF database.

A separate eCRF-Manual is available to support the data entry.

16.4 Investigator Site File

The trial site will be provided with an investigator site file (ISF) containing all sponsor-specific essential and trial specific documents. The monitor will regularly check the trial site file for accuracy and completeness. The trial site file has to be stored locked and secure. After end of trial or early termination of the trial the trial site file should be retained for 10 years at the site.

The ISF includes the subject identification list, where the investigator has to record the trial participation of each subject. This list allows identification of each subject and contains the subject number, the name, telephone number (if applicable), birth date and the date of inclusion of the subject into the trial, and will be reviewed by the monitor for completeness. After end of the trial the subject identification list remains with the subject site. In addition, trial participation of the subject should be recorded in the patient file (trial drug, screening/randomization number, start and end date of the trial).

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. This list will be provided with the ISF, too.

Furthermore, trial personnel responsible for documentation in the CRFs should be identifiable. Therefore a signature list with the name, signature, initials/abbreviation and trial responsibilities of all persons who are allowed to make entries into the CRF will be filed in the investigator's site file.

The trial documents provided by the sponsor/ Study Coordinating Center of the SZB are confidential and may not be made accessible to third parties not involved in the trial by the investigator or other staff members. All trial data are collected pseudonymously.

16.5 Archiving

16.5.1 Sponsor

The sponsor must retain all essential documents inclusively the case report forms (Subject Master File) for the duration of at least 10 years after end or stop of trial. The sponsor must archive all trial related documents according to regulatory requirements.

16.5.2 Investigator

The investigator should maintain all subject documents as specified in Essential Documents for conduct of a clinical trial (see ICH-GCP, section 8) and as required by the applicable regulatory requirement(s) after completion of the clinical trial so that they will be available for audits and inspections by the authorities. The investigator will be responsible for the storage.

The following retention periods will apply after completion or stop of the clinical trial:

- all essential documents and trial related data must be retained securely for at least 10 years (GCP-V § 13 (10)),
- medical records and other source documents for the longest possible period allowed by the hospital, the institution or the private practice.

The investigator/institution should take arrangements to prevent accidental or premature destruction and illegitimate access to these documents.

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e. g. CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, drug accountability and adequate documentation of relevant correspondence (e. g. letters, meeting minutes, telephone calls reports).

The trial site will maintain a file of essential subject documentation (Trial site File).

17 Quality Management

During the clinical trial, quality control and quality assurance will be ensured through monitoring, auditing and inspections by authorities.

17.1 Risk Based Quality Management

In line with ICH-GCP 5.0 the sponsor implements a quality management system using a risk-based approach that entails the identification of critical processes/ data and associated risks. The risk identification, evaluation, control, communication and review is performed according to standard operating procedures.

17.2 Monitoring

To ensure accurate, complete, consistent, and reliable data, the investigator's site(s) and trial procedures will be monitored by a representative of the sponsor.

The sponsor's representative will visit the site:

- to evaluate the progress and recruitment of the trial,
- to review the source documents and CRFs for protocol compliance, accuracy and validation,
- to assess facilities and equipment,
- to check for protocol compliance,
- to assure correct and timely AE/SAE and DLT reporting,
- to verify proper handling and dispensing of the IMP, and other factors.

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the CRA access to the medical records for the performance of SDV.

Source data as defined by ICH-GCP include data such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

Frequency and scope of the monitoring visits will be defined in the **Monitoring Plan** for this trial which also includes the extent of source data verification that is required.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, and therefore ensures the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial.

17.3 Audits and Inspections

In accordance with ICH GCP this trial may be selected for audit by representatives of the sponsor or for inspection by site responsible representatives of the local regulatory authority.

The investigator agrees to give the auditor access to all relevant documents for review and to support the sponsor to solve possible audit findings concerning the trial conduct at the respective site.

After every audit the auditee(s) will receive an audit confirmation by the auditor. This document has to be filed together with the trial documentation and has to be made available also to the authorities in case of an inspection.

At the end of the trial, a copy of the audit certificate(s) will be included in the final report.

18 Regulatory Aspects and Good Clinical Practice

The trial will be conducted in accordance with the ICH Guideline for Good Clinical Practice, the relevant national regulations and the Declaration of Helsinki.

18.1 Responsibilities of the Sponsor

According to German law (AMG §§ 40 – 42) the sponsor is responsible for obtaining the approval from the respective competent authority (PEI/BfArM) and the respective main research ethics committee (“federführende Ethikkommission”) before initiation of the trial. In addition the trial will be submitted to and approved by the appropriate independent research ethics committee for each participating centre, prior to entering any subject into the trial.

According to German law (§ 4 Abs. 25 and § 40 Abs. 1 Nr. 5 AMG) the sponsor announces a Leader of the clinical trial (LKP) who has more than two years of experience in the field of clinical trial and holds a medical license.

In addition the trial has to be reported to the local regulatory authority(ies) according to § 67 AMG before initiation of the trial (inclusion of the first subject).

18.2 Responsibilities of the Investigator

By signing this protocol the local investigator declares his/her commitment:

- to not enrol any person dependent on him/her or the sponsor in accordance with the principles of ICH-GCP
- to follow the applicable regulations for data security, e.g. according to § 7 Abs. 3, Nr. 15 GCP-V
- to inform the subjects of the transmission of their pseudonymized data according to documentation and transmission obligations (§ 12 and § 13 GCP-V) and to make sure that subjects unwilling to give consent to the processing of their data are not included into the trial
- to certify that he/she was informed of the pharmacological – toxicological issues and risks of the clinical trial according to § 40 Abs. 1, Satz 3 Nr. 7 AMG
- to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
- to be thoroughly familiar with the appropriate use of the trial drug(s), as described in the protocol, the product information and other information sources provided by the sponsor
- to be aware of, and comply with GCP and the applicable regulatory requirements
- to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties (if applicable).

18.3 Ethics Committee and Competent Authority(ies)

The clinical trial protocol and amendments have to be approved by the Competent Authorities (CA), in addition to protocol and amendments the subject information and informed consent, and any other written information to be provided to the trial subjects have to be approved by the respective main research ethics committee (“federführende Ethikkommission”) and by the appropriate independent research ethics committee for each participating site.

The sponsor delegated person will authorize the Study Coordinating Center of the SZB with submitting the documents to the Ethics Committee(s) (EC) and to the CA.

A copy of the written approval must be received by the sponsor before recruitment of subjects into the trial and shipment of trial drug.

Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol must also be sent to the EC/CA. Records of the EC review and opinion of all documents pertaining to this trial must be kept on file by the investigator and are subject to regulatory authority and / or sponsor inspection during or after completion of the trial.

The Study Coordinating Center of the SZB will provide a safety update of the trial to the EC(s)/CA, including line listing, individual reports of SUSARs, if applicable, annually or more frequently if requested.

At the end of the trial, the Study Coordinating Center of the SZB will notify the EC(s)/CA about the trial completion. A copy of all reports submitted to the EC will be sent to the sponsor.

18.4 Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the sponsor and the investigator. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/authority/ethics committee (unless subject safety is at risk, see below).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the subject subjects. The deviation or amendment should subsequently be reported to the ethics committee, the sponsor or sponsor delegated person and, if necessary, the competent authority, giving reasons.

18.5 Notification of General Amendments to the Protocol

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change:

- the safety of the persons concerned,
- the interpretation of the scientific trial documents or the scientific informational value of the trial results,
- the nature of management or conduct of the clinical trial (e.g. change of coordinating investigator (German LKP), sponsor or sponsor's deputy),
- the pharmaceutical quality or safety of the investigational medicinal products
- the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical trial with drugs consisting of or containing genetically modified organisms

require a new authorization of the Competent Authority and a new favourable opinion by the Ethics Committee.

The clinical trial may only be continued when a favourable opinion has been obtained from the competent ethics committee and if the competent authority has not raised any objections accompanied by reasons.

If applicable, an updated Informed Consent Form has to be signed by all subjects enrolled in the trial who are affected by the amendment.

Amendments which only have to be approved by the EC (e.g. changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial, also will be notified to the CA with the comment "For information only". Similarly, the EC will be informed of any substantial amendments for which only the CA is responsible (e.g. quality data).

Confidential

If administrative protocol changes (e.g. change of monitoring, telephone numbers) are necessary, the EC and CA will be notified only.

18.6 Notification of the end of the trial

The end of the clinical trial is the date of the last visit of the last subject undergoing the trial.

If required by national law the CA(s) and EC(s) will be notified after the end of the trial in the country concerned or when the complete trial has ended.

Within one year of the end of the complete trial a summary of the trial report will be provided to the CA(s) and EC(s).

18.7 Subject Information and Informed Consent

According to § 40 of the German "Arzneimittelgesetz (AMG)" every participating subject will be informed of nature, importance, treatment methods, risks and consequences of the trial by the local investigator. Details of indemnity and insurance are also stated.

The local investigator is responsible for obtaining written informed consent from a subject or legally acceptable representative, or for children and adolescents from subject's parents, before any protocol-specific screening procedures will be performed or any investigational products will be administered.. The written informed consent document has to be prepared and provided in the language(s) of the potential subject population.

It is also the responsibility of the investigator for asking the subject if he/she agrees to have her primary care physician informed of his/her participation in the clinical trial. If the subject agrees to such notification, the investigator shall inform the primary care physician of the subject's participation by sending a message letter.

Subjects must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, subjects must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The subject will be given ample of time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the subject and/or his/her legal representative. On the other hand by signing the consent form subjects give their consent to the evaluation, recording and usage of their personal data according to § 40 Abs. 2a AMG.

The written consent form will be personally dated and signed by the subject and the by investigator conducting the informed consent discussion. The informed consent forms will be filed in the Trial site File at each site.

The acquisition of informed consent and the subject's agreement or refusal of the notification of the primary care physician should be documented in the subject's medical record.

A copy of the signed and dated informed consent form will be given to the subject or legally acceptable representative and a copy will be held in the subject's medical notes. The existence of written informed consent will have to be confirmed before any trial-specific test/treatment has been performed.

In the case of substantial amendments, e.g. any new data providing information on the safety profile of any of the investigational medicinal product and leading to significant changes in the risk-benefit ratio, the subject must be informed with an appropriately revised subject information and the consent of the subject has to be obtained again.

Changed trial procedures can only be carried out if they have been approved by the competent authority and the leading Ethics Committee, and if the subject has been appropriately informed and has given his/her written consent.

18.8 Subject Insurance

Every subject participating in the trial is insured against any trial-related illness/injuries pursuant to the legal requirements which may occur during the trial, in Germany according to § 40 Abs. 1 Nr. 8 and Abs. 3 AMG.

Excluded from this, however, are injuries to health and deterioration of illnesses already in existence which would have continued to exist even if the subject had not taken part in the clinical trial.

The investigator will inform the subject of the existence of the insurance, including the obligations arising from it. The subject subjects must be afford access to insurance documents and provided with a copy of the general conditions of insurance on request.

The insurance cover is jeopardized if the subject fails to immediately report to the investigator or responsible physician any injury to health which might have resulted from the participation in the clinical trial, or if she/he undergoes any other medical treatment (except for emergency treatment) without the investigator's knowledge before her/his participation in the clinical trial has officially ended.

In case of any health impairment the subject, subject's parents (if applicable), or legally authorized representative is obliged to notify the insurance and additionally the investigator as soon as possible. The investigator is obliged to make a report to the sponsor.

The subject insurance will be arranged by the sponsor delegated person. The insurer will be:

Name of Insurer:	HDI Global SE
Insurance Number:	57 010323 03010/XXXXX
Address:	Riethorst 2 30659 Hannover
Represented by:	Niederlassung Düsseldorf Am Schönenkamp 45, 40599 Düsseldorf
Insurance Broker:	Ecclesia mildenberger HOSPITAL GmbH Ecclesiastraße 1-4, 32758 Detmold
Phone:	+49 (0)5231 / 603-6486
Fax:	+49 (0)5231 / 603-606486

This insurance covers trial related injuries to health up to a maximum of 500.000 Euro per subject.

18.9 Data Protection and Subject Confidentiality

The pertinent provisions of the country-specific legislation on data protection must be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to local applicable laws (Data Protection Act, General Data Protection Regulation). Prior to trial participation each subject must be informed by the investigator about the purpose and extent of the collection and use of personal data, particularly medical data and must give written informed consent.

The subjects must be informed that:

- a. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial – subject number-, year of birth) and will only be transmitted to
 - i. the coordinating investigator/sponsor/sponsor delegated person/data monitoring safety board for scientific and adverse event evaluation
 - ii. the responsible regulatory authority(ies) (local authority(ies)/BfArM or PEI), the ECs of the trial sites and the European Data Base (EudraCT data base) for verifying the proper conduct of the trial and for assessment of trial results and adverse events

2. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the local regulatory authority(ies) must have direct access to personal data. In this case, the investigator is released from confidential medical communication.
3. Consent to the collection and processing of personal data within the scope of this clinical trial can be revoked at any time. A patient is informed that he/she can terminate his/her participation in the clinical trial at any time - without giving reasons and without any of the following disadvantages. In the event of revocation of the declaration of consent, the data stored up to this point in time will continue to be used without mentioning names, insofar as this is necessary to determine the effects of the medicinal product under investigation and to ensure that the interests of the person concerned which are worthy of protection are not impaired, or to comply with the obligation to submit complete approval documents.

18.10 Data Sharing Statement

Individual participant data will be available. Individual participant data (including data dictionaries) that underlie results concerning primary or secondary endpoints reported in a published scientific article will be shared on demand after deidentification. Furthermore, the following documents will be made available: Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report.

The data will be shared beginning 6 months and ending 3 years following article publication.

Data are made available to researchers after a methodologically sound scientific proposal has been submitted to the Coordinating Investigator a steering committee consisting of the Coordinating Investigator, the representative of the Coordinating Investigator, and a SZB member has approved the proposal, and a data access agreement has been signed. Study protocol and the informed consent forms will be made available on demand or through the website of the Division of Clinical Neurooncology, University of Bonn, After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata.

18.11 Financing of the Trial

The present trial is an investigator initiated subject (IIT). The trial is financially sponsored by the German Federal Ministry of Education and Research (01EN2008).

18.11.1 Trial Agreement / Investigator Compensation

According to ICH-GCP 4.9.6, a trial agreement on the conduct of the clinical trial and the compensation for conducting the subject will be signed between the sponsor (donor) of the clinical trial and the investigators including their heads of administration (donee). A compensation will be paid for each fully documented, completed case.

18.11.2 Reimbursement of Subject Subjects

Subject subjects will not be compensated monetarily.

19 Trial Reports

19.1 Development Safety Update Report (DSUR)

Together with the notification of the end of the trial and once a year in case of long durations of the trial the sponsor/ sponsor delegated person will provide the CA(s) and EC(s) in the country concerned with a listing of all suspected serious adverse reactions which occurred over the trial period of the subject's safety.

19.2 Final Report

After completion of the analysis by the responsible biostatistician, the final integrated medical and statistical report will be prepared and signed jointly with the biostatistician.

Except when required by law, no one will disclose a result of the clinical trial to third parties unless all relevant parties involved have first agreed on the results of the analysis and their interpretation.

The final trial report will be written and signed in co-operation between the sponsor/coordinating investigator, the SZB and the statistician.

20 Publication

The coordinating principal investigator will have the right to publish such data and information without approval from the sponsor. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals. Participating center qualify for at least one co-authorship if the center accrues at least 5% of the patients of the ITT study population. The manuscript will be provided to every co-author before publication. All data collected in connection with the clinical trial will be treated in confidence by the sponsor/coordinating investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the coordinating investigator as the Sponsor Delegated Person.

21 Accompanying Scientific Program

- To evaluate the bioavailability of MFA, the intratumoral levels of MFA and metabolite I is measured in the tumor resected after the start of MFA treatment.
- MFA and metabolite I levels are measured in serum taken on day 1 2h after first MFA intake and in the morning of the resection day and 2h, 4h, 6h, 8h thereafter. Serum sampling 2h after morning intake between day 1 and resection day is optional.
- Histological, immunohistochemical, molecular and electrophysiological assessments of fresh frozen, PFA-fixed, and FFPE tumor tissue samples obtained during the trial for effects of MFA/TMZ vs. TMZ mono, for example number of TMs per cell, number of TM-based cell-cell connections per cell, TM-length, 3D-reconstruction of TM-based network architecture, intercellular gap-junction-mediated cytosolic traffic (calcein dye single cell injections), MEA und Calcium imaging, connectivity score
- Analysis of blood samples acquired at all MRI timepoints for factors potentially correlating with tumor progression. Analysis of extracellular vesicles is planned, biobanking of residual material for further analyses such as proteomic and miRNA profile.
- Histological, immunohistological and molecular assessments of FFPE and fresh frozen tumor tissue samples obtained from resections prior, during and or after the end of trial therapy: analyses for factors related with prognosis, response to therapy (MFA/MTZ or TMZ), immunological reaction against the tumor.
- Exploratory neuroradiological analysis with all MRIs documenting the course of the disease of the study patients: analysis of MRI parameters that could be associated with prognosis or response to therapy. This does also include the use of artificial intelligence (AI) algorithms.
- If available, EEG or MEG analysis at baseline, on day 28 after first MFA or TMZ intake (in phase II both arms) and at the first follow-up visit after discontinuation of MFA (MFA arm only)

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