



Clinical trial results:

A proof of concept clinical trial assessing the safety of the coordinated undermining of survival paths by 9 repurposed drugs combined with metronomic temozolomide (CUSP9v3 Treatment Protocol) for recurrent glioblastoma

Summary

EudraCT number	2014-004197-42
Trial protocol	DE
Global end of trial date	15 December 2020

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	CUSP9v3
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02770378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital of Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany,
Public contact	Clinical trials office, University Hospital of Ulm, 0049 73150045842, anke.hallmen@uniklinik-ulm.de
Scientific contact	Clinical trials office, University Hospital of Ulm, 0049 73150045842, anke.hallmen@uniklinik-ulm.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective

The primary objective is to assess the safety and tolerability of the CUSP9v3 Treatment Pro-tocol in patients with recurrent glioblastoma.

Phase Ib:

Evaluation of tolerability and safety with dose-limiting toxicity (DLT) in participating patients.

Phase IIa:

Assessment of overall response including complete response (CR), partial response (PR) and stable disease (SD).

Secondary Efficacy Objective

To evaluate overall survival (OS) and progression-free survival (PFS) according to Kaplan-Meier estimates in adult patients with recurrent or progressive glioblastoma.

To evaluate best tumor response according to the RANO criteria.

Safety Objectives

Incidence and intensity of adverse events (AEs) assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical and neurological examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Adverse events were coded and graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 of the US National Cancer Institute (<http://ctep.info.nih.gov/reporting/ctc.html>).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 13.11.2016

Last patient last visit: 11.12.2020

Ten patients were included between August 2016 and April 2018. A total of 12 patients were screened. One patient could not be included because of high serum transaminases and one because of acute deep vein thrombosis.

Pre-assignment

Screening details:

1. Patients with a diagnosis of glioblastoma WHO grade IV (histologically confirmed by a pathologist). Patients with prior low-grade glioma are eligible if histological transformation to WHO grade IV glioblastoma was confirmed.
2. Progression (according to RANO criteria) after prior radiation and temozolomide treatment

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	study treatment
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Arm description:

Treatment initiation encompassed the addition of the 9 drugs to uninterrupted temozolomide and comprised an induction cycle with 2 phases: a low-dose drug-by-drug addition phase followed by an up-dosing phase. Patients were hospitalized during the drug-by-drug addition phase, which lasted 18 days, to monitor tolerability and drug-drug interactions. The treatment started with temozolomide (20 mg/m² BSA b.i.d.) and aprepitant (80 mg q.d.) on day 1, followed by the addition of 1 drug every 2 days (day 3, day 5 etc.) at low-dose level. The last drug (auranofin) was added on day 17. On day 19, up-dosing phase started with the dose of only one drug being increased every 2 days. Doses of temozolomide and aprepitant remained unchanged, 7 drugs were up-dosed only once and 1 drug (ritonavir) was up-dosed twice. After reaching target doses of all drugs, the regimen remained unchanged until side effects (dose modifications and/or drug pausing) or until tumor progression continued CUSP9v3 regimen.

Arm type	Experimental
Investigational medicinal product name	Aprepitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

EMEND® 80 mg hard capsules.

Emend® was dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Emend® capsules were dispensed to the patient directly by the Hospital Pharmacy.

Emend® capsules were taken orally, with or without food.

Investigational medicinal product name	Disulfiram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Esperal® tablets 500 mg.

Esperal® tablets were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Esperal® tablets were dispensed to the patient directly by the

Hospital Pharmacy.

Esperal® tablets were taken orally. For further information, including information on the toxicity profile, please refer to the Summary of Product Characteristics.

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sertralin Hexal ® 100 mg tablets were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Sertralin Hexal ® tablets were dispensed to the patient directly by the Hospital Pharmacy.

Sertraline tablets were taken orally with or without food.

Investigational medicinal product name	Captopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Captopril AbZ 50 mg tablets.

Captopril tablets were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, captopril capsules were dispensed to the patient directly by the Hospital Pharmacy.

Captopril tablets were taken orally, with fluid, with or without food.

Investigational medicinal product name	Minocycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Minocyclin-ratiopharm® 50 mg capsules.

Minocycline tablets were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, minocycline tablets were dispensed to the patient directly by the Hospital Pharmacy.

Minocycline capsules were taken orally, with fluid (no milk), with a meal.

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Norvir ® 100 mg film-coated tablets.

Norvir® tablets were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Norvir® tablets were dispensed to the patient directly by the Hospital Pharmacy.

Norvir® tablets were taken orally, with food.

Investigational medicinal product name	Itraconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sempera® 100 mg Capsules.

Sempera® capsules were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Sempera® capsules were dispensed to the patient directly by the Hospital Pharmacy.

Sempera® capsules were taken orally directly after a meal.

Investigational medicinal product name	Auranofin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ridaura® capsules containing 3 mg auranofin

Ridaura® capsules were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Ridaura® capsules were dispensed to the patient directly by the Hospital Pharmacy.

Ridaura® capsules were taken orally with food.

Investigational medicinal product name	Celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Celebrex® 200 mg Capsules

Celebrex® capsules were dispensed to the patient on the hospital ward during the drug-by-drug addition phase of the induction cycle. Thereafter, Celebrex® capsules were dispensed to the patient directly by the Hospital Pharmacy.

Celebrex® tablets were taken orally with or without food.

Number of subjects in period 1	study treatment
Started	10
Completed	3
Not completed	7
Progression	7

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	41		
full range (min-max)	25 to 60	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	4	4	
Type of GBM			
Units: Subjects			
Primary	8	8	
Secondary	2	2	
KPS at baseline			
Units: Subjects			
100	4	4	
90	2	2	
80	1	1	
70	3	3	
Recurrence/progression at inclusion			
Units: Subjects			
First	6	6	
Second	4	4	
Tumor location at time of study entry			
Units: Subjects			
Frontal lobe	2	2	
Temporal lobe	2	2	
Parietal lobe	1	1	
Disseminated—basal ganglia	1	1	

Disseminated—midbrain and brainstem	2	2	
Disseminated—callosal	2	2	
Initial extent of resection			
Units: Subjects			
Gross total	7	7	
Subtotal	3	3	
MGMT promoter status			
Units: Subjects			
Hypermethylated	6	6	
Non-hypermethylated	4	4	
IDH1/2 status			
Units: Subjects			
Mutated	2	2	
Wild-type	8	8	
Prior therapies - other			
Other prior therapies than surgery, radiotherapy and temozolomide.			
Units: Subjects			
Bevacizumab	1	1	
Tetrahydrocannabinol	1	1	
TTFIELDS™	1	1	
No other prior therapy	7	7	

End points

End points reporting groups

Reporting group title	study treatment
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Reporting group description:

Treatment initiation encompassed the addition of the 9 drugs to uninterrupted temozolomide and comprised an induction cycle with 2 phases: a low-dose drug-by-drug addition phase followed by an up-dosing phase. Patients were hospitalized during the drug-by-drug addition phase, which lasted 18 days, to monitor tolerability and drug-drug interactions. The treatment started with temozolomide (20 mg/m² BSA b.i.d.) and aprepitant (80 mg q.d.) on day 1, followed by the addition of 1 drug every 2 days (day 3, day 5 etc.) at low-dose level. The last drug (auranofin) was added on day 17. On day 19, up-dosing phase started with the dose of only one drug being increased every 2 days. Doses of temozolomide and aprepitant remained unchanged, 7 drugs were up-dosed only once and 1 drug (ritonavir) was up-dosed twice. After reaching target doses of all drugs, the regimen remained unchanged until side effects (dose modifications and/or drug pausing) or until tumor progression continued CUSP9v3 regimen.

Primary: Best overall response

End point title	Best overall response ^[1]
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End point description:

End point type	Primary
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End point timeframe:

overall treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: For statistical analyses see linked publication.

End point values	study treatment			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: patients				
SD	6			
PD	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
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End point description:

The Kaplan-Meier method was used to calculate PFS and OS. The median PFS and OS, respectively, are presented along with their corresponding 95% confidence intervals (CI). All analyses were performed using SAS (version 9.4, www.sas.com) and R (version 3.5.2, www.r-project.org).

End point type	Secondary
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End point timeframe:

overall treatment period

End point values	study treatment			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: 100				
number (confidence interval 95%)	50 (27 to 93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
The Kaplan-Meier method was used to calculate PFS and OS. The median PFS and OS, respectively, are presented along with their corresponding 95% confidence intervals (CI). All analyses were performed using SAS (version 9.4, www.sas.com) and R (version 3.5.2, www.r-project.org).	
End point type	Secondary
End point timeframe:	
overall treatment period	

End point values	study treatment			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: 100				
number (confidence interval 95%)	50 (27 to 93)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall treatment period

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	study treatment
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Reporting group description:

Treatment initiation encompassed the addition of the 9 drugs to uninterrupted temozolomide and comprised an induction cycle with 2 phases: a low-dose drug-by-drug addition phase followed by an up-dosing phase. Patients were hospitalized during the drug-by-drug addition phase, which lasted 18 days, to monitor tolerability and drug-drug interactions. The treatment started with temozolomide (20 mg/m² BSA b.i.d.) and aprepitant (80 mg q.d.) on day 1, followed by the addition of 1 drug every 2 days (day 3, day 5 etc.) at low-dose level. The last drug (auranofin) was added on day 17. On day 19, up-dosing phase started with the dose of only one drug being increased every 2 days. Doses of temozolomide and aprepitant remained unchanged, 7 drugs were up-dosed only once and 1 drug (ritonavir) was up-dosed twice. After reaching target doses of all drugs, the regimen remained unchanged until side effects (dose modifications and/or drug pausing) or until tumor progression continued CUSP9v3 regimen.

Serious adverse events	study treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Edema cerebral			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pyramidal tract syndrome			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Facial nerve disorder			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle weakness lower limb			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	study treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumor progression subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 6		
Vascular disorders			
Hot flashes subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 9		
Hypotension subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3		
Thromboembolic event subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
General disorders and administration site conditions			
Dysphagia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 8		
Edema face subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Edema limbs subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 7		
Fatigue subjects affected / exposed occurrences (all)	9 / 10 (90.00%) 31		
Gait disturbance subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 10		
Malaise subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Immune system disorders			

Allergic reaction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Reproductive system and breast disorders Vaginal hemorrhage subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders other subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 7 1 / 10 (10.00%) 2 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1		
Psychiatric disorders Confusion subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Libido decreased subjects affected / exposed occurrences (all) Mania	2 / 10 (20.00%) 2 2 / 10 (20.00%) 2 3 / 10 (30.00%) 3 1 / 10 (10.00%) 1		

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Psychosis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	5		
GGT increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	9		
Platelet count decreased			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Weight loss			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
White blood cell decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			

Fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Wound complication subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Cardiac disorders			
Conduction disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Sinus bradycardia subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 5		
Ventricular arrhythmia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nervous system disorders			
Aphasia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Ataxia subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 12		
Concentration impairment subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Depressed level of consciousness subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dizziness subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5		
Dysesthesia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4		
Dysgeusia			

subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Dysphasia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Edema cerebral			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Extrapyramidal disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Facial muscle weakness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Facial nerve disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	8 / 10 (80.00%)		
occurrences (all)	28		
Hypoglossal nerve disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Intracranial hemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Movements involuntary			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nystagmus			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Oculomotor nerve disorder			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Paresthesia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Pyramidal tract syndrome			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Seizure			
subjects affected / exposed	7 / 10 (70.00%)		
occurrences (all)	9		
Syncope			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	10		
Vagus nerve disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders other			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Dry Eye			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Extraocular muscle paresis			

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distention			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Anal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Bloating			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Diarrhea			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	18		
Dry Mouth			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	8		
Fecal incontinence			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal Pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lower gastrointestinal hemorrhage			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	9 / 10 (90.00%)		
occurrences (all)	35		

Oral dysesthesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Stomach pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	11		
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Herpes			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Photosensitivity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Skin hyperpigmentation			

subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4		
Renal and urinary disorders Urinary frequency subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Urinary incontinence subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 5		
Urinary urgency subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Chest wall pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4		
Muscle weakness left-sided subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Muscle weakness lower limb subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Infections and infestations Lung infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2017	<ul style="list-style-type: none">- Temozolomide as standard therapy instead of IMP- Criteria for therapy continuation- Change of data capture process- Include some minor administrative-type changes.
03 July 2017	<ul style="list-style-type: none">- Manufacturer change of Captopril 50 mg- Include some minor administrative-type changes.
06 November 2017	<ul style="list-style-type: none">- Manufacturer change of Auranofin 3 mg- Handling of Auranofin at pharmacy university hospital Heidelberg- Update of the people involved – deputy change- Include some minor administrative-type changes.
21 August 2018	<ul style="list-style-type: none">- Inclusion of maintenance phase- Addition of primary endpoint phase 2a- Decision to take MR from induction cycle as baseline MR- Dose modifications added for QTc time prolongation- Inclusion aspects of data safety regulation (DSGVO)- Patient diary for maintenance phase
07 January 2020	<ul style="list-style-type: none">- Manufacturer change of Captopril 50 mg- Include some minor administrative-type changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/3437798>