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

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 Termi-nology Criteria for Adverse Events (CTCAE) v4.03.

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clini-cal laboratory test results, vital signs measurements, ECG findings, physical and neurological examination findings, monitoring of concomitant therapy. For each safety parameter, all find-ings (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 transfor-mation 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

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	
TTFieldsTM	1	1	
No other prior therapy	7	7	

End points

End points reporting groups

Reporting group title	study treatment

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]

End point description:

End point type	Primary

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)

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

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

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	study treatment

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

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

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	1 / 10 (10.00%)		
occurrences (all)	1		
Wound complication			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Sinus bradycardia			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Ventricular arrhythmia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Ataxia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	12		
Concentration impairment			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Depressed level of consciousness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Dysesthesia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	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 occurrences (all)	1 / 10 (10.00%) 3			
Stomach pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3			
Toothache subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Vomiting subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 11			
Gastrointestinal disorders - Other subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 5			
Herpes subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Hyperhydrosis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2			
Photosensitivity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Pruritus subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1			
Rash maculo-papular subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3			
Skin hyperpigmentation				

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2017	- 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	- Manufacturer change of Captopril 50 mg - Include some minor administrative-type changes.
06 November 2017	- 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	- 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	- 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