Clinical trial results:
Controlled clinical trial to evaluate the safety and efficacy of stereotactical photodynamic therapy with 5-aminolevulinic acid (Gliolan®) in recurrent glioblastoma

Summary

EudraCT number	2015-002727-25
Trial protocol	DE
Global end of trial date	30 January 2025

Results information

Result version number	v1
This version publication date	14 February 2026
First version publication date	14 February 2026

Trial information

Trial identification

Sponsor protocol code	UKM12_0017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04469699
WHO universal trial number (UTN)	U1111-1182-8541
Other trial identifiers	EUDAMED number: CIV-17-03-018624

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Münster, Germany, 48149
Public contact	Klinik für Neurochirurgie, Universitätsklinikum Münster, +49 1733802878, juliane.schroeteler@ukmuenster.de
Scientific contact	Klinik für Neurochirurgie, Universitätsklinikum Münster, +49 1733802878, juliane.schroeteler@ukmuenster.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	27 November 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2025
Global end of trial reached?	Yes
Global end of trial date	30 January 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study was initiated to compare the following treatment concepts of recurrent glioblastoma with respect to efficacy, safety and quality of life:
• iPDT (interstitial photodynamic therapy) with 5-Aminolevulinic hydrochloric acid (5-ALA) and consecutive therapy at the investigator’s discretion
• Therapy at the investigator’s discretion without iPDT and 5-ALA.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

Patients were randomized with 1:1 allocation ratio in two arms, either to receive a biopsy followed by iPDT with 5-ALA (treatment arm) or only a biopsy (control arm). All patients received best possible care at the investigator’s discretion. Treatment was started as soon as adequate after stereotactic intervention. The only treatment not allowed in this study was the administration of antiangiogenic drugs.

Evidence for comparator:

Due to the matter of fact, that there is no standard therapy in the recurrent situation of glioblastoma available, all patients received best possible therapy. Patients were not be disadvantaged in their treatment by participation in the study regarding standard treatment. The best possible conservative treatment was allowed.

Actual start date of recruitment	01 March 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	21
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From April 12, 2021, through October 16, 2024, a total of 30 patients were included in the study.

Pre-assignment

Screening details:

Each patient's eligibility was verified during a screening visit. Informed consent was obtained prior to any clinical procedures that are performed solely for study-related purposes. After obtaining informed consent, patients were randomized to either the treatment or control arm.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	5-ALA iPDT - randomization

Arm description:

Patients randomized to receive iPDT with 5-ALA (treatment arm / including screening failures).

Arm type	Experimental
Investigational medicinal product name	5-ALA
Investigational medicinal product code	
Other name	5-aminolevulinic acid (Gliolan®)
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Four hours (range: 3.5 to 4.5 hours) prior to anaesthesia for stereotactic surgery, patients receiving iPDT took 20 mg freshly dissolved 5-ALA HCL per kg body weight orally and under supervision.

Arm title	Control - randomization

Arm description:

Patients randomized to the contol arm (including screening failures)

Arm type	Therapy at investigator's discretion without iPDT

No investigational medicinal product assigned in this arm

Number of subjects in period 1	5-ALA iPDT - randomization	Control - randomization
Started	15	15
Completed	10	12
Not completed	5	3
During surgery, biopsy did not verify glioblastoma	3	2
Terminated trial before getting the procedure	2	1

Period 2

Period 2 title	Modified intention-to-treat set
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	5-ALA iPDT

Arm description:

Patient who were randomized to iPDT with 5-ALA and who had biopsy-confirmed glioblastoma (without screening failures).

Arm type	Experimental
Investigational medicinal product name	5-ALA
Investigational medicinal product code	
Other name	5-aminolevulinic acid (Gliolan®)
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Four hours (range: 3.5 to 4.5 hours) prior to anaesthesia for stereotactic surgery, patients receiving iPDT took 20 mg freshly dissolved 5-ALA HCL per kg body weight orally and under supervision.

Arm title	Control

Arm description:

Patient who were randomized to the control arm and who had biopsy-confirmed glioblastoma (without screening failures).

Arm type	Therapy at investigator's discretion without iPDT

No investigational medicinal product assigned in this arm

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: 22 patients were included in the modified intention-to-treat set (mITT). All 22 patients received treatment as planned. Because, there were no major protocol violations, the per protocol set is identical to the per protocol collective and to the safety set. 10 patients were analyzed in the 5-ALA iPDT arm and 12 patients in the control group.

Number of subjects in period 2[2]	5-ALA iPDT	Control
Started	10	12
Completed	10	12

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 30 Patients were randomized to the treatment group 5-ALA iPDT and control group. During surgery, the biopsy did not verify a glioblastoma for n=5 patients. 3 additional patients were excluded, because an exclusion criterion was met before starting with the treatment or the tumor recurrence was too big. These 8 patients were excluded as screening failures. They did not receive the assigned treatment and discontinued the trial immediately. No further follow-up data were collected.

Baseline characteristics

Reporting groups	
Reporting group title	5-ALA iPDT
Reporting group description:	
Patient who were randomized to iPDT with 5-ALA and who had biopsy-confirmed glioblastoma (without screening failures).	
Reporting group title	Control
Reporting group description:	
Patient who were randomized to the control arm and who had biopsy-confirmed glioblastoma (without screening failures).	

Reporting group values	5-ALA iPDT	Control	Total
Number of subjects	10	12	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	6	15
From 65-84 years	1	6	7
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.4	59.8	
standard deviation	± 13.31	± 12.50	-
Gender categorical Units: Subjects			
Female	2	7	9
Male	8	5	13
NIHSS total score (baseline) Units: Subjects			
Score = 0	6	5	11
Score = 1	2	4	6
Score = 2	2	0	2
Score = 3	0	1	1
Score = 4	0	2	2
Karnofsky Performance Score (baseline) Units: Subjects			
unable to carry on normal activity	1	0	1
some signs or symptoms of disease	1	2	3
minor signs or symptoms of disease	6	6	12
no complaints; no evidence of disease	2	4	6

Karnofsky Performance Score (baseline) Units: Karnofsky Performance Score			
median	90.0	90.0	
inter-quartile range (Q1-Q3)	90.0 to 90.0	90.0 to 100.0	-
Mini-Mental state examination score (baseline) Units: Mini-Mental state examination score			
median	26.0	28.0	
inter-quartile range (Q1-Q3)	24.0 to 30.0	25.0 to 30.0	-
QLQ-C30 Summary Score (baseline) Units: QLQ-C30 Summary Score			
median	81.6	77.8	
inter-quartile range (Q1-Q3)	78.0 to 90.2	70.4 to 93.3	-

End points

End points reporting groups

Reporting group title	5-ALA iPDT - randomization
Reporting group description:	
Patients randomized to receive iPDT with 5-ALA (treatment arm / including screening failures).	
Reporting group title	Control - randomization
Reporting group description:	
Patients randomized to the contol arm (including screening failures)	
Reporting group title	5-ALA iPDT
Reporting group description:	
Patient who were randomized to iPDT with 5-ALA and who had biopsy-confirmed glioblastoma (without screening failures).	
Reporting group title	Control
Reporting group description:	
Patient who were randomized to the control arm and who had biopsy-confirmed glioblastoma (without screening failures).	
Subject analysis set title	modified ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomized. Not included in the modified ITT (mITT) population are patients who were randomized but do not have histological confirmation of glioblastoma during surgery, or patients who were incorrectly randomized although an inclusion criterion was not met or an exclusion criterion was met and those who terminated study participation before the start of surgery. These patient were excluded as screening failures.	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	
The primary endpoint was progression-free survival (PFS) defined as number of days from randomization until diagnosis of progressive disease as determined by MRI according to RANO criteria or death from any cause. For a patient with none of these events before the end of follow-up, observation of PFS was censored at the date of last follow-up.	
End point type	Primary
End point timeframe:	
From randomization until diagnosis of progressive disease or death or last follow-up.	

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Patients (progression or death)	8	7		

Attachments (see zip file)	Kaplan-Meier plot of progression-free survival/KM_PFS_mITT.

Statistical analyses

Statistical analysis title	Adaptive analysis (two-sided)

Statistical analysis description:

Two adaptive one-sided two-stage designs using an Pocock-type alpha-spending function and the inverse normal combination method were applied. Since the study ended before any interim analysis was performed, the one-sided alpha spending functions in the two-stage adaptive design were set to 2.5%. Consequently, the initial adaptive design now corresponds to a two-sided log-rank test with a 5% significance level. Analysis was performed in the in the modified ITT set.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.346
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.602
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.207
upper limit	1.749

Notes:

[1] - It could not be demonstrated that the 5-ALA iPDT group differed significantly from the control group in terms of PFS. The observed PFS curves were in favor of 5-ALA iPDT with a hazard ratio of 0.602 (95% CI 0.207, 1.749).

Statistical analysis title	Adapt. 2-stage design f. superiority of 5-ALA iPDT

Statistical analysis description:

An adaptive one-sided two-stage design for the superiority hypothesis using an Pocock-type alpha-spending function and the inverse normal combination method were applied. Since the study ended before any interim analysis was performed, the one-sided alpha spending function in the two-stage adaptive design was set to 2.5%. Analysis was performed in the in the modified ITT set.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1732
Method	Logrank

Statistical analysis title	Adapt. 2-stage design f. inferiority of 5-ALA iPDT

Statistical analysis description:

An adaptive one-sided two-stage design for the inferiority hypothesis using an Pocock-type alpha-spending function and the inverse normal combination method were applied. Since the study ended before any interim analysis was performed, the one-sided alpha spending function in the two-stage adaptive design was set to 2.5%. Analysis was performed in the in the modified ITT set.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8268
Method	Logrank

Secondary: 6-month rate of progression free survival (PFS)

End point title	6-month rate of progression free survival (PFS)

End point description:

PFS until 6 months is defined as number of days from randomization until diagnosis of progressive disease as determined by MRI according to RANO criteria or death from any cause until 6 months. All observations and events beyond 6 months were censored at 6 months. Event-free rates will be reported as Kaplan-Meier estimates with 95% confidence interval (complementary log-log-transformed).

End point type	Secondary

End point timeframe:

From randomization until diagnosis of progressive disease or death or last follow-up.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Percent				
number (confidence interval 95%)	78.8 (38.1 to 94.3)	40.9 (10.0 to 70.7)		

Statistical analyses

Statistical analysis title	Two-sided logrank test
Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.105
Method	Two-sided log-rank test

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS started at randomization and ended at the day of death. Patients alive were censored at the date of their last follow-up.

End point type	Secondary

End point timeframe:

From the day of randomization until death or last follow-up.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Deceased patients	5	4		

Attachments (see zip file)	Kaplan-Meier plot of overall survival/KM_OS_mITT.png

Statistical analyses

Statistical analysis title	Two-sided logrank test

Statistical analysis description:

OS after randomization was compared between the treatment groups in the modified ITT set using a two-sided log-rank test.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.413
Method	Two-sided log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	2.22

Notes:

[2] - Median OS was 24 months (95% CI 5.6 - NE) and 7.9 (5.1 - NE) months.

Secondary: 12-month overall survival (OS) rate

End point title	12-month overall survival (OS) rate

End point description:

Alive patients were censored at the time of their last follow-up, but at the latest after 12 months. All events beyond 12 months were censored at 12 months. Overall survival time began at randomization and ended on the day of death if this occurred earlier than 12 months after randomization. Event-free rates at 12 months are reported as Kaplan-Meier estimates with 95% confidence interval (complementary log-log-transformed).

End point type	Secondary

End point timeframe:

From randomization until 12 months after randomization.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Percent				
number (confidence interval 95%)	77.8 (36.5 to 93.9)	43.8 (10.1 to 74.2)		

Statistical analyses

Statistical analysis title	Two-sided logrank test

Statistical analysis description:

OS until 12 months after randomization was compared between the treatment groups in the modified ITT set using a two-sided log-rank test. Therefore, all observations and events beyond 12 months were censored at 12 months. The analysis was performed using all available patients in the modified ITT set.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.147
Method	Two-sided log-rank test

Secondary: Occurrence of brain edema

End point title	Occurrence of brain edema

End point description:

Occurrence of brain edema as assessed by MRI (yes/no) in the first 48 hours after iPDT.

End point type	Secondary

End point timeframe:

Within 26-48 hours after iPDT / biopsy.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Patients with brain edema	2	1		

Statistical analyses

Statistical analysis title	Occurrence of brain edema in the first 48h
Comparison groups	5-ALA iPDT v Control

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.586
Method	Fisher exact

Secondary: Response rate 26-48h after treatment

End point title	Response rate 26-48h after treatment

End point description:

26-48h response rate on MRI according to RANO (CR/PR/SD/PD) after treatment with iPDT or after biopsy.

End point type	Secondary

End point timeframe:

26-48h after treatment with iPDT or after biopsy.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Patients affected				
CR (Complete Response)	0	2		
PR (Partial Response)	1	3		
SD (Stable Disease)	7	5		
PD (Progressive Disease)	1	0		
Not assessable	1	1		

Statistical analyses

Statistical analysis title	Fisher's exakt test

Statistical analysis description:

The categorical endpoint is compared between the treatment groups in the mITT set using Fisher's exact test. Only patients with available response measurements are included. Patients who are deceased or had no response evaluation at this timepoint are not considered.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4925
Method	Fisher exact

Notes:

[3] - Response evaluation on MRI 26-48h after surgery, revealed that 5 of 11 available control patient reached at least a PR (PR: n=3, CR: n=2), where only one 5-ALA iPDT patient reached a PR.

Secondary: Response rate one month after randomisation

End point title	Response rate one month after randomisation

End point description:

One month response rate on MRI according to RANO (CR/PR/SD/PD) after randomisation.

End point type	Secondary

End point timeframe:

One month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	5		
Units: Patients affected				
CR (Complete Response)	1	0		
PR (Partial Response)	1	0		
SD (Stable Disease)	7	2		
PD (Progressive Disease)	0	3		
Not assessable	1	0		

Statistical analyses

Statistical analysis title	Fisher's exakt test

Statistical analysis description:

The categorical endpoint is compared between the treatment groups in the mITT set using Fisher's exact test. Only patients with available response measurements are included. Patients who are deceased or had no response evaluation at this timepoint are not considered.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0709
Method	Fisher exact

Notes:

[4] - One month after treatment, none of the 5 control patients with MRI measurement has reached a PR, where one 5-ALA iPDT patient reached a CR and one a PR.

Secondary: Change in contrast medium volume uptake 26-48h after treatment

End point title	Change in contrast medium volume uptake 26-48h after treatment

End point description:

Change in contrast medium volume uptake between baseline and the MRI performed 26-48 hours after treatment as categorical variable T1-Gd+ (no change, ≥50% decrease, <50% decrease but <25% increase, ≥25% increase).

End point type	Secondary

End point timeframe:

26-48 hours after treatment.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Patients affected				
No change	1	3		
>= 50% decrease	1	2		
<50% decrease but <25% increase	8	5		
>=25% increase	0	1		

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

The categorical endpoint is compared between the treatment groups in the mITT set using Fisher's exact test. Only patients with available measurements are included. Patients who are deceased or missing values at this timepoint are not considered.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4381
Method	Fisher exact

Secondary: Change in contrast medium volume uptake 1 month after randomisation

End point title	Change in contrast medium volume uptake 1 month after randomisation

End point description:

Change in contrast medium volume uptake between baseline and the MRI performed one month after randomisation as categorical variable T1-Gd+ (no change, ≥50% decrease, <50% decrease but <25% increase, ≥25% increase).

End point type	Secondary

End point timeframe:

One month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	5		
Units: Patients affected				
No change	2	1		
>= 50% decrease	1	0		
<50% decrease but <25% increase	7	3		
>=25% increase	0	1		

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

The categorical endpoint is compared between the treatment groups in the mITT set using Fisher's exact test. Only patients with available measurements are included. Patients who are deceased or missing values at this timepoint are not considered.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7902
Method	Fisher exact

Secondary: Difference EORTC QLQ-C30 Summary Score - baseline to discharge / d7

End point title	Difference EORTC QLQ-C30 Summary Score - baseline to discharge / d7

End point description:

The difference in the EORTC QLQ-C30 Summary Score from baseline to discharge / d7.

End point type	Secondary

End point timeframe:

From baseline to discharge / d7.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: QLQ-C30 Summary Score				
median (inter-quartile range (Q1-Q3))	-4.10 (-13.57 to 1.71)	-6.97 (-11.24 to 0.13)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9829
Method	exact Mann-Whitney U test

Secondary: Difference EORTC QLQ-C30 Summary Score - baseline to 1 month after randomisation

End point title	Difference EORTC QLQ-C30 Summary Score - baseline to 1 month after randomisation

End point description:

The difference in the EORTC QLQ-C30 Summary Score from baseline to 1 month after randomisation.

End point type	Secondary

End point timeframe:

From baseline to 1 month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: QLQ-C30 Summary Score				
median (inter-quartile range (Q1-Q3))	-1.45 (-4.57 to 7.26)	-9.53 (-18.46 to -3.21)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1932
Method	Exact Mann-Whitney U test

Secondary: Difference EORTC QLQ-BN20 Summary Score - baseline to discharge / d7

End point title	Difference EORTC QLQ-BN20 Summary Score - baseline to discharge / d7

End point description:

The difference in the EORTC QLQ-BN20 Summary Score from baseline to discharge / d7.

End point type	Secondary

End point timeframe:

From baseline to discharge / d7.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: EORTC QLQ-BN20 Summary Score				
median (inter-quartile range (Q1-Q3))	4.17 (-4.67 to 8.71)	3.03 (-11.87 to 8.08)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6058
Method	Exact Mann-Whitney U test

Secondary: Difference EORTC QLQ-BN20 Summary Score - baseline to 1 month after randomisation

End point title	Difference EORTC QLQ-BN20 Summary Score - baseline to 1 month after randomisation

End point description:

The difference in the EORTC QLQ-BN20 Summary Score from baseline to 1 month after randomisation.

End point type	Secondary

End point timeframe:

From baseline to 1 month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: EORTC QLQ-BN20 Summary Score				
median (inter-quartile range (Q1-Q3))	5.05 (3.28 to 5.81)	-12.37 (-18.18 to 4.55)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0907
Method	Exact Mann-Whitney U test

Secondary: Difference Karnofsky Performance Score - baseline to 26-48h after treatment

End point title	Difference Karnofsky Performance Score - baseline to 26-48h after treatment

End point description:

The difference in the Karnofsky Performance Score from baseline to 26-48h after treatment.

End point type	Secondary

End point timeframe:

From baseline to 26-48h after treatment.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Karnofsky Performance Score				
median (inter-quartile range (Q1-Q3))	0.00 (-10.00 to 0.00)	-10.00 (-20.00 to 0.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1905
Method	Exact Mann-Whitney U test

Secondary: Difference Karnofsky Performance Score - baseline to discharge / d7

End point title	Difference Karnofsky Performance Score - baseline to discharge / d7

End point description:

The difference in the Karnofsky Performance Score from baseline to discharge / d7.

End point type	Secondary

End point timeframe:

From baseline to discharge / d7.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Karnofsky Performance Score				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 0.00)	-10.00 (-10.00 to 0.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0903
Method	Exact Mann-Whitney U test

Secondary: Difference Karnofsky Performance Score - baseline to 1 month after randomisation

End point title	Difference Karnofsky Performance Score - baseline to 1 month after randomisation

End point description:

The difference in the Karnofsky Performance Score from baseline to 1 month after randomisation.

End point type	Secondary

End point timeframe:

From baseline to 1 month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Karnofsky Performance Score				
median (inter-quartile range (Q1-Q3))	-10.00 (-10.00 to 0.00)	-5.00 (-10.00 to 0.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.764
Method	Exact Mann-Whitney U test

Secondary: Difference Mini-Mental state examination score - baseline to 26-48h after treatment

End point title	Difference Mini-Mental state examination score - baseline to 26-48h after treatment

End point description:

The difference in the Mini-Mental state examination score from baseline to 26-48h after treatment.

End point type	Secondary

End point timeframe:

From baseline to 26-48h after treatment.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: Mini-Mental state examination score				
median (inter-quartile range (Q1-Q3))	0.00 (-1.00 to 0.00)	0.00 (-1.00 to 1.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8941
Method	Exact Mann-Whitney U test

Secondary: Difference Mini-Mental state examination score - baseline to discharge / d7

End point title	Difference Mini-Mental state examination score - baseline to discharge / d7

End point description:

The difference in the Mini-Mental state examination score from baseline to discharge / d7.

End point type	Secondary

End point timeframe:

From baseline to discharge / d7.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: Mini-Mental state examination score				
median (inter-quartile range (Q1-Q3))	0.00 (-1.00 to 0.00)	0.00 (-1.00 to 3.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5187
Method	Exact Mann-Whitney U test

Secondary: Difference Mini-Mental state examination score - baseline to 1 month after randomisation

End point title	Difference Mini-Mental state examination score - baseline to 1 month after randomisation

End point description:

The difference in the Mini-Mental state examination score from baseline to 1 month after randomisation.

End point type	Secondary

End point timeframe:

From baseline to 1 month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Mini-Mental state examination score				
median (inter-quartile range (Q1-Q3))	0.00 (-2.00 to 2.00)	-1.00 (-2.00 to -1.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5748
Method	Exact Mann-Whitney U test

Secondary: Difference NIHSS total score - baseline to 26-48h after treatment

End point title	Difference NIHSS total score - baseline to 26-48h after treatment

End point description:

The difference in the NIHSS total score from baseline to 26-48h after treatment.

End point type	Secondary

End point timeframe:

From baseline to 26-48h after treatment.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: NIHSS total score				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 0.00)	0.00 (0.00 to 1.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8042
Method	Exact Mann-Whitney U test

Secondary: Difference NIHSS total score - baseline to discharge / d7

End point title	Difference NIHSS total score - baseline to discharge / d7

End point description:

The difference in the NIHSS total score from baseline to discharge / d7.

End point type	Secondary

End point timeframe:

From baseline to discharge / d7.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: NIHSS total score				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 0.00)	0.00 (0.00 to 1.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8672
Method	Exact Mann-Whitney U test

Secondary: Difference NIHSS total score - baseline to 1 month after randomisation

End point title	Difference NIHSS total score - baseline to 1 month after randomisation

End point description:

The difference in the NIHSS total score from baseline to 1 month after randomisation.

End point type	Secondary

End point timeframe:

From baseline to 1 month after randomisation.

End point values	5-ALA iPDT	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: NIHSS total score				
median (inter-quartile range (Q1-Q3))	1.00 (0.00 to 2.00)	1.00 (0.00 to 2.00)		

Statistical analyses

Statistical analysis title	Exact Mann-Whitney U test

Statistical analysis description:

The change is compared between the treatment groups in the mITT set using an exact Mann-Whitney U test. Only patients with available measurements at baseline and this follow-up time were included.

Comparison groups	5-ALA iPDT v Control

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8689
Method	Exact Mann-Whitney U test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were documented from the time the informed consent was signed until 3 months after surgery. All serious AEs (SAEs) were documented until end of individual trial participation or until disease progression whichever occured earlier.

Adverse event reporting additional description:

AEs occurred in 12 patients (5-ALA iPDT n=6, control n=6), and SAEs occurred in 9 patients (5-ALA iPDT n=5, control n=4). There were 14 MedDRA codes reported in the 5-ALA iPDT group and 10 in the group. 15 of them were SAEs (5-ALA iPDT n=9, control n=6). In addition to MedDRA version 26.0, versions 26.1, 27.0 and 28.1 were also used.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	5-ALA iPDT (Safety set)

Reporting group description:

Patients receiving iPDT with 5-ALA (treatment arm), identical to the modified ITT treatment arm.

Reporting group title	Control (Safety set)

Reporting group description:

Patients receiving therapy at the investigator’s discretion without iPDT (control arm), identical to the modified ITT control arm.

Serious adverse events	5-ALA iPDT (Safety set)	Control (Safety set)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	4 / 12 (33.33%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	3 / 10 (30.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Personality disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Brain abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	5-ALA iPDT (Safety set)	Control (Safety set)	
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 10 (20.00%)	3 / 12 (25.00%)	
Vascular disorders Haemorrhage subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Nervous system disorders Ataxia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Dizziness subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Hemianopia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Monoparesis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Partial seizures subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Quadrantanopia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Seizure subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2021	The study was initiated with study protocol version 5.2 dated October 31, 2019. During the course of the study, the protocol was amended once to version 5.3 dated July 29, 2021. The chapter "Assessment of safety" has been adapted to the new medical device legislation. There have also been changes to the accompanying research project. Immunophenotyping has been removed. Instead, additional blood plasma tests will be conducted. It is clarified that the translational studies are optional and will only be performed on patients who have given their separate consent. In addition, due to the delayed start of the study, the schedule was adjusted and the change of address of the project manager was included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the prematurely termination of the study and small sample size, the generalizability of the study results is severely limited. Furthermore, relevant differences between the treatment arms cannot be demonstrated with the small number of cases.

Notes: