Clinical trial results:
Comparison of Fluorescein-INtra-VItal microscopy Versus conventional frozen section diagnosis for intraOperative histopathological evaluation

Summary

EudraCT number	2019-004512-58
Trial protocol	DE
Global end of trial date	17 June 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023
Summary attachment (see zip file)	CSR_INVIVO (Ergebnisbericht_INVIVO_V1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	INV-GEM-0200-I

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04597801
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Helen Bidner, Münchner Studienzentrum, 0049 8941406312, helen.bidner@mri.tum.de
Scientific contact	Prof. Dr. med. Jens Gempt, Klinik und Poliklinik für Neurochirurgie , 0049 8941402151, nch-office@mri.tum.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	06 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2022
Global end of trial reached?	Yes
Global end of trial date	17 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the clinical trial is to compare the significance of intravenously applied fluorescein as staining agent for assessment of brain tissue texture via in-vivo confocal microscopy with the conventional intraoperative histological frozen section analysis of identical brain tissue samples in the same patient. Both methods will be compared in terms of their accuracy using the standard of practice, the final pathological diagnosis (immunochemistry/molecular pathology).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP).
All participants have been informed in detail about the clinical trial in a personal interview. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 210
Worldwide total number of subjects	210
EEA total number of subjects	210

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)	123
From 65 to 84 years	84
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted multicentric (3 study sites) in Germany. The recruitment took place between November 30, 2020 (first patient recruited) and June 30, 2022 (last patient completed)

Pre-assignment

Screening details:

During Screening, the preoperative routine measures (demographics, medical/surgical history and pregnancy test) are carried out and in addition the inclusion-, exclusion criteria have to be checked and the ICF must be obtained before each study specific procedure.

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	All patients

Arm description:

Contains all patients who entered the study

Arm type	Experimental
Investigational medicinal product name	Fluorescein Alcon 10%
Investigational medicinal product code	SUB13905MIG
Other name	FLUORESCEIN SODIUM
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5mg per kg bodyweight

Number of subjects in period 1	All patients
Started	210
Completed	201
Not completed	9
Adverse event, serious fatal	1
No surgery	4
Lost to follow-up	1
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	210	210	
Age categorical Units: Subjects			
Adults (18-64 years)	123	123	
From 65-84 years	84	84	
85 years and over	3	3	
Gender categorical Units: Subjects			
Female	117	117	
Male	93	93	

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consists of all patients who entered the clinical trial, received Fluorescein, and had surgery. Patients with missing primary endpoint assessments were excluded from this analysis set.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol set consists of all patients in the FAS who had no major protocol violations.

Reporting group values	FAS	PPS	
Number of subjects	203	202	
Age categorical Units: Subjects			
Adults (18-64 years)	119	118	
From 65-84 years	81	81	
85 years and over	3	3	
Gender categorical Units: Subjects			
Female	112	112	
Male	91	90	

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

Contains all patients who entered the study

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consists of all patients who entered the clinical trial, received Fluorescein, and had surgery. Patients with missing primary endpoint assessments were excluded from this analysis set.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol set consists of all patients in the FAS who had no major protocol violations.

Primary: Difference in accuracy

End point title	Difference in accuracy[1]

End point description:

The accuracy of Convivo and the accuracy of Frozen Section were computed and their difference is presented including a 95%CI. The Non-inferiority margin was -0.05. As the lower boundary of the CI is below -0.05, non-inferiority of Convivo over Frozen Section could not be shown.

End point type	Primary

End point timeframe:

Measured at study end

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: n.a.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	202		
Units: fraction				
number (confidence interval 95%)	-0.0394 (-0.1009 to 0.0221)	-0.0396 (-0.1013 to 0.0221)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Convivo assessments

End point title	Duration of Convivo assessments

End point description:

End point type	Secondary

End point timeframe:

Collected during surgery

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: minute				
arithmetic mean (standard deviation)	2.9 (± 1.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of frozen section analysis

End point title	Duration of frozen section analysis

End point description:

End point type	Secondary

End point timeframe:

Collected during surgery

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: minute				
arithmetic mean (standard deviation)	30.5 (± 14.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The Adverse Events have been reported at begin of visit 1 (baseline) and ended at visit 3.	
Adverse event reporting additional description:	
Some hospital admissions, as defined by the study protocol, were not considered SAEs.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Safety Analysis Set
Reporting group description:	
The safety analysis set contains all patients who received IMP.	

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 205 (1.95%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral haemorrhage			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			

subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CNS ventriculitis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 205 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 205 (25.85%)		
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 205 (11.71%)		
occurrences (all)	25		
Eye disorders			
Eye swelling			
subjects affected / exposed	8 / 205 (3.90%)		
occurrences (all)	8		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	22 / 205 (10.73%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	11 / 205 (5.37%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported