



Clinical trial results:

Pilot study to optimise the use and to evaluate the diagnostic value of intraoperative contrast-enhanced 3D-ultrasound with SonoVue® for imaging of intracranial tumors

Summary

EudraCT number	2010-022057-42
Trial protocol	DE
Global end of trial date	23 December 2013

Results information

Result version number	v1 (current)
This version publication date	12 August 2020
First version publication date	12 August 2020
Summary attachment (see zip file)	Trial Synopsis of the 3D-iUS-NCH Study (3D-iUS_NCH_Ergebnisbericht_final1.0_2014-12-19.pdf)

Trial information

Trial identification

Sponsor protocol code	3D-iUS-NCH
-----------------------	------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	university of Leipzig
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany, 04109
Public contact	Dr. Dirk Lindner, University of Leipzig Neurochirurgie, 0049 3419717500,
Scientific contact	Dr. Dirk Lindner, University of Leipzig Neurochirurgie, 0049 3419717500,

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	26 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2013
Global end of trial reached?	Yes
Global end of trial date	23 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparison of intraoperative, 3D reconstructed and contrast enhanced, transdural ultrasound with the preoperative 3D- MRI as Gold Standard.

Comparison of intraoperative, 3D reconstructed and contrast enhanced ultrasound after tumor resection to verify the extent of resection as well as accuracy of navigation with the early post operative 3D- MRI as Gold Standard

Protection of trial subjects:

patients with planned surgery were included in this methodological study; in all of them an OP indication was stated due to intracranial tumor; the contrast-enhancing substance applied should allow a more precise identification of the margins of the tumor for surgery and the brain shift during surgery. SonoVue/Schwefelhexafluorid was already approved for application in cerebral arteries.

(S)AE were systematically collected and analysed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2011
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	65
From 65 to 84 years	34
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

inclusion of a consecutive sample of patients with intracranial tumors a who fulfil the in/exclusion criteria in a single centre and into a single-armed study

Pre-assignment

Screening details:

consecutive sample of patients with intracranial tumors a who fulfil the in/exclusion criteria with planned surgery in a single centre

Period 1

Period 1 title	application
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	all patients
-----------	--------------

Arm description:

This study aimed at a methodological comparison of imaging methods and analysed the precision of 3D-US imaging with/ without application of contrast- enhancing application of SonoVue compared to pre/post MRI for intra-operative navigation and resection control in the surgery of intracranial tumors.

Arm type	all Patients
Investigational medicinal product name	SonoVue (Schwefelhexafluorid)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intracavernous use

Dosage and administration details:

4.8 mL (216 µgram) two times during surgery

Number of subjects in period 1	all patients
Started	100
Completed	100

Period 2

Period 2 title	post-surgery short-term FUP
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	all patients
Arm description: -	
Arm type	Safety analysis population
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	all patients
Started	100
Completed	100

Baseline characteristics

Reporting groups

Reporting group title	application
-----------------------	-------------

Reporting group description:

all patients in whom an intracranial surgery was indicated/ planned

Reporting group values	application	Total	
Number of subjects	100	100	
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	60		
inter-quartile range (Q1-Q3)	50.3 to 69	-	
Gender categorical			
Units: Subjects			
Female	38	38	
Male	62	62	
tumor class			
Units: Subjects			
Glioblastoma multiforme	48	48	
Meningeom	5	5	
astrocytome	11	11	
oligodendrogliom	2	2	
metastasis in primum	32	32	
no rest identifiable	1	1	
not reported	1	1	
smoker			
Units: Subjects			
yes	15	15	
no	85	85	
complete resection planned			
Units: Subjects			
no	26	26	
yes	70	70	
not reported	4	4	
serious AE reported			

without SAE reporting requirements according to trail protocol			
Units: Subjects			
yes	12	12	
no	88	88	

Subject analysis sets

Subject analysis set title	all patients
Subject analysis set type	Safety analysis

Subject analysis set description:

Since the study aimed at methodological comparison of different imaging method in intracranial surgery, the primary analysis reported here is the safety of patients regarding the contrast enhancing IMP applied

Reporting group values	all patients		
Number of subjects	100		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female	38		
Male	62		
tumor class			
Units: Subjects			
Glioblastoma multiforme	48		
Meningeom	5		
astrocytome	11		
oligodendrogliom	2		
metastasis in primum	32		
no rest identifyable	1		
not reported	1		
smoker			
Units: Subjects			
yes	15		
no	85		
complete resection planned			
Units: Subjects			

no	26		
yes	70		
not reported	4		
serious AE reported			
without SAE reporting requirements according to trail protocol			
Units: Subjects			
yes	12		
no	88		

End points

End points reporting groups

Reporting group title	all patients
-----------------------	--------------

Reporting group description:

This study aimed at a methodological comparison of imaging methods and analysed the precision of 3D-US imaging with/ without application of contrast- enhancing application of SonoVue compared to pre/post MRI for intra-operative navigation and resection control in the surgery of intracranial tumors.

Reporting group title	all patients
-----------------------	--------------

Reporting group description: -

Subject analysis set title	all patients
----------------------------	--------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

Since the study aimed at methodological comparison of different imaging method in intracranial surgery, the primary analysis reported here is the safety of patients regarding the contrast enhancing IMP applied

Primary: size of tumor (3D-US / MRT)

End point title	size of tumor (3D-US / MRT) ^[1]
-----------------	--

End point description:

within the most frequently class of tumors met (glioblastoma, metastases) in the study sample; and using all images which were segmented/ analysed estimates with 95% confidence limits were calculated and compared between the different imagin procedures

End point type	Primary
----------------	---------

End point timeframe:

before surgical tumor resection via 3D-US / MR imaging

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: This was a single armed study to compare different imaging methods in intracranial surgery.

The 95% confidence intervals for the tumor size before surgery (according to the imaging method) resulted in :

- MRI: 30,2 [17,9; 42,5] ml,
- 3D-US with SonoVue: 25,2 [14,2; 36,8] ml,
- 3D-US without SonoVue: 24,2 [15,0; 33,4] ml.

Therefore, the contrast-enhanced US provided 15.6% smaller values in tumor size.

End point values	all patients	all patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21 ^[2]	21 ^[3]		
Units: ml				
median (inter-quartile range (Q1-Q3))	39.3 (1.2 to 242.9)	39.3 (1.2 to 242.9)		

Notes:

[2] - with glioblastoma

[3] - in patients with glioblastoma

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from time of SonoVue-application until MRT investigation post surgery (SAE) resp. discharge of the hospital (AE)

Adverse event reporting additional description:

No SAE was reported during the course of study.

A single AE (pneumonia) with fatal outcome occurred during the hospitalisation of the patient. A causality to SonoVue is not possible since death occurred on 21 Sept. 2011 (surgery/ application of SonoVue on 6 Sept. 2011)

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	SAE reporting period
-----------------------	----------------------

Reporting group description:

from first application until ≤48h post surgery/ 2nd MRT imaging;

exception: events during surgery and without relationship to SonoVue were only to be documented as AE acc. to protocol.

Reporting group title	all patients until discharge from hospital
-----------------------	--

Reporting group description:

The death reported after pneumonia (as serious AE) during hospitalisation occurred later than the end of SAE reporting period.

Serious adverse events	SAE reporting period	all patients until discharge from hospital	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 100 (0.00%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	SAE reporting period	all patients until discharge from hospital	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	13 / 100 (13.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 100 (0.00%)	4 / 100 (4.00%)	
occurrences (all)	0	1	

Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 100 (0.00%)	4 / 100 (4.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: since this AE with fatal outcome occurred after the SAE reporting period (acc. to trial protocol) but within the observation of patients no SAE report was necessary		
subjects affected / exposed	0 / 100 (0.00%)	1 / 100 (1.00%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 100 (0.00%)	8 / 100 (8.00%)	
occurrences (all)	0	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2013	1) Administration of 2.4 mL of (108 micro gram) SonoVue® (sulfurhexafluoride) was changed to 4,8 mL SonoVue® (216 µg Schwefelhexafluorid). 2) The study was prolonged

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.

At the end of the study the data on segmented/analysed images was not complete yet but the safety data were completely available. Therefore the study report was finalized.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26883549>