Clinical trial results:
Optical measurement with 5-ALA during surgical resection of brain tumors in children

Summary

EudraCT number	2013-005565-40
Trial protocol	SE
Global end of trial date	28 October 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2020
First version publication date	23 February 2020

Trial information

Trial identification

Sponsor protocol code	OTP-B-Linköping

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Linköping University
Sponsor organisation address	Department of Biomedical Engineering, Linköping, Sweden, 581 85
Public contact	Linköping University , Department of Biomedical Engineering, 46 13286716, neda.haj.hosseini@liu.se
Scientific contact	Linköping University , Department of Biomedical Engineering, 46 13286716, neda.haj.hosseini@liu.se

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	07 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2018
Global end of trial reached?	Yes
Global end of trial date	28 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Improve brain tumour resection in children.

Protection of trial subjects:

5-ALA induced fluorescence guided brain tumor surgery is well established on adults and 5-ALA is approved by FDA and European and Swedish Medical Product Agencies and adheres Good Manufacturing Practice (GMP). In this study 5-ALA induced fluorescence guided surgery is applied in children. Inclusion and exclusion criteria are clearly described. Before start the patients and two next of kin gave written informed consent.
Monitoring and quality control are done to ensure the safety and integrity of the participant subjects, the data quality and that the study is compliant with the current version of the Declaration of Helsinki, ICH GCP, national regulations and scientific integrity. The Sponsor has delegated the monitoring to the CRO at the University, an independent party, who perform on-site monitoring before, during and after the study. The monitoring included source data verification. To enable this, the monitor has been given access to relevant medical records.

Background therapy:

Patients were acutely admitted without any background therapy.

Evidence for comparator:

No comparators.

Actual start date of recruitment	03 October 2014
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	Sweden: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	12
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited prior to their brain tumor operation within the time period 2014-05-15 to 2018-10-28.
1-4 cases were recruited per year.
The trial was kept open until 2019-09-11, but no more subjects were enrolled during this extra year.
All subjects came from Sweden.

Pre-assignment

Screening details:

15 children and their two next of kin (parents) were asked to participate. One child was not included due to inadequate blood values.
14 children aged 4 to 17 years participated after informed written consent from the children and the two parents.

Pre-assignment period milestones

Number of subjects started	14
Number of subjects completed	14

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	Fluorescence guided surgery

Arm description:

All patients received an oral dose of 5-ALA prior to surgery. Measurements and data collection of fluorescence with a hand held probe and through the neurosurgical blue-light microscope was done during surgery. Biopsies were taken and sent for analysis. At the end of surgery another probe was used for recording of spectra from the skin. Data analysis was done postoperatively.

Arm type	Neurosurgery
Investigational medicinal product name	5-ALA
Investigational medicinal product code	L01XD04
Other name	5 aminulevulinic acid
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

One oral dose of 20 mg/kg milligram(s)/kilogram

Number of subjects in period 1	Fluorescence guided surgery
Started	14
Completed	14

Baseline characteristics

Reporting groups	
Reporting group title	Fluorescence guided surgery

Reporting group description:

All patients received an oral dose of 5-ALA prior to surgery. Measurements and data collection of fluorescence with a hand held probe and through the neurosurgical blue-light microscope was done during surgery. Biopsies were taken and sent for analysis. At the end of surgery another probe was used for recording of spectra from the skin. Data analysis was done postoperatively.

Reporting group values	Fluorescence guided surgery	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	12	12	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	6	6	
Male	8	8	

End points

End points reporting groups

Reporting group title	Fluorescence guided surgery

Reporting group description:

All patients received an oral dose of 5-ALA prior to surgery. Measurements and data collection of fluorescence with a hand held probe and through the neurosurgical blue-light microscope was done during surgery. Biopsies were taken and sent for analysis. At the end of surgery another probe was used for recording of spectra from the skin. Data analysis was done postoperatively.

Primary: Tumor fluorescence

End point title	Tumor fluorescence[1]

End point description:

Fluorescence in the neurosurgical microscope was graded as "none", "weak" or "strong". "None" was set to 0 and "weak" and "strong" were set to "1" .
Fluorescence measured with the probe was measured as the size of the peak at 635 nm. No peak was set to 0 and peak was set to 1.
Probe measurements on the skin was measured as no peak (0) and peak (1).
The results were linked to the location in the brain (infratentorial and supratentorial) and to to the histopathology analysis i.e. as high-grade tumour or low-grade tumour.
Summary of the result is attached as a pdf-file.

End point type	Primary

End point timeframe:

During surgery

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: Descriptive data and analysis is used. No hypothesis testing with statistical analysis is motivated.

End point values	Fluorescence guided surgery			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: aribitrary				
number (not applicable)	14			

Attachments (see zip file)	OTP-B/OTP-B-Result.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From inclusion to 3 days post surgery.	
Adverse event reporting additional description: Hospitalized patient with continuous reporting.	
Assessment type	Systematic

Dictionary used	
Dictionary name	No dictionary used
Dictionary version	0

Reporting groups	
Reporting group title	Total data set
Reporting group description: Tongue swelling after intubation.	

Serious adverse events	Total data set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Toung swelling during intubation			
subjects affected / exposed	1 / 14 (7.14%)		
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	Total data set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 14 (50.00%)		
Blood and lymphatic system disorders			
Infleunce on heamatology	Additional description: Result from blood samples (differential count of reticulocyte CRP, leukocyte, thrombocyte, hemoglobin, erythrocyte, MVC, MCHC). Subtile changes probably postoperatively induced.		
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	1		
Hepatobiliary disorders			

Reduced liver function	Additional description: Result from blood samples after surgery (ALAT, ASAT, ALP, Bilirubin). Subtile changes probably postoperatively induced.		
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	Exclusion criteria: Blood samples taken before surgery deviates more than +/ 10% from reference values Blood samples post surgery deviates from reference values more than +/ 10% and longer than 3 days, these are continued to be followed up. Per-oral administration of 5-ALA at least 2 hrs prior to surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported