Clinical trial results:
Carbon Dioxide for the Treatment of Febrile Seizures

Summary

EudraCT number	2011-001403-12
Trial protocol	DE
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2022
First version publication date	05 May 2022
Summary attachment (see zip file)	pre-ended-statement_CARDIF (pre-ended-statement_2011-001403-12.pdf)

Trial information

Trial identification

Sponsor protocol code	CARDIF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01370044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Universitaetsmedizin Berlin, Charite Universitaetsmedizin Berlin, +49 304505566112, markus.schuelke@charite.de
Scientific contact	Universitaetsmedizin Berlin, Charité - Universitaetsmedizin Berlin, +49 304505566112, markus.schuelke@charite.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	Interim
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2015
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a carbogen-inhalation in patients with febrile seizures compared to a placebo-inhalation

Protection of trial subjects:

The safety of the therapy with carbogen-inhalation in patients with febrile seizures assessed by physical examination, vital signs, and evaluation of adverse events. Furthermore, the patients were monitored for spontaneous complaints after treatments.
The study will be performed in accordance with the Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, the German Medical Drug Law and Data Protection Laws in their current or effective versions. An extensive GCP monitoring will be conducted. Additionally, we put strategies in place to maximize data quality, such as intensive training of the study team, nursing personal and parents. Adverse event management will be done according to standard regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2012
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	12
Children (2-11 years)	8
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited from the Children’s University Hospital of the Charité in Berlin. Parents or custodians of potential participants will be thoroughly informed about the study rationale, procedures, potential risks and benefits.

Pre-assignment

Screening details:

Assessed for eligibility: 97;
Excluded: 3;
94 were randomized.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum Group

Arm description:

Carbogen is a gas mixture composed of 5% CO2 and 95% O2, which is stored in compressed gas cylinders.
the application of CO2-enriched air or of medical carbogen (5% CO2 plus 95% O2), which ensures that the blood pCO2 does not increase and the pO2 does not drop beyond certain limits. The added oxygen even improves oxygenation and prevents hypoxia. As febrile seizures usually occur at home, where no blood gas monitoring is possible, we opted for carbogen to be used in our clinical trial.

Arm type	Experimental
Investigational medicinal product name	Carbogengas
Investigational medicinal product code	
Other name	CO2
Pharmaceutical forms	Inhalation vapour
Routes of administration	Respiratory use

Dosage and administration details:

CO2 (5%) with O2(95%) inhalation of 6 liters carbogen over 3 minutes once the seizure occur

Arm title	Placebo Group

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	100% O2
Pharmaceutical forms	Inhalation vapour
Routes of administration	Respiratory use

Dosage and administration details:

100% O2 (Low-pressure can containing 6 liter of Oxygen). Administration once the seizure has started over 3min.

Number of subjects in period 1	Verum Group	Placebo Group
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups

Reporting group title	Verum Group

Reporting group description:

Carbogen is a gas mixture composed of 5% CO2 and 95% O2, which is stored in compressed gas cylinders.
the application of CO2-enriched air or of medical carbogen (5% CO2 plus 95% O2), which ensures that the blood pCO2 does not increase and the pO2 does not drop beyond certain limits. The added oxygen even improves oxygenation and prevents hypoxia. As febrile seizures usually occur at home, where no blood gas monitoring is possible, we opted for carbogen to be used in our clinical trial.

Reporting group title	Placebo Group

Reporting group description: -

Reporting group values	Verum Group	Placebo Group	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
28 days - 23 months	5	7	12
14 months - 2 years	5	3	8
Gender categorical Units: Subjects			
female	6	5	11
male	4	5	9

Subject analysis sets

Subject analysis set title	Crossover patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

After the first seizure recurrence a crossover occurs. With this, regardless of the result of the first treatment, patients who received placebo for the first seizure recurrence receive verum for the second one or vice versa. From the third seizure recurrence onwards, all patients receive open label verum. Since it is anticipated that only a minority of patients will suffer from a second seizure recurrence and thus enter the crossover arm, the study is not a true crossover study. Data from the "crossover" and the open label extension phase will thus only be considered for secondary analyses. The primary analysis will only include the first seizure recurrence, while the secondary analyses consider all seizure recurrences per patient.

Reporting group values	Crossover patients		
Number of subjects	5		
Age categorical Units: Subjects			
28 days - 23 months	4		
14 months - 2 years	1		
Gender categorical Units: Subjects			
female	3		
male	2		

End points

End points reporting groups

Reporting group title	Verum Group

Reporting group description:

Carbogen is a gas mixture composed of 5% CO2 and 95% O2, which is stored in compressed gas cylinders.
the application of CO2-enriched air or of medical carbogen (5% CO2 plus 95% O2), which ensures that the blood pCO2 does not increase and the pO2 does not drop beyond certain limits. The added oxygen even improves oxygenation and prevents hypoxia. As febrile seizures usually occur at home, where no blood gas monitoring is possible, we opted for carbogen to be used in our clinical trial.

Reporting group title	Placebo Group

Reporting group description: -

Subject analysis set title	Crossover patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

After the first seizure recurrence a crossover occurs. With this, regardless of the result of the first treatment, patients who received placebo for the first seizure recurrence receive verum for the second one or vice versa. From the third seizure recurrence onwards, all patients receive open label verum. Since it is anticipated that only a minority of patients will suffer from a second seizure recurrence and thus enter the crossover arm, the study is not a true crossover study. Data from the "crossover" and the open label extension phase will thus only be considered for secondary analyses. The primary analysis will only include the first seizure recurrence, while the secondary analyses consider all seizure recurrences per patient.

Primary: Efficacy of a Carbogen inhalation

End point title	Efficacy of a Carbogen inhalation

End point description:

End point type	Primary

End point timeframe:

24 months study period

End point values	Verum Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Subjects				
adjourned: yes	2	7		
adjourned: no	8	3		

Statistical analyses

Statistical analysis title	Determation of the success rate

Statistical analysis description:

Statistical planning is based on the modified intention-to-treat principle, i.e. only patients suffering from a febrile seizure recurrence during the study period of 24 months will be assigned to the intention-to-treat population.

Comparison groups	Verum Group v Placebo Group

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	> 0.3 [2]
Method	Fisher exact

Notes:

[1] - The aim of the study is the proof of the superiority of the experimental intervention (carbogen) versus control (oxygen) to suppress a seizure recurrence within 3 minutes. Success rates under intervention and control being p_i and p_K, the statistical null hypothesis is pI = pK, and the alternative hypothesis pI ≠ pK. The analyses will be carried out according to Bauer & Köhne with α=0.025, cα= 0.00380 and α0=0.5 (in each case one-sided).

[2] - the p-value of the exact Fischer test was p = 0.07 and for the one sided fischer exact test was p=0.035 in favor of Placebo. Hence the formal criteria was p_0 > 0.3

Secondary: Crossover confirmation

End point title	Crossover confirmation

End point description:

After the first seizure recurrence a crossover occurs. With this, regardless of the result of the first treatment, patients who received placebo for the first seizure recurrence receive verum for the second one or vice versa. From the third seizure recurrence onwards, all patients receive open label verum. Since it is anticipated that only a minority of patients will suffer from a second seizure recurrence and thus enter the crossover arm, the study is not a true crossover study. Data from the "crossover" and the open label extension phase will thus only be considered for secondary analyses. The primary analysis will only include the first seizure recurrence, while the secondary analyses consider all seizure recurrences per patient.

End point type	Secondary

End point timeframe:

within the study duration: 24months

End point values	Crossover patients			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Subjects				
Confirming Verum	1			
Confirming Placebo	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 24 months study period	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	own
Dictionary version	1

Reporting groups	
Reporting group title	Verum Group
Reporting group description: -	
Reporting group title	Placebo Group
Reporting group description: -	
Reporting group title	Medication not taken
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported

Serious adverse events	Verum Group	Placebo Group	Medication not taken
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	2 / 10 (20.00%)	2 / 2 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
febrile seizures			
subjects affected / exposed	3 / 10 (30.00%)	1 / 10 (10.00%)	2 / 2 (100.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Verum Group	Placebo Group	Medication not taken
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 2 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2012	late registration PI
28 December 2012	LKP-Change: EK-Vote
01 January 2013	Bfarm-Vote; new protocol verion 1.2 (13th of Dec, 2012)

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.

The study was prematurely ended due to futility.
In the interim analysis of the CARDIF study results were unexpectedly found in favor of an inferiority of the verum compound. For this reason the study had to be aborted ("stopping for futility"). Si

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23806032