Clinical trial results:
Association between variations in CYP pheno- and genotypes and plasma concentration of chlordiazepoxide in the treatment of alcohol withdrawal symptoms

Summary

EudraCT number	2021-002188-23
Trial protocol	DK
Global end of trial date	11 June 2023

Results information

Result version number	v1 (current)
This version publication date	26 June 2024
First version publication date	26 June 2024

Trial information

Trial identification

Sponsor protocol code	KLOPOXID2021

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bispebjerg and Frederiksberg Hospital
Sponsor organisation address	Bispebjerg Bakke 23, opgang 20c st. th., København NV, Denmark, 2400
Public contact	Christian Sylvest Meyhoff, Bispebjerg and Frederiksberg Hospital, +45 24910542, christian.sylvest.meyhoff@regionh.dk
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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	21 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to elucidate if CYP phenotypes, variations in CYP genotypes and dose of chlordiazepoxide are correlated to the concentration of chlordiazepoxide in patients admitted to ICU or Intermediate Care Department (ICD) for respiratory insufficiency and/or agitation in relation to alcohol
withdrawal symptoms.

Protection of trial subjects:

No specific measure were taken to protect trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	18
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients aged more than 18 years who had been treated with at least 200 mg of chlordizapoxide for alcohol withdrawal symptoms and were admitted to either ICU or HDU due to somnolence respiratory insufficiency or agitation were elligible for inclusion. Patients were included no later than 12 hours after ICU or HDU admittance.

Pre-assignment

Screening details:

Patients aged more than 18 years who had been treated with at least 200 mg of chlordizapoxide for alcohol withdrawal symptoms and were admitted to either ICU or HDU due to somnolence respiratory insufficiency or agitation were screened for inclusion.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients were not blinded.

Arms

Arm title	Included

Arm description:

treatment with chlordizapoxide preceeded inclusion. No intervention was performed during the study period.

Arm type	No Intervention
Investigational medicinal product name	No Product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlordizepoxide was administered before inclusion in the study.

Number of subjects in period 1	Included
Started	27
Completed	26
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
Adults (18-64 years)	18	18	
From 65-84 years	8	8	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	61		
standard deviation	± 12	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	21	21	
Not Recorded	1	1	

End points

End points reporting groups

Reporting group title	Included

Reporting group description:

treatment with chlordizapoxide preceeded inclusion. No intervention was performed during the study period.

Primary: plasma concentration of chlordiazepoxide

End point title	plasma concentration of chlordiazepoxide[1]

End point description:

End point type	Primary

End point timeframe:

At inclusion and 12 h after inclusion.

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: In this study there were no comparisons between arms. All patients were included after having recieved Chlordizepoxide. The study population was divided into two groups according to phenotypes. Phenotypes were analyzed after inclusion.
Results are presented in tables under "Charts".

End point values	Included			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: µg/mL				
number (not applicable)				
CYP3A4 Normal/ CYP2C19 Slow	8			
CYP3A4 Normal/ CYP2C19 Normal	9			
CYP3A4 Normal/ CYP2C19 Fast	7			
CYP3A4 Fast/ CYP2C19 Fast	2			

Attachments (see zip file)	Pheno- and genotypes associated to plasma conc./Tabel geno- Table 2. Association between CYP phenotypes and p-/Tabel Table 3. Association between treatment with invasi/Tabel Ass

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative dose of chlordiazepoxide before admission to ICU/ICD

End point title	Cumulative dose of chlordiazepoxide before admission to ICU/ICD

End point description:

End point type	Secondary

End point timeframe:

February 2023-june 2023

End point values	Included			
Subject group type	Reporting group			
Number of subjects analysed	26[2]			
Units: mg				
Cumulative dose of chlordizapoxide before ICU/HDU	825			

Notes:

[2] - 825 [200 - 2100]
median [5-95 Percentile]

Statistical analyses

No statistical analyses for this end point

Secondary: ICU length of stay (LOS)

End point title	ICU length of stay (LOS)

End point description:

End point type	Secondary

End point timeframe:

February 2023-june 2023

End point values	Included			
Subject group type	Reporting group			
Number of subjects analysed	26[3]			
Units: Days				
Median LOS in ICU	7			
Median LOS in ICU/HDU	3			

Notes:

[3] - ICU: 6.5 [1.8 - 17]
ICU/HDU: 3.2 [1.5 - 18.4]

median [5 - 95 percentile]

Statistical analyses

No statistical analyses for this end point

Secondary: Need for Invasive mechanical ventilation

End point title	Need for Invasive mechanical ventilation

End point description:

End point type	Secondary

End point timeframe:
February 2023-june 2023

End point values	Included			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: yes/no				
yes	8			
No	18			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From inclusion until 12 h after inclusion

Assessment type	Systematic

Dictionary used

Dictionary name	Meriam-Webster
Dictionary version	2024

Reporting groups

Reporting group title	Overall study

Reporting group description:

26 patients were included in the overall study.

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: Non serious adverse events were not recorded. Chlordiazepoxide was administered before inclusion in the study and was not administered during the 12 h study period.

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Vasopressive therapy	Additional description: One patient was sedated in association with mechanical ventilation and needed norepinephrine due to hypotension induced by sedation. Need for vasopressive therapy is unlikely associated to blood sampling or the study pharmacological probes.		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Mechanical ventilation	Additional description: Mechanical ventilation was used in treatment of severe pneumonia and lung embolus during the 12 h study period. Both conditions are often treated with mechanical ventilation, and therefore expected, and unlikely associated to the study.		
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		

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