Clinical trial results:
The significance of deviation in time from the 12-hour standard serum-clozapine monitoring

Summary

EudraCT number	2015-002520-82
Trial protocol	DK
Global end of trial date	09 December 2015

Results information

Result version number	v1 (current)
This version publication date	29 March 2017
First version publication date	29 March 2017
Summary attachment (see zip file)	Article manuscript (Article manuscript_The significance of sampling-time in therapeutic drug monitoring of clozapine.pdf) Figure 1 (Fig.1.pdf) Table 1 (Table1.pdf) Table 2 (Table2.pdf) Table 3 (Table3.pdf) Table 4 (Table4.pdf) Supporting Information (Figure.S1.Supporting Information.pdf)

Trial information

Trial identification

Sponsor protocol code	CLO-MEAS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02625103
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Psychiatric Centre Copenhagen
Sponsor organisation address	Edel Sauntes Alle 10, Copenhagen O, Denmark, 2100
Public contact	Psykiatrisk Afdeling O, Psykiatrisk Center København, 0045 38647072, a.fink-jensen@dadlnet.dk
Scientific contact	Psykiatrisk Afdeling O, Psykiatrisk Center København, 0045 38647072, a.fink-jensen@dadlnet.dk

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	28 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2015
Global end of trial reached?	Yes
Global end of trial date	09 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the significance of deviation in time from the 12-hour standard blood sampling timepoint when Therapeutic Drug monitoring (TDM) clozapine

Protection of trial subjects:

none

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2015
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: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from outpatient services in the Capital Region of Denmark. Patients were included from September 2015 to December 2015.

Pre-assignment

Screening details:

54 subjects were screened and 48 subjects (88.9 %) were included in the study. 2 subjects were subsequently excluded: 1 patient suffered a serious adverse reaction (SAR) i.e. agranulocytosis and sepsis, during sampling time, and 1 patient had had a clozapine dose-adjustment 10 days prior to the trial and was excluded as a screening failure.

Period 1

Period 1 title	Primary inclusion
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Included subjects

Arm description:

Subjects are patients in stable treatment with clozapine

Arm type	Experimental
Investigational medicinal product name	Clozapine
Investigational medicinal product code	
Other name	Leponex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As for habitual individual use

Number of subjects in period 1	Included subjects
Started	48
Subject exclusion	46
Completed	46
Not completed	2
Adverse event, non-fatal	1
Protocol deviation	1

Period 2

Period 2 title	Final inclusion
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Final inclusion

Arm description:

Included subjects are patients in stable treatment with clozapine

Arm type	Experimental
Investigational medicinal product name	Clozapine
Investigational medicinal product code	
Other name	Leponex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As for habitual individual use

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: 2 of the enrolled subjects were excluded after trial participation. Period 2 is the baseline period after the extraction of excluded data.
See article-manuscript for clarification.

Number of subjects in period 2[2]	Final inclusion
Started	46
Completed	46

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 of the enrolled subjects were subsequently excluded. Only data from the remaining 46 subjects of final inclusion were used for data analysis.
See article-manuscript for clarification.

Baseline characteristics

Reporting groups

Reporting group title	Final inclusion

Reporting group description: -

Reporting group values	Final inclusion	Total	
Number of subjects	46	46	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	46	46	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	42		
full range (min-max)	20 to 59	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	26	26	
Smoking status Units: Subjects			
Smokers	17	17	
Non-smoker	29	29	
CRP status Units: Subjects			
CRP > 5 mg/L	16	16	
CRP < 5 mg/L	30	30	
Chronic blood dyscrasia			
Habitual WBC differential status within a six months retrospective data collection period was assessed. Chronic blood dyscrasia was defined as a minimum of 50% of the retrospective observations, for a given cell line, located either under or above the normal reference range. Only subjects with three or more WBC differential observations, within the retrospective period, were included for chronic blood dyscrasia evaluation. See up-loaded Table 1 and manuscript for clarification.			
Units: Subjects			
Chronic blood dyscrasia	31	31	
No chronic blood dyscrasia	15	15	
Number of daily clozapine administrations Units: Subjects			
1 daily administration	29	29	

2 daily administratio2	12	12	
3 daily administrations	4	4	
4 daily administrations	1	1	
Co-medications of relevance			
Relevant co-administrations was defined as drug-groups with known affecters of clozapine concentration. See up-loaded Table 1 and manuscript for clarification.			
Units: Subjects			
Relevantly co-medicated	34	34	
Not relevantly co-medicted	12	12	
Study specific age Units: Subjects			
Age > 45 years	21	21	
Age < 45 years	25	25	
BMI Units: kg/cm2			
median	30.9		
full range (min-max)	20.1 to 48.8	-	
Daily caffeine consumption Units: mg			
median	744.9		
full range (min-max)	0 to 2224.2	-	
Clozapine evening dose Units: mg			
median	237.5		
full range (min-max)	50 to 500	-	
Clozapine day doses Units: mg			
median	300		
full range (min-max)	50 to 800	-	

Subject analysis sets

Subject analysis set title	Chronic blood dyscrasia
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Habitual WBC differential status within a six months retrospective data collection period was assessed. Chronic blood dyscrasia was defined as a minimum of 50% of the retrospective observations, for a given cell line, located either under or above the normal reference range. Only subjects with three or more WBC differential observations, within the retrospective period, were included for chronic blood dyscrasia evaluation.

Reporting group values	Chronic blood dyscrasia		
Number of subjects	42		
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 full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
Smoking status Units: Subjects			
Smokers Non-smoker			
CRP status Units: Subjects			
CRP > 5 mg/L CRP < 5 mg/L			
Chronic blood dyscrasia			
Habitual WBC differential status within a six months retrospective data collection period was assessed. Chronic blood dyscrasia was defined as a minimum of 50% of the retrospective observations, for a given cell line, located either under or above the normal reference range. Only subjects with three or more WBC differential observations, within the retrospective period, were included for chronic blood dyscrasia evaluation. See up-loaded Table 1 and manuscript for clarification.			
Units: Subjects			
Chronic blood dyscrasia No chronic blood dyscrasia	31 11		
Number of daily clozapine administrations Units: Subjects			
1 daily administration 2 daily administratio2 3 daily administrations 4 daily administrations			
Co-medications of relevance			
Relevant co-administrations was defined as drug-groups with known affecters of clozapine concentration. See up-loaded Table 1 and manuscript for clarification.			
Units: Subjects			
Relevantly co-medicated Not relevantly co-medicted			
Study specific age Units: Subjects			
Age > 45 years Age < 45 years			
BMI Units: kg/cm2 median full range (min-max)			
Daily caffeine consumption			

Units: mg median full range (min-max)			
Clozapine evening dose Units: mg median full range (min-max)			
Clozapine day doses Units: mg median full range (min-max)			

End points

End points reporting groups

Reporting group title	Included subjects
Reporting group description: Subjects are patients in stable treatment with clozapine	
Reporting group title	Final inclusion
Reporting group description: Included subjects are patients in stable treatment with clozapine	
Subject analysis set title	Chronic blood dyscrasia
Subject analysis set type	Sub-group analysis
Subject analysis set description: Habitual WBC differential status within a six months retrospective data collection period was assessed. Chronic blood dyscrasia was defined as a minimum of 50% of the retrospective observations, for a given cell line, located either under or above the normal reference range. Only subjects with three or more WBC differential observations, within the retrospective period, were included for chronic blood dyscrasia evaluation.	

Primary: Differences in clozapine concentrations within a four-hour time span, 10-14 hours post-dose.

End point title	Differences in clozapine concentrations within a four-hour time span, 10-14 hours post-dose.[1]
End point description:	
End point type	Primary
End point timeframe: 10-14 hours post-dose	

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: Primary end-point was a observational record of percentage difference in clozapine serum concentrations, between 2 time-points. No statistical analysis was pre-specified.
See article-manuscript and up-loaded Table 2 for clarification.

End point values	Final inclusion			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: percentages				
median (full range (min-max))				
12-hour values vs. 10-hour values	8.4 (-32.2 to 52.6)			
12-hour values vs. 11-hour values	8 (-37.5 to 50.8)			
12-hour values vs. 13-hour values	-3.4 (-30.5 to 25.9)			
12-hour values vs. 14-hour values	-1.5 (-31.1 to 44)			
11-hour values vs. 13-hour values	-8.6 (-39.1 to 23.5)			
10-hour values vs. 14-hour values	-8.4 (-42.8 to 20.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Differences in norclozapine concentrations within a four-hour time span, 10-14 hours post-dose.

End point title	Differences in norclozapine concentrations within a four-hour time span, 10-14 hours post-dose.[2]

End point description:

End point type	Primary

End point timeframe:

10-14 hours post-dose

Notes:

[2] - 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: Primary end-point was a observational record of percentage difference in norclozapine serum concentrations, between 2 time-points. No statistical analysis was pre-specified.
See article-manuscript and up-loaded Table 2 for clarification.

End point values	Final inclusion			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Percentages				
median (full range (min-max))				
12-hour values vs. 10-hour values	6.2 (-28.1 to 105)			
12-hour values vs. 11-hour values	0.8 (-24.8 to 53)			
12-hour values vs. 13-hour values	4.2 (-16.3 to 31.3)			
12-hour values vs. 14-hour values	7.3 (-25.6 to 37.5)			
11-hour values vs. 13-hour values	2.7 (-23.6 to 31.3)			
10-hour values vs. 14-hour values	1.2 (-38.4 to 35.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From last clozapine night ingestion the night before trial blood sampling until ended sampling time at inclusion day.

Assessment type	Systematic

Dictionary used

Dictionary name	Directive 2001/20/EC
Dictionary version	2011/C 172

Reporting groups

Reporting group title	Primary inclusion

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: Only 1 adverse event occured during the trial, and this was a serious adverse event.
See article-manuscript for clarification.

Serious adverse events	Primary inclusion		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Primary inclusion		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 48 (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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27922183