Clinical trial results:
Serum-monitoring of anti-dementia drugs, and the relevance to side-effects, clinical efficacy and compliance

Summary

EudraCT number	2017-002707-10
Trial protocol	DK
Global end of trial date	16 February 2023

Results information

Result version number	v1 (current)
This version publication date	09 October 2024
First version publication date	09 October 2024

Trial information

Trial identification

Sponsor protocol code	SJ-596

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04117178
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Neurology ZUH
Sponsor organisation address	Vestermarksvej 4000, Roskilde, Denmark,
Public contact	RVD, Regional Dementia Research Centre, Dept of Neurology, 0045 47322800, phh@regionsjaelland.dk
Scientific contact	RVD, Regional Dementia Research Centre, Dept of Neurology, 0045 47322800, suh-neu@regionsjaelland.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	02 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2023
Global end of trial reached?	Yes
Global end of trial date	16 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether serum-monitoring of anti-dementia drugs may reduce side-effects and improve clinical efficacy and patient compliance.

NOTA BENE: two fictonal (male 'in utero') study participants (from Åland Islands) have been added to this report because the webside does not allow for validation without this ridiculous amendment.

Protection of trial subjects:

the trial was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Both the regional scientific ethics committee (Videnskabsetisk komité for Region Sjælland, file no.: SJ-596) and the Danish Medicines Agency approved the trial . The trial protocol was approved by the local data supervisory authority (Datatilsynet Region Sjælland, approval no.: REG-007-2018). The Good Clinical Practice (GCP) unit of Copenhagen monitored the study externally and conducted regular site inspections.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2020
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	Denmark: 132
Country: Number of subjects enrolled	Åland Islands: 2
Worldwide total number of subjects	134
EEA total number of subjects	132

Notes:

Subjects enrolled per age group

In utero	2
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)	16
From 65 to 84 years	105
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 132 participants were enrolled from February 12th, 2020, to February 24th, 2022. Of the 132 participants, 25 were registered as drop-outs either due to participant decision to withdraw or if treatment was changed to an anti-dementia drug not investigated in the trial (galanmantine, rivastigmine).

Pre-assignment

Screening details:

Patients attending the study site for patient visits were screened according to the inlcusion and exclusion criteria.
Elegibile patients were offered trial participation during the visit where the diagnosis and treatment options were presented.

Period 1

Period 1 title	Single-blinded RCT (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Assessor of clinical end points blinded to group allocation of participants. Also, the statistical analysis was done in a blinded manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control group

Arm description:

Standard of care

Arm type	Active comparator
Investigational medicinal product name	Standard care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

participants had their treatment titrated according to the standard of care at the study site. Hence, participants scheduled for donepezil were prescribed 5 mg./d for 4 weeks and then if well-tolerated the dose was increased to 10 mg./d. Participants scheduled for memantine were initially prescribed 5 mg./d, with a gradual dose-increase of 5 mg. the following weeks to a maximum of 20 mg./d.

Arm title	Intervention group

Arm description:

Dosing of donepezil or memantine based on therapeutic drug monitoring

Arm type	Experimental
Investigational medicinal product name	TDM based dosing
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the IG, the PI adjusted treatment at the 6 months visit according to the serum concentration of the study drug in addition to relevant clinical information identical to that of the CG. We presumed that the lower limit of the TRR for serum donepezil (S-donepezil) was 50ng/mL. Accordingly, for participants in

the IG, if the 10 mg/d dosage was well-tolerated and the serum concentration was below the 50ng/mL threshold we increased to daily dose to 15 or 20 mg/d. We applied the same procedure for treatment with memantine, with the lower limit set at serum memantine (S-memantine) 90 ng/mL. The maximum allowed daily dose in the study was 20 mg/d and 30 mg/d for donepezil and memantine respectively.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The assessor of clinical endpoints was blinded to group allocation

Number of subjects in period 1	Control group	Intervention group
Started	65	67
Completed	49	58
Not completed	17	10
Adverse event, serious fatal	2	2
Consent withdrawn by subject	3	3
Adverse event, non-fatal	11	4
test	1	1
Joined	1	1
test	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Control group
Reporting group description:	
Standard of care	
Reporting group title	Intervention group
Reporting group description:	
Dosing of donepezil or memantine based on therapeutic drug monitoring	

Reporting group values	Control group	Intervention group	Total
Number of subjects	66	68	134
Age categorical			
Intervention group mean age: 74.4 Control group mean age: 76.0			
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			
arithmetic mean	76.0	74.4	
standard deviation	± 7.9	± 8.1	-
Gender categorical			
Units: Subjects			
Female	37	21	58
Male	29	47	76

End points

End points reporting groups

Reporting group title	Control group
Reporting group description: Standard of care	
Reporting group title	Intervention group
Reporting group description: Dosing of donepezil or memantine based on therapeutic drug monitoring	

Primary: Mean change on Addenbrooke's Cognitive Exam from baseline to 12-month follow-up

End point title	Mean change on Addenbrooke's Cognitive Exam from baseline to 12-month follow-up
End point description:	
End point type	Primary
End point timeframe: From baseline to 12-month follow-up	

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[1]	58[2]		
Units: ACE				
arithmetic mean (standard deviation)	-0.27 (± 3.19)	-0.90 (± 3.56)		

Notes:

[1] - Due to dropout the number of subjects at 12 month was 49

[2] - Due to withdrawal 58 subjects were assessed at 12 months

Statistical analyses

Statistical analysis title	Linear regression models with GEE

Statistical analysis description:

We assessed the clinical outcomes at 12 months follow-up in linear regression models. Clinical outcomes were assessed using linear regression models comparing the difference between the baseline effect (difference in outcome between the randomization arms at study start) and the 12-month follow-up effect (difference in outcome between the randomization arms at the 12-month follow-up). We used generalized estimating equations (GEE) to accommodate for repeated measurements on the same study partic

Comparison groups	Control group v Intervention group
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Linear

Primary: Change on MMSE

End point title	Change on MMSE[3]

End point description:

End point type	Primary

End point timeframe:

From baseline to 12 month follow-up

Notes:

[3] - 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: It was presumed that at least 50% of serum concentrations would be out of the recommended range without TDM based dose optimization and that the use of TDM based dose optimization would result in at least 75% of participants reaching a serum concentration within the TRR. Hence 55 participants were needed in each group with a significance level of 5% and a power of 80% in a Z-test for absolute difference in proportions.

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[4]	58[5]		
Units: score				
arithmetic mean (standard deviation)	-0.27 (± 3.19)	-0.90 (± 3.56)		

Notes:

[4] - Due to dropout the number of subjects at 12 months was 49

[5] - Due to dropout the number of subjects at 12 months was 58

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Geriatric Depression Scale

End point title	Change on Geriatric Depression Scale

End point description:

End point type	Secondary

End point timeframe:

From baseline to 12 month follow-up

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[6]	58[7]		
Units: score				
arithmetic mean (standard deviation)	-0.57 (± 2.47)	0.79 (± 2.55)		

Notes:

[6] - Due to dropout the number of subjects at 12 months was 49

[7] - Due to dropout the number of subjects at 12 months was 58

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Neuropsychiatric Inventory

End point title	Change on Neuropsychiatric Inventory

End point description:

End point type	Secondary

End point timeframe:

From baseline to 12 month follow-up

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[8]	58[9]		
Units: score				
arithmetic mean (standard deviation)	2.40 (± 6.34)	1.30 (± 3.18)		

Notes:

[8] - Due to dropout the number of subjects at 12 months was 49

[9] - Due to dropout the number of subjects at 12 months was 58

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Disability Assessment in Dementia

End point title	Change on Disability Assessment in Dementia

End point description:

End point type	Secondary

End point timeframe:

From baseline to 12 month follow-up

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[10]	58[11]		
Units: score				
arithmetic mean (standard deviation)	-0.07 (± 0.13)	-0.10 (± 0.16)		

Notes:

[10] - Due to dropout the number of subjects at 12 months was 49

[11] - Due to dropout the number of subjects at 12 months was 49

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Clinical Global Impression Scale Improvement

End point title	Change on Clinical Global Impression Scale Improvement

End point description:

End point type	Secondary

End point timeframe:

From baseline to 12 month follow-up

End point values	Control group	Intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[12]	58[13]		
Units: score				
arithmetic mean (standard deviation)	4.68 (± 1.06)	4.62 (± 0.95)		

Notes:

[12] - Due to dropout the number of subjects at 12 months was 49

[13] - Due to dropout the number of subjects at 12 months was 58

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to 12 month follow-up	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	medicine prod. info
Dictionary version	1
Reporting groups	
Reporting group title	Intervention group
Reporting group description: Participants in intervention group	
Reporting group title	Control group
Reporting group description: -	

Serious adverse events	Intervention group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 67 (10.45%)	6 / 65 (9.23%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebral metastases			
subjects affected / exposed	0 / 67 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Donepezil overdose	Additional description: Non-fatal serious adverse reaction. Hospitalized. No treatment necessary.		
subjects affected / exposed	1 / 67 (1.49%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Sugery for hip fracture			
subjects affected / exposed	0 / 67 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			

syncope			
subjects affected / exposed	1 / 67 (1.49%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	2 / 67 (2.99%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
headache			
subjects affected / exposed	1 / 67 (1.49%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychosis			
subjects affected / exposed	1 / 67 (1.49%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Antebrachium fracture	Additional description: Fracture due to fall. Surgery performed.		
subjects affected / exposed	0 / 67 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 67 (2.99%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 67 (68.66%)	42 / 65 (64.62%)	
General disorders and administration site conditions			
Non-related, non serious adverse events	Additional description: various minor non-related events		
subjects affected / exposed	46 / 67 (68.66%)	42 / 65 (64.62%)	
occurrences (all)	46	42	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study did not support general usage of TDM based dose optimization for donepezil and memantine in dementia, albeit important study limitations and caveats to the external validity of the results apply.

Notes: