



## Clinical trial results: Memory, Ageing, and the Cholinergic System a combined fMRI and PET study

### Summary

EudraCT number	2008-008896-32
Trial protocol	DE
Global end of trial date	07 May 2014

### Results information

Result version number	v1 (current)
This version publication date	14 August 2020
First version publication date	14 August 2020

### Trial information

#### Trial identification

Sponsor protocol code	MACS(Uni-Koeln-1260)
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Universität zu Köln
Sponsor organisation address	Albertus-Magnus-Platz, Köln, Germany, 50937
Public contact	Univeritätsklinikum Köln Klinik und Poliklinik für Neurologie AG Altern und Demenz, Univeritätsklinikum Köln Klinik und Poliklinik für Neurologie, 049 0221-478-97493, oezguer.onur@uk-koeln.de
Scientific contact	Univeritätsklinikum Köln Klinik und Poliklinik für Neurologie AG Altern und Demenz, Univeritätsklinikum Köln Klinik und Poliklinik für Neurologie, 049 0221-478-97493, oezguer.onur@uk-koeln.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	Final
Date of interim/final analysis	07 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2014
Global end of trial reached?	Yes
Global end of trial date	07 May 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

We want to investigate the effects of cholinergic stimulation on brain activity underlying memory in healthy older subjects and patients with mild cognitive impairment (MCI). In a double-blind, placebo-controlled crossover design we want to administer rivastigmine or placebo prior to measuring brain activity during memory paradigm using fMRI. We expect that cholinergic stimulation will enhance cognitive performance and the underlying brain activity in patients with MCI more than in healthy older controls.

Therefore we will test whether there is a group difference between healthy subjects and MCI patients in the correlation of regional MP4A-PET activity (visualising the cerebral cholinergic system) and brain activity underlying memory and attention functions. We will furthermore investigate whether the effect of cholinergic stimulation (using rivastigmine) is dependent on the MP4A-PET activity and whether there is a group difference.

Protection of trial subjects:

Participants remained under observation for an additional hour after the MRI measurements on the visits when they received trial medication.

If experiencing severe nausea after application of the trial medication, participants received antiemetics. Participants were instructed not to drive motor vehicles for the remainder of the day after receiving trial medication.

Background therapy:

Participants continued to take their regular medication (antihypertensives, thyroid medication, etc.) during the course of the trial. None of the participants were taking centrally acting medications, other than the trial medication, during the course of the trial.

Evidence for comparator:

Participants received rivastigmine and placebo in a double-blind cross-over design. The placebo was given to account for the placebo effect.

Actual start date of recruitment	21 May 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: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

<b>Subjects enrolled per age group</b>	
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)	12
From 65 to 84 years	30
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from the Memory Clinic at the Dept. of Neurology of the University Hospital of Cologne from may 2012 until march 2014. Control participants were recruited from the public using flyers during the same time period.

### Pre-assignment

Screening details:

Cognitively normal volunteers and patients with mild cognitive impairment (MCI) and CSF and/or imaging findings indicative of Alzheimer's disease were screened. Exclusion criteria were other major medical, neurological or psychiatric conditions, contraindications to MRI and centrally acting medication.

### Period 1

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

### Arms

Arm title	Experimental
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Arm description:

Application of a single dose of rivastigmine 3mg p.o. and placebo in a double blind cross-over design

Arm type	Experimental
Investigational medicinal product name	Rivastigmine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3mg of Rivastigmine p.o. as single dose

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

single capsule of placebo applied p.o.

Number of subjects in period 1	Experimental
Started	42
Completed	37
Not completed	5
Consent withdrawn by subject	1
Adverse event, non-fatal	1
incidental MRI finding	1

MRI contraindication	2
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## Baseline characteristics

### Reporting groups

Reporting group title	Experimental
Reporting group description:	
Application of a single dose of rivastigmine 3mg p.o. and placebo in a double blind cross-over design	

Reporting group values	Experimental	Total	
Number of subjects	42	42	
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)	12	12	
From 65-84 years	30	30	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	25	25	

### Subject analysis sets

Subject analysis set title	Control group
Subject analysis set type	Per protocol

Subject analysis set description:

Cognitively normal controls, that completed experiment under rivastigmine and placebo, with complete imaging data.

Subject analysis set title	MCI patients
Subject analysis set type	Per protocol

Subject analysis set description:

MCI patients, that completed experiment under rivastigmine and placebo, with complete imaging data.

Subject analysis set title	all participants
Subject analysis set type	Per protocol

Subject analysis set description:

16 control participants and 14 MCI patients

Reporting group values	Control group	MCI patients	all participants
Number of subjects	16	14	30
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)	7	5	12
From 65-84 years	9	9	18
85 years and over			
Gender categorical			
Units: Subjects			
Female	7	7	14
Male	9	7	16

## End points

### End points reporting groups

Reporting group title	Experimental
Reporting group description:	
Application of a single dose of rivastigmine 3mg p.o. and placebo in a double blind cross-over design	
Subject analysis set title	Control group
Subject analysis set type	Per protocol
Subject analysis set description:	
Cognitively normal controls, that completed experiment under rivastigmine and placebo, with complete imaging data.	
Subject analysis set title	MCI patients
Subject analysis set type	Per protocol
Subject analysis set description:	
MCI patients, that completed experiment under rivastigmine and placebo, with complete imaging data.	
Subject analysis set title	all participants
Subject analysis set type	Per protocol
Subject analysis set description:	
16 control participants and 14 MCI patients	

### Primary: Effect of cholinergic stimulation on memory-related activation of the fusiform gyrus

End point title	Effect of cholinergic stimulation on memory-related activation of the fusiform gyrus
End point description:	
End point type	Primary
End point timeframe:	
during the functional MRI measurements - 30 min duration - about 2 hours after the application of the trial medication	

End point values	Control group	MCI patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: parameter estimates				
arithmetic mean (standard deviation)	-7.65 ( $\pm$ 10.85)	6.38 ( $\pm$ 13.76)		

### Statistical analyses

Statistical analysis title	Group comparison
Statistical analysis description:	
The significance of the group difference in the change of neural activation after application of rivastigmine is assessed.	
Comparison groups	MCI patients v Control group



Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	t-test, 2-sided

### Primary: Effect of cholinergic stimulation on memory-related activation of the posterior cingulate

End point title	Effect of cholinergic stimulation on memory-related activation of the posterior cingulate
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End point description:

End point type	Primary
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End point timeframe:

duration of the functional MRI measurements - (30min duration - about 2 hours after the application of the trial medication)

End point values	Control group	MCI patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: parameter estimates				
arithmetic mean (standard deviation)	12.95 (± 14.08)	-4.22 (± 10.72)		

### Statistical analyses

Statistical analysis title	Group comparison
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Statistical analysis description:

The significance of the group difference in the change of neural activation after application of rivastigmine is assessed.

Comparison groups	Control group v MCI patients
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	t-test, 2-sided

### Secondary: Effect of rivastigmine on task performance

End point title	Effect of rivastigmine on task performance
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End point description:

End point type	Secondary
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End point timeframe:

duration of the memory task, about 30 min duration, 2 hours after application of the trial medication

End point values	Control group	MCI patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: d-prime				
arithmetic mean (standard deviation)	0.184 ( $\pm$ 0.444)	0.08 ( $\pm$ 0.439)		

### Statistical analyses

Statistical analysis title	ANOVA
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Statistical analysis description:

The group by treatment effect is examined.

Comparison groups	MCI patients v Control group
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.114
Method	ANOVA

Notes:

[1] - Group comparison of difference in treatment effect (rivastigmine).

Statistical analysis title	ANCOVA
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Statistical analysis description:

Group comparison of difference in treatment effect (rivastigmine), adjusted for change in well-being and hippocampal atrophy.

Comparison groups	MCI patients v Control group
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.026
Method	ANCOVA

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported if taking place during the time between the application of the first dose of trial medication and 24 hours after application of the last dose of trial medication.

Adverse event reporting additional description:

Participants were interviewed 7 days after each application of trial medication to find out if adverse events had taken place.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1-17.1
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### Reporting groups

Reporting group title	control participants
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Reporting group description: -

Reporting group title	MCI patients
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Reporting group description: -

Serious adverse events	control participants	MCI patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	control participants	MCI patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	5 / 14 (35.71%)	
Vascular disorders			
Elevated blood pressure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Orthostatic dysregulation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3	2 / 14 (14.29%) 2	
Headache subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
Blood and lymphatic system disorders			
Granulocyte count	Additional description: Finding in routine blood sample. Neutrophils decreased, eosinophils increased. Minor deviations, no treatment indicated.		
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	5 / 16 (31.25%) 5	4 / 14 (28.57%) 4	
Psychiatric disorders			
Psychomotor agitation	Additional description: Transient. No persistent impairment. No hospitalization necessary.		
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	
Endocrine disorders			
free T4 decreased	Additional description: minor deviation, normal TSH, no treatment indicated		
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	
Musculoskeletal and connective tissue disorders			
Sprained ankle subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
Lumbar disk prolapse	Additional description: Treatment by general practitioner with local injections. No persistent impairment.		
subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	
Metabolism and nutrition disorders			
Elevated serum lipids subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2010	Unclassifiable and unclassified events are also considered as side-effects of the trial medication to increase patient safety.  Contact list was updated.
02 March 2011	Radiation safety officer was updated. Trial time frame was updated. Change in randomisation protocol - this is now performed by the Insitute for medical statistics of the University of Cologne Neuropsychological testing battery was modified.
03 August 2012	Contacts updated. The first MRI is now performed before the PET-scan to avoid unnecessary radiation exposure. Adjustment of fMRI protocol to reduce demand on participants. Update of exclusion criteria to reflect the rivastigmine investigators brochure of April 2012. Added lab for analysis of serum rivastigmine to protocol. Time frame for reporting of adverse events was rephrased more clearly. Procedure for SAE follow-up was explicitly defined. Procedure for the annual safety report was updated to reflect ICH-Guideline E2F.
22 March 2013	Adjusted exclusion criteria to allow participation of individuals that had previously undergone exams by nuclear medicine or radiotherapy. MR-compatible implants are no longer an exclusion criterion. Several minor changes to the protocol to improve detection of AE's, including a telephone interview 7 days after the final trial medication. Inclusion and exclusion criteria are listed in the consent form.

Notes:

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### 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.

Small sample size. Single dose of rivastigmine (3mg) orally.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29309600>