Clinical trial results:
Downstream targets of SSRI effect in treatment of Major Depressive Disorder

Summary

EudraCT number	2019-002232-82
Trial protocol	SE
Global end of trial date	30 April 2022

Results information

Result version number	v1 (current)
This version publication date	05 January 2025
First version publication date	05 January 2025

Trial information

Trial identification

Sponsor protocol code	KIH18001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Nobels väg 6, Solna, Sweden,
Public contact	Mikael Tiger, Karolinska Institutet PET centre, mikael.tiger@ki.se
Scientific contact	Mikael Tiger, Karolinska Institutet PET centre, mikael.tiger@ki.se

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	25 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2022
Global end of trial reached?	Yes
Global end of trial date	30 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a clinical study of the downstream mechanism of action of SSRI treatment for MDD.
Primary research questions (outcomes):
- Does SSRI for MDD reduce serotonin 1B (5-HT1B) receptor binding in the raphe nuclei and increase 5-HT1B receptor binding in serotonin projection areas?
- Is this putative change in 5-HT1B receptor binding related to change in MDD symptom rating scores or side effects?

Protection of trial subjects:

All participants provided oral and written consent before initiation of any study-related event. The study was approved by the Swedish Ethical Review Authority in Stockholm and the Swedish Medical Products Agency in Uppsala.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2019
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	Sweden: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study participants were recruited either via Gustavsberg University Primary Care Center or through online advertising.
The diagnosis of MDD was confirmed by a psychiatrist (M.G.or M.T.) at a face-to-face visit using the Mini-International Neuropsychiatric Interview

Period 1

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

Arms

Arm title	Escitalopram

Arm description:

Escitalopram

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

Dosage and administration details:

Escitalopram 10 mg daily the day after their first PET examination (PET 1).

Number of subjects in period 1	Escitalopram
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	8	8	
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)	8	8	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.4		
standard deviation	± 7.58	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	4	4	
PET 1: Anterior cingulate cortex Units: Score			
arithmetic mean	1.16		
standard deviation	± 0.18	-	
PET 1: Orbitofrontal cortex Units: Score			
arithmetic mean	1.17		
standard deviation	± 0.19	-	
PET 1: Hippocampus Units: Score			
arithmetic mean	0.38		
standard deviation	± 0.14	-	
PET 1: Dorsal brainstem Units: Score			
arithmetic mean	0.71		
standard deviation	± 0.37	-	
PET 1: MADRS Units: Score			
arithmetic mean	25.5		
standard deviation	± 2.28	-	

End points

End points reporting groups

Reporting group title	Escitalopram
Reporting group description:	
Escitalopram	
Subject analysis set title	PET 1
Subject analysis set type	Full analysis
Subject analysis set description:	
PET 1 is the first PET examination before the patients with moderate to severe major depressive disorder (MDD) underwent treatment with the SSRI escitalopram 10 mg daily for 3 to 4 weeks.	

Primary: PET 2: Anterior cingulate cortex

End point title	PET 2: Anterior cingulate cortex
End point description:	
End point type	Primary
End point timeframe:	
PET 2 was performed after 3 to 4 weeks (mean ± SD = 3.5 ± 0.5) of daily treatment with the SSRI escitalopram 10 mg.	

End point values	Escitalopram	PET 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Score				
arithmetic mean (standard deviation)	1.19 (± 0.29)	1.16 (± 0.18)		

Statistical analyses

Statistical analysis title	Change in Anterior cingulate cortex
Statistical analysis description:	
Change in 5-HT1B receptor binding potential, Anterior cingulate cortex between PET 1 and PET 2.	
Comparison groups	Escitalopram v PET 1
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.391
Method	t-test, 1-sided

Notes:

[1] - 5-HT1B receptor change after escitalopram treatment.

Primary: PET 2: Orbitofrontal cortex

End point title	PET 2: Orbitofrontal cortex
End point description:	

End point type	Primary

End point timeframe:

PET 2 was performed after 3 to 4 weeks (mean ± SD = 3.5 ± 0.5) of daily treatment with the SSRI escitalopram 10 mg.

End point values	Escitalopram	PET 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Score				
arithmetic mean (standard deviation)	1.20 (± 0.26)	1.17 (± 0.19)		

Statistical analyses

Statistical analysis title	Change in Orbitofrontal cortex

Statistical analysis description:

Change in 5-HT1B receptor binding potential, Orbitofrontal cortex between PET 1 and PET 2.

Comparison groups	Escitalopram v PET 1
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.362
Method	t-test, 1-sided

Notes:

[2] - 5-HT1B receptor change after escitalopram treatment.

Primary: PET 2: Hippocampus

End point title	PET 2: Hippocampus

End point description:

End point type	Primary

End point timeframe:

PET 2 was performed after 3 to 4 weeks (mean ± SD = 3.5 ± 0.5) of daily treatment with the SSRI escitalopram 10 mg.

End point values	Escitalopram	PET 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Score				
arithmetic mean (standard deviation)	0.36 (± 0.18)	0.38 (± 0.14)		

Statistical analyses

Statistical analysis title	Change in Hippocampus

Statistical analysis description:

Change in 5-HT1B receptor binding potential, Hippocampus between PET 1 and PET 2.

Comparison groups	Escitalopram v PET 1
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.738
Method	t-test, 1-sided

Notes:

[3] - 5-HT1B receptor change after escitalopram treatment.

Primary: PET 2: Dorsal brainstem

End point title	PET 2: Dorsal brainstem

End point description:

End point type	Primary

End point timeframe:

PET 2 was performed after 3 to 4 weeks (mean ± SD = 3.5 ± 0.5) of daily treatment with the SSRI escitalopram 10 mg.

End point values	Escitalopram	PET 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Score				
arithmetic mean (standard deviation)	0.57 (± 0.33)	0.71 (± 0.37)		

Statistical analyses

Statistical analysis title	Change in Dorsal brainstem

Statistical analysis description:

Change in 5-HT1B receptor binding potential, Dorsal brainstem between PET 1 and PET 2.

Comparison groups	Escitalopram v PET 1
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.036
Method	t-test, 1-sided

Notes:

[4] - 5-HT1B receptor change after escitalopram treatment.

Primary: PET 2: MADRS

End point title	PET 2: MADRS

End point description:

End point type	Primary

End point timeframe:

PET 2 was performed after 3 to 4 weeks (mean ± SD = 3.5 ± 0.5) of daily treatment with the SSRI escitalopram 10 mg.

End point values	Escitalopram	PET 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Score				
arithmetic mean (standard deviation)	14.00 (± 9.24)	25.5 (± 2.28)		

Statistical analyses

Statistical analysis title	MADRS change

Statistical analysis description:

MADRS change after escitalopram treatment.

Comparison groups	Escitalopram v PET 1
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.009
Method	t-test, 2-sided

Notes:

[5] - Change in MADRS between PET 1 and PET 2.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 07 Oct 2020 - 30 Apr 2022.	
Assessment type	Systematic

Dictionary used	
Dictionary name	UKU
Dictionary version	NA

Reporting groups	
Reporting group title	Overall group

Reporting group description: -

Serious adverse events	Overall group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
Reproductive system and breast disorders			
Sexual dysfunction			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

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? Yes

Date	Interruption	Restart date
13 March 2020	COVID-19 restrictions	17 August 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38695786