



Clinical trial results:

OSU6162 IN THE TREATMENT OF FATIGUE AND OTHER NEUROPSYCHOLOGICAL SEQUELAE AFTER ANEURYSMAL SUBARACHNOIDAL HEMORRHAGE - A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY

Summary

EudraCT number	2016-004739-19
Trial protocol	NO
Global end of trial date	13 September 2019

Results information

Result version number	v1 (current)
This version publication date	16 November 2021
First version publication date	16 November 2021

Trial information

Trial identification

Sponsor protocol code	OSU6162aSAH
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03209830
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Sognvannsveien 20, Oslo, Norway,
Public contact	Rikshospitalet, Dept.of Neurosurger, Oslo University Hospital, 47 23074300, angelika.sorteberg@ous-hf.no
Scientific contact	Rikshospitalet, Dept.of Neurosurger, Oslo University Hospital, 47 23074300, angelika.sorteberg@ous-hf.no

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 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2019
Global end of trial reached?	Yes
Global end of trial date	13 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of OSU6162 with respect to sequela after aneurysmal subarachnoid haemorrhage with special emphasis on fatigue. The primary endpoint was change from baseline in Fatigue Severity Scale (FSS) after 12 weeks of treatment with (-)-OSU6162 or placebo, with data collection at weeks 1, 4, 8, 12, and 20 (20=8 weeks after treatment).

The secondary endpoints include change from baseline in total score on the following questionnaires:

- Beck Depression Inventory (BDI-II)
- Beck Anxiety Inventory (BAI)
- Mental Fatigue Scale (MFS)
- Short Form 36 (SF-36)
at week 4, 12, and 20 (i.e. at 8 weeks after treatment)

Change in neuropsychological test performance from baseline to week 12 of treatment

Protection of trial subjects:

Vital signs were checked at every visit along with ECG at every visit in order to detect any changes in QTc interval. Monthly pregnancy test in women of childbearing potential. Check of vital signs, physical and neurological examinations at every visit. Safety blood tests, and urine samples at week 8 and 12

Study participants were handed out a telephone number that was answered 24/7/365 and they were encouraged to make contact for any questions in relation to the study and to report any new symptoms, signs of discomfort, or when they needed to start a new concomitant medication

Background therapy:

None

Evidence for comparator:

Fatigue represents a major problem in good outcome survivors of aneurysmal subarachnoid hemorrhage. The character of this fatigue is mostly a mental fatigue. The underlying cause of central fatigue is not well understood, but imbalance of serotonin and foremost dopamine have been suggested (dopamine imbalance theory). Dopamine is a regulator of motivation and effortful behaviour and imbalance in the dopaminergic pathways has been linked to fatigue and cognitive dysfunction. The serotonergic system is important for neuroplasticity, emotional responses and sleep. (-)-OSU6162 is a monoaminergic stabilizer affecting both neurotransmitter systems. Clinical trials investigating the effect of (-)-OSU6162 on fatigue and other sequels after stroke and traumatic brain injury have shown promising results and these two disease are closely related to the patient cohort investigated in this study. (-)-OSU6162 also mitigated fatigue and improved mood and health-related quality of life in patients with chronic fatigue syndrome or multiple sclerosis. Hitherto no effective treatment of post aneurysmal hemorrhage fatigue is known.

Actual start date of recruitment	01 May 2017
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	Norway: 96
Worldwide total number of subjects	96
EEA total number of subjects	96

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)	84
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients with aneurysmal subarachnoid hemorrhage (aSAH) between January 2012 and March 2018 were identified and phoned for an interview that included assessment of the Fatigue Severity Scale (FSS). Those with mean FSS score ≥ 4 and without exclusion criteria were invited to a screening visit.

Pre-assignment

Screening details:

There were 749 eligible patients with aSAH. Of these, 216 were dead and 103 did not meet the inclusion criteria. 430 had a telephone interview. Of these 156 did not meet the inclusion criteria, 30 could not be traced, 62 had medical exclusion criteria and 82 did not want to participate.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	(-)-OSU6162

Arm description:

(-)-OSU6162 came as tablets containing 15mg of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride. (-)-OSU6162 is a monoaminergic stabilizer affecting the dopaminergic and serotonergic neurotransmitter systems by acting antagonistic at the D2 dopamine receptor and partially agonistic on the serotonergic 5-hydroxytryptamine 2A (5-HT_{2A})

Arm type	Active comparator
Investigational medicinal product name	(-)-OSU6162
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The initial dosage was 30mg/day (15mg x 2). After at least 1 week of treatment, those with less than 1.5 points of improvement on the mean FSS or without other convincing positive effects had their dose increased to 60mg/day (30mg x 2). Given some positive effect (but not full response) at week 1, the dosage increase could be postponed to week 4 or 8. If not tolerated, 60mg/day was reduced immediately to 30mg/day. The tablets were swallowed whole with a glass of water before breakfast and before lunch (approximately at 08:00 and 13:00 hours).

Arm title	placebo
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Arm description:

placebo. The placebo were round, white, 15mg strength tablets with identical coating as the active (-)-OSU6162 weighing 242mg. Inactive ingredients: cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

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

Dosage and administration details:

15mg x 2 that could be increased to 30mg x 2. Tablets are swallowed whole before breakfast and before lunch (approximately 08:00 and 13:00 hours) with a glass of water

Number of subjects in period 1	(-)-OSU6162	placebo
Started	49	47
Completed	47	44
Not completed	2	3
Adverse event, non-fatal	2	-
Lack of efficacy	-	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	(-)-OSU6162
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Reporting group description:

(-)-OSU6162 came as tablets containing 15mg of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride. (-)-OSU6162 is a monoaminergic stabilizer affecting the dopaminergic and serotonergic neurotransmitter systems by acting antagonistic at the D2 dopamine receptor and partially agonistic on the serotonergic 5-hydroxytryptamine 2A (5-HT2A)

Reporting group title	placebo
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Reporting group description:

placebo. The placebo were round, white, 15mg strength tablets with identical coating as the active (-)-OSU6162 weighing 242mg. Inactive ingredients: cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

Reporting group values	(-)-OSU6162	placebo	Total
Number of subjects	49	47	96
Age categorical			
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	54.4	56.2	
standard deviation	± 9.5	± 10.6	-
Gender categorical			
Units: Subjects			
Female	35	30	65
Male	14	17	31
FSS mean score			
mean value of the 9 items of the Fatigue Severity Score			
Units: points			
arithmetic mean	6.04	5.91	
standard deviation	± 0.66	± 0.90	-
MFS sum score			
Mental Fatigue Score			
Units: points			
arithmetic mean	17.9	18.4	
standard deviation	± 4.7	± 6.4	-
BAI			
Beck Anxiety Inventory sum score			
Units: points			

arithmetic mean	7.9	9.9	
standard deviation	± 6.3	± 7.7	-
BDI-II			
Beck depression Inventory II sum score			
Units: points			
arithmetic mean	15.98	17.53	
standard deviation	± 8.11	± 9.30	-
SF-36 physical function			
t-score			
Units: t-score			
median	43.3	43.3	
inter-quartile range (Q1-Q3)	37.2 to 52.8	34.5 to 50.6	-
SF-36 physical role function			
Units: t-score			
median	38.6	36.5	
inter-quartile range (Q1-Q3)	32.4 to 47.1	32.4 to 42.4	-
SF-36 bodily pain			
Units: t-score			
median	44.7	43.7	
inter-quartile range (Q1-Q3)	37.4 to 53.2	37.8 to 53.3	-
SF-36 general health			
Units: t-score			
median	39.9	40.7	
inter-quartile range (Q1-Q3)	36.5 to 44.4	38.3 to 45.1	-
SF-36 Vitality			
Units: t-score			
median	37.3	37.3	
inter-quartile range (Q1-Q3)	30.7 to 43.0	27.1 to 42.6	-
SF-36 Social function			
Units: t-score			
median	40.0	36.4	
inter-quartile range (Q1-Q3)	35.2 to 44.4	27.8 to 42.2	-
SF-36 emotional role functioning			
Units: t-score			
median	53.8	47.0	
inter-quartile range (Q1-Q3)	31.2 to 54.8	30.0 to 54.8	-
SF-36 Mental health			
Units: t-score			
median	44.8	46.9	
inter-quartile range (Q1-Q3)	34.9 to 52.2	34.4 to 52.2	-
sensorimotor function			
neuropsychological test domaine			
Units: z-score			
median	-0.65	-0.50	
inter-quartile range (Q1-Q3)	-1.35 to 0	-1.10 to 0	-
Attention			
Neuropsychological test domaine			
Units: z-score			
median	0	0	
inter-quartile range (Q1-Q3)	-0.65 to 0.60	-0.68 to 0.40	-
psychomotor speed			
Neuropsychological test domaine			

Units: z-score			
median	0	0	
inter-quartile range (Q1-Q3)	-0.65 to 0.65	-0.65 to 0.65	-
Verbal learning			
Neuropsychological test domaine			
Units: z-score			
median	-0.80	-0.50	
inter-quartile range (Q1-Q3)	-1.50 to 0	-1.00 to 0	-
verbal memory			
Neuropsychological test domaine			
Units: z-score			
median	0	0	
inter-quartile range (Q1-Q3)	-1.00 to 0.50	-1.00 to 0.50	-
executive function			
Neuropsychological test domaine			
Units: z-score			
median	0	0.35	
inter-quartile range (Q1-Q3)	-0.65 to 0.65	-0.65 to 0.65	-

End points

End points reporting groups

Reporting group title	(-)-OSU6162
Reporting group description:	(-)-OSU6162 came as tablets containing 15mg of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride. (-)-OSU6162 is a monoaminergic stabilizer affecting the dopaminergic and serotonergic neurotransmitter systems by acting antagonistic at the D2 dopamine receptor and partially agonistic on the serotonergic 5-hydroxytryptamine 2A (5-HT2A)
Reporting group title	placebo
Reporting group description:	placebo. The placebo were round, white, 15mg strength tablets with identical coating as the active (-)-OSU6162 weighing 242mg. Inactive ingredients: cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

Primary: change in FSS to week 12

End point title	change in FSS to week 12
End point description:	
End point type	Primary
End point timeframe:	baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: points				
median (inter-quartile range (Q1-Q3))	-0.33 (-1.17 to 0.03)	-0.56 (-1.44 to 0)		

Attachments (see zip file)	change in FSS mean score/ema FSS.pdf
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Statistical analyses

Statistical analysis title	Statistical analysis FSS
Comparison groups	(-)-OSU6162 v placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.428 ^[2]
Method	t-test, 2-sided
Parameter estimate	Cohens d
Point estimate	-0.168

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.581
upper limit	0.247
Variability estimate	Standard error of the mean
Dispersion value	0.225

Notes:

[1] - Difference between FSS mean score at baseline and at week 12 - comparison of (-)-OSU6162 group to placebo group

[2] - (-)-OSU6162 was not superior to placebo in changing the FSS mean score from baseline to week 12 of treatment

Statistical analysis title	Alleviation of fatigue (FSS) by (-)-OSU6162
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Statistical analysis description:

change in FSS mean score from baseline to 12 weeks of treatment; i.e. treatment effect of (-)-OSU6162

Comparison groups	(-)-OSU6162 v placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0 [3]
Method	t-test, 2-sided
Parameter estimate	Cohens d
Point estimate	0.562
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.251
upper limit	0.867
Variability estimate	Standard error of the mean
Dispersion value	0.181

Notes:

[3] - The FSS mean score had decreased significantly from baseline to week 12 of treatment with (-)-OSU6162

Statistical analysis title	Alleviation of fatigue (FSS) by placebo
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Comparison groups	placebo v (-)-OSU6162
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0 [5]
Method	t-test, 2-sided
Parameter estimate	Cohens d
Point estimate	0.756
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.417
upper limit	1.089
Variability estimate	Standard error of the mean
Dispersion value	0.157

Notes:

[4] - Here, we merely look at the treatment effect in the placebo arm

[5] - The FSS mean score was reduced significantly from baseline to 12 weeks of treatment with placebo

Secondary: change in MFS sum score to week 12

End point title | change in MFS sum score to week 12

End point description:

End point type | Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: points				
arithmetic mean (standard deviation)	-2.81 (± 4.08)	-4.69 (± 5.83)		

Attachments (see zip file) | change in MFS sum score/ema MFS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: change in BDI to week 12

End point title | change in BDI to week 12

End point description:

End point type | Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: points				
arithmetic mean (standard deviation)	-2.68 (± 7.38)	-6.39 (± 8.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: change in BAI to week 12

End point title change in BAI to week 12

End point description:

End point type Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: points				
arithmetic mean (standard deviation)	-0.96 (\pm 5.01)	-3.66 (\pm 4.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 physical function

End point title change in SF-36 physical function

End point description:

End point type Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	2.21 (\pm 4.92)	1.54 (\pm 5.66)		

Attachments (see zip file) change in physical function/ema SF36 physical function.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 physical role function at week 12

End point title	change in SF-36 physical role function at week 12
End point description:	
End point type	Secondary
End point timeframe: baseline to week 12 of treatment	

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	2.99 (\pm 10.87)	1.81 (\pm 9.26)		

Attachments (see zip file)	change in physical role function/ema SF36 physical role
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Statistical analyses

No statistical analyses for this end point

Secondary: change in FS-36 bodily pain at week 12

End point title	change in FS-36 bodily pain at week 12
End point description:	
End point type	Secondary
End point timeframe: baseline to week 12 of treatment	

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	1.58 (\pm 9.03)	4.21 (\pm 7.46)		

Attachments (see zip file)	change in bodily pain/ema SF36 bodily pain.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in FS-36 bodily pain at week 12

End point title | change in FS-36 bodily pain at week 12

End point description:

End point type | Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	1.57 (\pm 9.03)	4.21 (\pm 7.46)		

Attachments (see zip file) | change in bodily pain/ema SF36 bodily pain.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 general health

End point title | change in SF-36 general health

End point description:

End point type | Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	0.80 (\pm 4.05)	1.37 (\pm 3.48)		

Attachments (see zip file) | change in general health/ema SF36 general health.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 social function

End point title change in SF-36 social function

End point description:

End point type Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	4.27 (\pm 7.89)	6.52 (\pm 9.15)		

Attachments (see zip file) change in vitality/ema SF36 Vitality.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 social function

End point title change in SF-36 social function

End point description:

End point type Secondary

End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	0.64 (\pm 7.64)	3.51 (\pm 7.35)		

Attachments (see zip file)	change in social function/ema SF36 social function.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 emotional role function

End point title	change in SF-36 emotional role function
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End point description:

End point type	Secondary
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End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	3.31 (\pm 14.69)	5.92 (\pm 13.52)		

Attachments (see zip file)	change in emotional role/ema SF36 emotional role function.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in SF-36 mental health

End point title	change in SF-36 mental health
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End point description:

End point type	Secondary
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End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: t-score				
arithmetic mean (standard deviation)	1.88 (\pm 8.33)	4.29 (\pm 10.29)		

Attachments (see zip file)	change in mental health/ema SF36 mental health.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in sensorimotor function at week 12

End point title	change in sensorimotor function at week 12
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End point description:

End point type	Secondary
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End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
median (inter-quartile range (Q1-Q3))	-0.10 (-0.65 to 0.40)	0 (-0.65 to 0.40)		

Attachments (see zip file)	change in sensorimotor function /ema sensorimotor function.
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Statistical analyses

No statistical analyses for this end point

Secondary: change in psychomotor speed at week 12

End point title	change in psychomotor speed at week 12
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End point description:

End point type	Secondary
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End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
arithmetic mean (inter-quartile range (Q1-Q3))	0 (-0.65 to 0.35)	0 (-0.35 to 0.34)		

Attachments (see zip file)	change in psychomotor speed/ema psychomotor speed.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in attention at week 12

End point title	change in attention at week 12
End point description:	
End point type	Secondary
End point timeframe:	baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
median (inter-quartile range (Q1-Q3))	-0.10 (-0.60 to 0.30)	0 (-0.65 to 0.20)		

Attachments (see zip file)	change in attention/ema attention.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in executive function at week 12

End point title	change in executive function at week 12
End point description:	
End point type	Secondary
End point timeframe:	baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
median (inter-quartile range (Q1-Q3))	0 (-0.33 to 0.30)	0 (-0.35 to 0.30)		

Attachments (see zip file)	change in executive function/ema executive function.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in verbal learning at week 12

End point title	change in verbal learning at week 12
End point description:	
End point type	Secondary
End point timeframe:	baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
median (inter-quartile range (Q1-Q3))	0 (-0.50 to 0.50)	0 (-0.50 to 0.50)		

Attachments (see zip file)	change in verbal learning/ema verbal learning.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: change in verbal memory at week 12

End point title	change in verbal memory at week 12
End point description:	
End point type	Secondary

End point timeframe:
baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: z-score				
median (inter-quartile range (Q1-Q3))	0 (-0.50 to 1.00)	0 (-0.50 to 1.00)		

Attachments (see zip file)	change in verbal memory/ema verbal memory.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Safety endpoint QTc interval change from baseline to week 12

End point title	Safety endpoint QTc interval change from baseline to week 12
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End point description:

End point type	Secondary
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End point timeframe:

change from baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: ms				
arithmetic mean (standard deviation)	1.19 (\pm 16.36)	1.70 (\pm 14.78)		

Statistical analyses

Statistical analysis title	change in QTc interval from baseline
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Statistical analysis description:

Difference between treatment groups for change in QTc interval from baseline to week 12

Comparison groups	(-)-OSU6162 v placebo
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Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.676 ^[6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - There was no difference in changes in QTc interval from baseline to week 12 between treatment groups

Secondary: Safety endpoint diastolic blood pressure change at week 12

End point title	Safety endpoint diastolic blood pressure change at week 12
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End point description:

End point type	Secondary
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End point timeframe:

change from baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: mmHg				
arithmetic mean (standard deviation)	-0.38 (± 7.87)	-4.02 (± 8.85)		

Statistical analyses

Statistical analysis title	change in diastolic blood pressure at week 12
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Statistical analysis description:

change in diastolic blood pressure from baseline to week 12 in both treatment groups

Comparison groups	(-)-OSU6162 v placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.042 ^[7]
Method	t-test, 2-sided
Parameter estimate	Cohens d
Point estimate	-0.436
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.018
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[7] - diastolic blood pressure decreased from baseline to week 12 in the placebo group

Secondary: safety endpoint change in systolic blood pressure at week 12

End point title	safety endpoint change in systolic blood pressure at week 12
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End point description:

End point type	Secondary
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End point timeframe:

baseline to week 12 of treatment

End point values	(-)-OSU6162	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: mmHg				
arithmetic mean (standard deviation)	0.43 (\pm 13.90)	-5.23 (\pm 12.20)		

Statistical analyses

Statistical analysis title	change in systolic blood pressure
Comparison groups	(-)-OSU6162 v placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.042 ^[8]
Method	t-test, 2-sided
Parameter estimate	Cohens d
Point estimate	-0.431
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.846
upper limit	-0.014
Variability estimate	Standard error of the mean
Dispersion value	2.738

Notes:

[8] - The systolic blood pressure decreased significantly from baseline to week 12 of treatment in the placebo group, but not in the (-)-OSU6162 group

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to follow-up (8 weeks after treatment)

Adverse event reporting additional description:

Study participants were questioned systematically for AEs at each visit and at the telephone interview. In addition, patients had a phone number and instruction to call at any time a health-related event happened. All AEs were registered in the eCRF.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	(-)-OSU6162
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Reporting group description:

(-)-OSU6162 came as tablets containing 15mg of 3-(3-methanesulfonyl-phenyl)-1-propyl-piperidine hydrochloride. (-)-OSU6162 is a monoaminergic stabilizer affecting the dopaminergic and serotonergic neurotransmitter systems by acting antagonistic at the D2 dopamine receptor and partially agonistic on the serotonergic 5-hydroxytryptamine 2A (5-HT2A)

Reporting group title	placebo
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Reporting group description:

placebo. The placebo were round, white, 15mg strength tablets with identical coating as the active (-)-OSU6162 weighing 242mg. Inactive ingredients: cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

Serious adverse events	(-)-OSU6162	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	3 / 47 (6.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fractured wrist	Additional description: The patient stumbled and broke the wrist, needed a cast. No dizziness or any special reason that caused the stumbling and fall		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 49 (2.04%)	0 / 47 (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			
Cerebellar embolism	Additional description: Patient admitted to the hospital due to severe vertigo. There was a cerebellar embolism from a vertebral artery atherosclerosis. Completely recovered.		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 49 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety attack	Additional description: Patient experienced an anxiety attack few days after completion of treatment with placebo. The attack lead to a few hours of hospital admission - patient was scared of the study being concluded		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection bacterial	Additional description: Urinary tract infection requiring hospital admission for intravenous antibiotic treatment		
subjects affected / exposed	0 / 49 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	(-)-OSU6162	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 49 (87.76%)	38 / 47 (80.85%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 49 (6.12%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
ECG changes, asymptomatic			
subjects affected / exposed	3 / 49 (6.12%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Nervous system disorders			
Sleep disorder			
subjects affected / exposed	11 / 49 (22.45%)	4 / 47 (8.51%)	
occurrences (all)	12	4	
Fatigue, increased			
subjects affected / exposed	10 / 49 (20.41%)	10 / 47 (21.28%)	
occurrences (all)	10	10	
Headache	Additional description: New headache or aggravation of pre-existing headache		

subjects affected / exposed occurrences (all)	15 / 49 (30.61%) 17	11 / 47 (23.40%) 12	
Dizziness subjects affected / exposed occurrences (all)	14 / 49 (28.57%) 14	3 / 47 (6.38%) 3	
Dysaesthesia subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 6	5 / 47 (10.64%) 6	
Blood and lymphatic system disorders Blood test abnormal subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 5	6 / 47 (12.77%) 7	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 5	6 / 47 (12.77%) 6	
Nausea subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 11	7 / 47 (14.89%) 8	
Appetite disorder subjects affected / exposed occurrences (all)	7 / 49 (14.29%) 7	3 / 47 (6.38%) 3	
Respiratory, thoracic and mediastinal disorders Common cold subjects affected / exposed occurrences (all)	10 / 49 (20.41%) 11	8 / 47 (17.02%) 9	
Influenza like illness subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4	2 / 47 (4.26%) 2	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	9 / 47 (19.15%) 13	
Renal and urinary disorders Urge incontinence			

subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 5	2 / 47 (4.26%) 2	
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4	5 / 47 (10.64%) 5	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	9 / 49 (18.37%) 9	8 / 47 (17.02%) 10	
Infections and infestations Urinary tract infection bacterial subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4	2 / 47 (4.26%) 2	
Metabolism and nutrition disorders Hot flush subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 5	3 / 47 (6.38%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2017	The protocol specified that the IMP dosage could be increased after 1 week of treatment, but did not say explicitly that the dosage could be increased at a later point of time. We asked for the possibility to postpone the increase of dosage of (-)-OSU6162/placebo beyond week 1 if an increase in dosage was deemed necessary by the investigator. The amendment was approved 20.10.2017.

Notes:

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.

none

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34715650>