Clinical trial results:
Add-on spironolactone for the treatment of schizophrenia.

Summary

EudraCT number	2014-001968-35
Trial protocol	DE
Global end of trial date	11 August 2020

Results information

Result version number	v1 (current)
This version publication date	22 February 2024
First version publication date	02 February 2023
Summary attachment (see zip file)	CSR-SPIRO (Ergebnisbericht_SPIROTREAT_20210815_final.pdf)

Trial information

Trial identification

Sponsor protocol code	SPIROTREAT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Klinikum der Universität München, vertreten durch den Vorstand
Sponsor organisation address	Marchioninistraße 15, München , Germany, 81377
Public contact	PD Dr. rer nat. Peter Zill , Klinikum der Universität München - AöR vertreten durch den Vorstand des Bereichs Humanmedizin, 0049 89 4400 52741, Peter.Zill@med.uni-muenchen.de
Scientific contact	Prof. Dr. med. Alkomiet Hasan, Klinikum der Universität München - AöR vertreten durch den Vorstand des Bereichs Humanmedizin, 0049 821 4803 1001, alkomiet.hasan@med.uni-augsburg.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	15 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2020
Global end of trial reached?	Yes
Global end of trial date	11 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary endpoint: Improvement of working memory in n-back after 3 weeks.

Primary Objective
• To evaluate the improvement of working memory according to the n-Back performance (2-back level, relative hit rate) before and after the intervention period (V1 vs V10)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP).
Each participating subject signed informed consent form and they could withdraw from the study at any time without any disadvantages and without giving reasons for this decision.
The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained. The competent Ethics Committee and the German competent authorities approved the clinical trial.

Background therapy:

Ongoing stable antipsychotic treatment (standard of care) for at least one week.

Evidence for comparator:

n.a.

Actual start date of recruitment	08 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The placebo-controlled, double blind and three-arm clinical trial was conducted in Germany at three sites. Between July 2015 and May 2020 all patients were randomised in one of the three arms. A randomization did not take place until a final check conforms that all inclusion or no exclusion criteria applied.

Pre-assignment

Screening details:

Pre-screening processes were in place, a total of 162 patients were scheduled for screening. The pre-screening and the screening phases took place in the two weeks prior to randomization.
Suitable patients were approached by the investigators regarding participation in the study. No study-specific procedures took place in the pre-screening phase.

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	Investigator, Monitor, Data analyst, Carer, Subject

Blinding implementation details:

In every group, participants receive two identical capsules per day to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Add-on 100

Arm description:

Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase)

Arm type	Experimental
Investigational medicinal product name	Spironolactone
Investigational medicinal product code	C03DA01
Other name	Spironolacton HEXAL, SPIRONOLACTONE, SUB10631MIG
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Group I: Spironolactone 100 mg
At day (D) 1 capsule with 50 mg spironolactone and 1 capsule with placebo, from D2 to D21 two capsules with 50 mg spironolactone (100 mg in total) per day.

Arm title	Add-on 200

Arm description:

Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase)

Arm type	Experimental
Investigational medicinal product name	Spironolactone
Investigational medicinal product code	C03DA01
Other name	Spironolacton HEXAL, SPIRONOLACTONE, SUB10631MIG
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Group II: Spironolactone 200 mg
At D1 one capsule with 50 mg spironolactone and one capsule with placebo, at D2 two capsules with 50 mg spironolactone (100 mg in total), at D3 one capsule with 50 mg spironolactone and one capsule with 100 mg spironolactone (150 mg in total) and from D4 to D21 two capsules with 100 mg spironolactone per day (200 mg in total).

Arm title	Add-on

Arm description:

Add-on placebo (3 weeks of double-blind intervention phase)

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

Dosage and administration details:

Group III: Placebo
In group III (placebo), two capsules with placebo from D 1 to D 21.

Number of subjects in period 1	Add-on 100	Add-on 200	Add-on
Started	30	28	26
Completed	29	25	19
Not completed	1	3	7
Not randomized, no study medication	-	-	1
Consent withdrawn by subject	-	2	2
Other reasons	-	1	1
Lost to follow-up	-	-	1
Protocol deviation	1	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Add-on 100
Reporting group description:	
Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase)	
Reporting group title	Add-on 200
Reporting group description:	
Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase)	
Reporting group title	Add-on
Reporting group description:	
Add-on placebo (3 weeks of double-blind intervention phase)	

Reporting group values	Add-on 100	Add-on 200	Add-on
Number of subjects	30	28	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	28	26
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	36.5	35.5	35.5
full range (min-max)	20 to 62	19 to 57	18 to 58
Gender categorical Units: Subjects			
Female	9	9	5
Male	21	19	21
Course of the disease			
Course of the disease (no. continuous / no. episodic)			
Units: Subjects			
No. continous	14	7	9
No. episodic	16	21	17
Age at first hospitilisation			
Age of first indication-related hospital stay			
Units: Years			
median	25	24	26
full range (min-max)	17 to 56	17 to 44	16 to 48
Duration of illness Units: months			
median	72	114	114

full range (min-max)	7 to 432	8 to 324	11 to 456
Number of hospitalizations			
Units: Number			
median	3	2	3
full range (min-max)	1 to 30	1 to 20	3 to 30
Duration of school education			
Units: years			
median	10	12	11
full range (min-max)	8 to 15	9 to 17	8 to 17
Duration school and Vocational Training			
Units: years			
median	13	15	13
full range (min-max)	8 to 23	9 to 26	9 to 23
Blood pressure sys			
Blood pressure systolisch at baseline			
Units: mmHg			
median	120.0	124.5	125.5
full range (min-max)	101 to 164	103 to 160	96 to 145
Blood pressure dia			
Blood pressure diastolisch at baseline			
Units: mmHg			
median	79	83	82
full range (min-max)	62 to 103	62 to 102	57 to 96
Heart Frequence			
Units: bpm			
median	80,5	83	85,5
full range (min-max)	61 to 101	55 to 120	64 to 105
Weight			
Units: kg			
median	79.1	87.45	88
full range (min-max)	54 to 114	50,3 to 116	59 to 157
Height			
Units: cm			
median	172	178.5	179
full range (min-max)	153 to 193	162 to 191	158 to 193
Body-Mass-Index			
BMI at baseline			
Units: BMI			
median	26.5	26.4	28.1
full range (min-max)	17.9 to 40.4	18.4 to 38.6	23.2 to 44.1
PANSS pos			
PANSS positive score baseline			
Units: Score			
median	11.5	12	12
full range (min-max)	7 to 19	7 to 20	7 to 20
PANSS neg			
PANSS negative score baseline			
Units: Score			
median	14.5	13	15
full range (min-max)	7 to 24	8 to 25	8 to 22
PANSS general			
PANSS general score baseline			

Units: Score			
median	26.5	24	27
full range (min-max)	18 to 43	16 to 35	16 to 38
PANSS total			
PANSS total score baseline			
Units: Score			
median	50.5	51.5	53.5
full range (min-max)	36 to 72	32 to 75	33 to 71

Reporting group values	Total		
Number of subjects	84		
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)	84		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	23		
Male	61		
Course of the disease			
Course of the disease (no. continuous / no. episodic)			
Units: Subjects			
No. continous	30		
No. episodic	54		
Age at first hospitilisation			
Age of first indication-related hospital stay			
Units: Years			
median			
full range (min-max)	-		
Duration of illness			
Units: months			
median			
full range (min-max)	-		
Number of hospitalizations			
Units: Number			
median			
full range (min-max)	-		
Duration of school education			
Units: years			

median			
full range (min-max)	-		
Duration school and Vocational Training			
Units: years			
median			
full range (min-max)	-		
Blood pressure sys			
Blood pressure systolisch at baseline			
Units: mmHg			
median			
full range (min-max)	-		
Blood pressure dia			
Blood pressure diastolisch at baseline			
Units: mmHg			
median			
full range (min-max)	-		
Heart Frequence			
Units: bpm			
median			
full range (min-max)	-		
Weight			
Units: kg			
median			
full range (min-max)	-		
Height			
Units: cm			
median			
full range (min-max)	-		
Body-Mass-Index			
BMI at baseline			
Units: BMI			
median			
full range (min-max)	-		
PANSS pos			
PANSS positive score baseline			
Units: Score			
median			
full range (min-max)	-		
PANSS neg			
PANSS negative score baseline			
Units: Score			
median			
full range (min-max)	-		
PANSS general			
PANSS general score baseline			
Units: Score			
median			
full range (min-max)	-		
PANSS total			
PANSS total score baseline			
Units: Score			
median			

full range (min-max)	-		

Subject analysis sets	
Subject analysis set title	IIT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who received at least one dose of IMP	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized patients who received at least one dose of IMP	

Reporting group values	IIT	PP	
Number of subjects	84	73	
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)	84	73	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	36	36	
full range (min-max)	18 to 62	18 to 62	
Gender categorical			
Units: Subjects			
Female	23	19	
Male	61	54	
Course of the disease			
Course of the disease (no. continuous / no. episodic)			
Units: Subjects			
No. continous	29	23	
No. episodic	54	49	
Age at first hospitilisation			
Age of first indication-related hospital stay			
Units: Years			
median	25	27	
full range (min-max)	17 to 56	16 to 56	
Duration of illness			
Units: months			
median	100	96	
full range (min-max)	7 to 456	7 to 456	

Number of hospitalizations Units: Number median full range (min-max)	 2,67 1 to 30	 2,8 1 to 30	
Duration of school education Units: years median full range (min-max)	 11 8 to 17	 11 8 to 17	
Duration school and Vocational Training Units: years median full range (min-max)	 13,66 8 to 26	 13,5 8 to 26	
Blood pressure sys			
Blood pressure systolisch at baseline			
Units: mmHg median full range (min-max)	 124 101 to 164	 124 103 to 164	
Blood pressure dia			
Blood pressure diastolisch at baseline			
Units: mmHg median full range (min-max)	 81,3 57 to 103	 81,2 62 to 103	
Heart Frequence Units: bpm median full range (min-max)	 83 55 to 120	 82 55 to 120	
Weight Units: kg median full range (min-max)	 84.9 50.3 to 157	 85 50.3 to 157	
Height Units: cm median full range (min-max)	 176 153 to 193	 175.5 157 to 193	
Body-Mass-Index			
BMI at baseline			
Units: BMI median full range (min-max)	 27.0 17.9 to 40.4	 27.5 17.9 to 44.1	
PANSS pos			
PANSS positive score baseline			
Units: Score median full range (min-max)	 12 7 to 20	 12 7 to 20	
PANSS neg			
PANSS negative score baseline			
Units: Score median full range (min-max)	 15 7 to 25	 15 7 to 25	
PANSS general			
PANSS general score baseline			
Units: Score			

median	26	26	
full range (min-max)	16 to 43	16 to 43	
PANSS total			
PANSS total score baseline			
Units: Score			
median	52	52	
full range (min-max)	32 to 75	32 to 75	

End points

End points reporting groups

Reporting group title	Add-on 100
Reporting group description:	
Add-on 100 mg spironolactone (3 weeks of double-blind intervention phase)	
Reporting group title	Add-on 200
Reporting group description:	
Add-on 200 mg spironolactone (3 weeks of double-blind intervention phase)	
Reporting group title	Add-on
Reporting group description:	
Add-on placebo (3 weeks of double-blind intervention phase)	
Subject analysis set title	IIT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who received at least one dose of IMP	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized patients who received at least one dose of IMP	

Primary: Change in 2-back relative hits of n-back test on ITT

End point title	Change in 2-back relative hits of n-back test on ITT
End point description:	
Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.	
End point type	Primary
End point timeframe:	
Change between V1 and V10	

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: Points				
arithmetic mean (standard deviation)	-7.96 (± 13.23)	-10.39 (± 22.86)	-2.98 (± 15.47)	

Statistical analyses

Statistical analysis title	Interaction between time and group
Statistical analysis description:	
Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.	
Comparison groups	Add-on 100 v Add-on 200 v Add-on

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.548
Method	Mixed models analysis

Secondary: Change in 2-back relative hits of n-back test on PP

End point title	Change in 2-back relative hits of n-back test on PP

End point description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[1]	26[2]	21[3]	
Units: Points				
arithmetic mean (standard deviation)	-6.84 (± 12.98)	-10.33 (± 23.7)	-3.4 (± 16.74)	

Notes:

[1] - Per protocol set

[2] - Per protocol set

[3] - Per protocol set

Statistical analyses

Statistical analysis title	Interaction between time and group on PP

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor on the per protocol set. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.869
Method	Mixed models analysis

Secondary: Change in 1-back relative hits of n-back test on ITT

End point title	Change in 1-back relative hits of n-back test on ITT

End point description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

End point type	Secondary
End point timeframe:	
Change between V1 and V10	

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-6.41 (± 17.07)	-8.93 (± 24.87)	-5.68 (± 15.76)	

Statistical analyses

Statistical analysis title	Interaction between time and group
Statistical analysis description:	
Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.	
Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586
Method	Mixed models analysis

Secondary: Change in 0-back relative hits of n-back test on ITT

End point title	Change in 0-back relative hits of n-back test on ITT
End point description:	
Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.	
End point type	Secondary
End point timeframe:	
Change between V1 and V10	

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-4.64 (± 16.1)	1.23 (± 13.55)	-4.65 (± 16.33)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.967
Method	Mixed models analysis

Secondary: VLMT 5th trial

End point title	VLMT 5th trial

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-0.17 (± 1.46)	0.3 (± 1.92)	-0.38 (± 2.33)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	Mixed models analysis

Secondary: VLMT 7th trial

End point title	VLMT 7th trial

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	0.1 (± 2.63)	0.27 (± 2.63)	-0.1 (± 2.7)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687
Method	Mixed models analysis

Secondary: VLMT recognition V1

End point title	VLMT recognition V1

End point description:

End point type	Secondary

End point timeframe:

Measured at Visit 1

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	25	
Units: points				
arithmetic mean (standard deviation)	37.93 (± 12.000)	12.39 (± 3.337)	10.68 (± 4.394)	

Statistical analyses

Statistical analysis title	VLMT recognition at V1
Statistical analysis description: Kruskal-Wallis Test	
Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173
Method	Kruskal-wallis

Secondary: VLMT recognition V10

End point title	VLMT recognition V10
End point description:	
End point type	Secondary
End point timeframe: Measured at Visit 10.	

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	27	21	
Units: points				
arithmetic mean (standard deviation)	28.38 (± 10.304)	10.63 (± 5.443)	9.86 (± 5.053)	

Statistical analyses

Statistical analysis title	VLMT recognition at V10
Statistical analysis description: Kruskal-Wallis Test	
Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	Kruskal-wallis

Secondary: TMT A	
End point title	TMT A
End point description:	
End point type	Secondary
End point timeframe: Change between V1 and V10	

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: second				
arithmetic mean (standard deviation)	6.6 (± 10.12)	6.04 (± 10.96)	2.77 (± 8.8)	

Statistical analyses

Statistical analysis title	Interaction between time and group
Statistical analysis description: Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.	
Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443
Method	Mixed models analysis

Secondary: TMT B	
End point title	TMT B
End point description:	

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: second				
arithmetic mean (standard deviation)	6.3 (± 42.56)	11.19 (± 30.01)	4.45 (± 32.57)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378
Method	Mixed models analysis

Secondary: TMT B-A

End point title	TMT B-A

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: second				
arithmetic mean (standard deviation)	-0.3 (± 45.62)	5.15 (± 28.33)	1.68 (± 30.96)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Mixed models analysis

Secondary: d2 total signs

End point title	d2 total signs

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-14.36 (± 43.57)	-29.22 (± 39.93)	-33.95 (± 50.83)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Mixed models analysis

Secondary: d2 failures

End point title	d2 failures

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	5.11 (± 10.92)	4.52 (± 15.55)	2.38 (± 18.47)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.969
Method	Mixed models analysis

Secondary: d2 concentration score

End point title	d2 concentration score

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-12.57 (± 15.94)	-18.52 (± 16.1)	-6.86 (± 64.17)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.649
Method	Mixed models analysis

Secondary: GAF

End point title	GAF

End point description:

End point type	Secondary

End point timeframe:

Change between V1 and V10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: points				
arithmetic mean (standard deviation)	-6.7 (± 7.42)	-1.52 (± 5.6)	-2.23 (± 7.26)	

Statistical analyses

Statistical analysis title	Interaction between time and group

Statistical analysis description:

Analyzed with a linear mixed model with group as a fixed factor and time as a within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group.

Comparison groups	Add-on 100 v Add-on 200 v Add-on

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis

Secondary: CDSS at V1

End point title	CDSS at V1

End point description:

End point type	Secondary

End point timeframe:

Measured at Visit 1

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	26	
Units: points				
arithmetic mean (standard deviation)	3.82 (± 3.300)	2.07 (± 3.066)	2.81 (± 2.191)	

Statistical analyses

Statistical analysis title	CDSS at V1

Statistical analysis description:

Kruskal-Wallis test

Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Kruskal-wallis

Secondary: SDSS at V10

End point title	SDSS at V10

End point description:

End point type	Secondary

End point timeframe:

Measured at Visit 10

End point values	Add-on 100	Add-on 200	Add-on	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	22	
Units: points				
arithmetic mean (standard deviation)	3.10 (± 2.869)	2.15 (± 2.797)	3.68 (± 4.674)	

Statistical analyses

Statistical analysis title	CDSS at V10
Statistical analysis description: Kruskal-Wallis test	
Comparison groups	Add-on 100 v Add-on 200 v Add-on
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305
Method	Kruskal-wallis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the follow-up period (starts after V11), hospitalization to a psychiatric hospital due to schizophrenia was a priori defined not to be considered a SAE.

Adverse event reporting additional description:

Adverse events (AE), severe adverse events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR) were to be documented following established definitions and legal requirements.The intensity of AEs was defined according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Overall study

Reporting group description:

The safety set consisted of all patients who entered the trial and was used for conducting all safety analyses.

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 84 (2.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Psychotic disorder			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 84 (46.43%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	5		

Dizziness subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5 4 / 84 (4.76%) 5		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	10 / 84 (11.90%) 10		
Psychiatric disorders Psychotic disorder subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 6		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	10 / 84 (11.90%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2015	The following major changes were included in AM 2: extension of inclusion criterion 3 (not only patients with monotherapy, but with two antipsychotics allowed) and clearer definition of inclusion criterion 5 and exclusion criterion 8.
11 October 2016	The following major changes were included in AM 3: additional inclusion of women allowed (not pregnant, contraception according to CTFG guideline), clearer definition of excluded antipsychotics.
18 April 2017	The following major changes were included in AM 4: Additional site Regensburg, clarification of the negative wording of an exclusion criterion, extension of study period.
25 June 2018	The following major changes were included in AM 6: change in IMP Manufacturer and add-on to patient information to reflect new regulation on data protection.
31 October 2019	The following major changes were included in AM 7: adapted description in power planning and statistical analysis and improved specification of secondary endpoints.

Notes:

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/32072071