SPIRO-TREAT

Add-on spironolactone for the treatment of schizophrenia

(Evaluation der Effektivität der add-on Behandlung von Spironolacton bei Patienten mit einer Schizophrenie)

Phase IIb Clinical Trial

Clinical Study Report

Test product: Spironolacton / Placebo

Study Code: SPIRO-TREAT

Eudra-CT Number: 2014-001968-35

First Patient First Visit: 08.07.2015 **– Last Patient Last Visit:** 11.08.2020

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Name of Active Ingredient/Name of Finished Product
Spironolactone / Placebo

Study Title
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Participating Study Centres (multicentre)

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Publication
Contemporary Clinical Trials Communications. Volume 17, March 2020, 100537 (publication of trial protocol). Parts of this report were taken from this publication as direct citation.
https://www.sciencedirect.com/science/article/pii/S2451865420300211?via%3Dihub

Study period
First patient first visit (FPFV): 08.07.2015; Last patient in (LPI): 25.05.2020; Last patient last visit (LPLV): 11.08.2020

Approvals and Amendments
Approval: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM): 23.02.2015; Ethics Committee (EC): 11.03.2015.
Clinical Study Protocol (CSP) Version 1.0, 07.01.2015; Informed Consent Form (ICF) Version 07.01.2015

Amendments (AM) and changes in conduct to the clinical trial (AM1 - AM7)
Approval AM1: BfArM: 08.04.2015; EC: 02.04.2015
The following major changes were included in AM 1: Prof. Falkai is SDP site 1, SOFAS assessments have been removed from study visits as it is the same examination as GAF assessments; description of inclusion & exclusion criteria as in CSP under 4.2 and 4.3. The first

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patient was included after approval of AM 1. CSP Version 2.0, 12.03.2015; ICF Version 1.0 07.01.2015

Approval AM 2: BfArM: 30.09.2015; EC: 15.10.2015
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. CSP Version 3.0, 22.09.2015; ICF Version 1.1, 21.09.2015

Approval AM 3: BfArM: 11.10.2016; EC: 04.10.2016
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. CSP Version 4.1, 19.09.2016; ICF Version 2.0, 06.09.2016

Approval AM 4: BfArM: 18.04.2017; EC:18.04.2017
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
CSP Version 4.2, 23.02.2017

AM 5: EC: 24.04.2018 (submission to BfArM for information: 21.03.2018)
The following non-substantial changes were included in AM 5: clarification that exclusion of anamnestic epileptic seizures concerns only subjects participating in TMS part of the clinical trial.
CSP Version 4.3. 08.02.2018

Approval AM 6: BfArM: 25.06.2018; EC: 25.06.2018
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
CSP Version 4.4, 23.05.2018

Approval AM 7: BfArM: 31.10.2019; EC: 08.11.2019
The following major changes were included in AM 7: adapted description in power planning and statistical analysis and improved specification of secondary endpoints
CSP Version 4.5, 17.10.2019

Study Design
Prospective, multicenter randomized, placebo-controlled, double blind, three-arm clinical trial with two arms investigating an active compound (spironolactone 100 mg, and 200 mg respectively) and one placebo arm.

Methodology
To investigate add-on spironolactone for the treatment of schizophrenia, 90 patients with schizophrenia were enrolled (after having obtained written informed consent and fulfilling all inclusion and none of the exclusion criteria) and randomized into either one of two interventional groups receiving spironolactone (group 1: 100 mg or group 2: 200 mg per day) or into the control group receiving placebo (group 3) orally. Each group was to take IMP for three weeks (intervention phase) and then followed-up for additional nine weeks (until V12).

To evaluate whether spironolactone added to an ongoing antipsychotic treatment improves cognitive functioning in schizophrenia, we investigated changes in working memory before (V1) and at the end of the intervention phase (V10) as primary outcome. Eighty-one patients with complete data were intended to be evaluable for the primary endpoint. Secondary endpoints included other measures of cognition, psychopathology, safety, and biological measures.

The trial was registered at: International Clinical Trials Registry Platform: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-001968-35-DE

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Figures 1 and 2 display main aspects of the trial design including the detailed study steps and the milestones per patient in the trial.

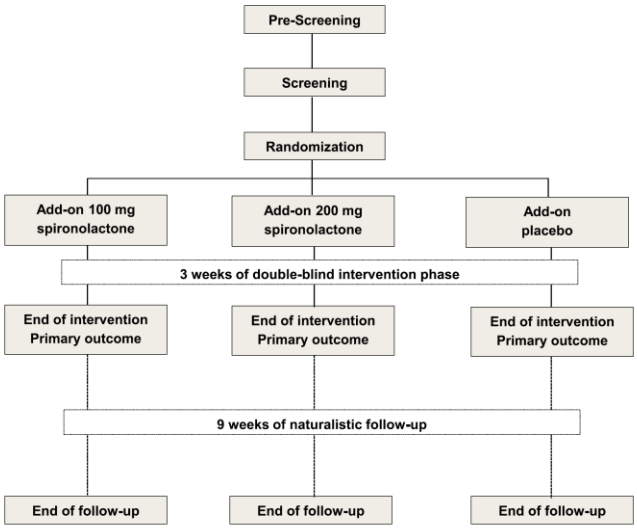

Figure 1: Trial Design (from Hasan et al. 2020)

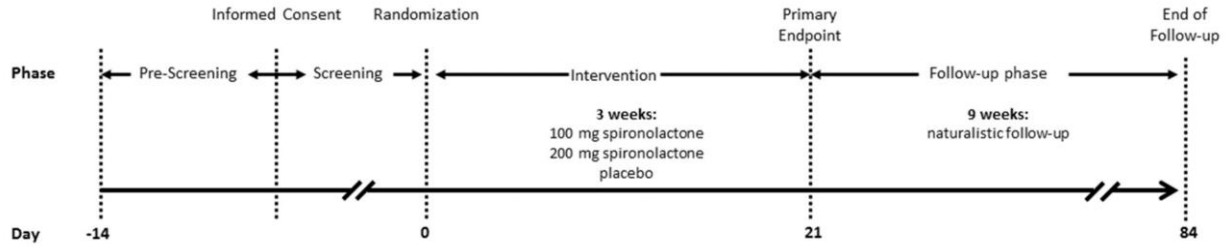

Figure 2: Sequence of trial milestones per patients (from Hasan et al. 2020)

Objectives

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)

Secondary Objectives

- Improvement of other neurocognitive functions after 3 and 12 weeks (verbal memory, working speed), changes in psychopathology of Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS), changes in Clinical Global Impression (CGI) and Global Assessment of Functioning (GAF), occurrence of single side effects, changes of cortical inhibition and changes in ERBB4 metabolic pathway (these two objectives were additional investigations)

→ Please see more details of the objectives and outcome measures below

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Sample size (planned/analysed)
Planned:

- **90** patients

Analyzed:

- **84** patients in the Intention-to-Treat (ITT) population
- **84** patients in Safety Population
- **73** patients in the Per-protocol (PP) population

Inclusion criteria

- In- and outpatients (men and women) aged between 18 and 65 years with a primary diagnosis of schizophrenia according to ICD-10 confirmed by the Mini-International Neuropsychiatric Interview,
- Participants are able to sign informed consent,
- Participants must receive a stable antipsychotic treatment for at least one week,
- Participants must not be treated with more than two antipsychotics,
- Participants must have a PANSS total score ≤75,
- Participants must have a duration of illness of at least six months,
- Female participants must have a negative pregnancy test (serum) at baseline and must use a method of contraception that is medically approved by the health authority („Recommendations related to contraception and pregnancy testing in clinical trials (CTFG 2014).

Exclusion Criteria

- Incapacity to give informed consent,
- Suicidality or endangerment of others,
- Severe somatic or neurological comorbidities,
- History or assumption of relevant non-compliance that interferes with the ability to participate in a clinical trial,
- Current antipsychotic treatment with clozapine or an antipsychotic with exclusive renal elimination (e.g. amisulpride),
- Planned initiation of a treatment with an antidepressant or mood stabilizer during the intervention period (a prior treatment with an non-renal eliminated antidepressant or a mood-stabilizer other than lithium is permitted),
- Diagnoses of drug dependency other than tobacco or caffeine within the last 6 months prior to inclusion,
- History of seizures (only relevant for the physiological investigation with transcranial magnetic stimulation (TMS)),
- Documented intolerance to a treatment with spironolactone or placebo capsules
- Acute kidney failure or anuria, or severe kidney insufficiency (creatinine clearance < 30 ml/min per 1.73 m^2 or serum creatinine > 1.8 mg/dl),
- Clinically relevant hyperkalemia or hyponatremia,
- Clinically relevant hypotension (RR < 100/80 mmHg),
- Simultaneous use of potassium-sparing diuretics, ACE inhibitors, ATIIantagonists, non-steroidal anti-inflammatory drugs (NSAID), thiazide, diuretics, carbenoxolone, digoxin or neomycin,
- Coercive treatment,
- Treatment-resistant or treatment-naïve schizophrenia,
- Insufficient understanding of German language,

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- Pregnancy,
- Absent safe and approved methods of contraception.

Study treatment
Spironolactone, Spironolacton Hexal encapsulation (1x50 or 2x50mg per capsule)

Dose intended per day**:** In 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. In 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). In group III (placebo), two capsules with placebo from D 1 to D 21.

Route: oral use

Placebo capsules Bulk: 20150508A, 20160414A, 20170320A, 20170802P, 20180419P, 20180719P, 20190326B, 20200220P

Spironolactone 50 mg Capsules Bulk:

Internally Batch:	Batch finished IP:
20150508B,	Osyrol 50mg 124071/A3
20160415B,	Osyrol 50 mg 124071/A3
20170327A,	Osyrol 50 mg 124071/A3
Internally Batch:	Batch finished IP:
20170803C,	Osyrol 50 mg 154501/A2
20180419C,	Osyrol 50 mg 154501/A2
20180716A,	Spironolacton Hexal 50 mg HX4993
20190326A,	Spironolacton Hexal 50 mg JP9670
20200220A,	Spironolacton Hexal 50 mg JY3667

Spironolactone 100 mg Capsules:

Internally Batch:	Batch finished IP:
20150508C,	Osyrol 50mg 124071/A3
20160415C,	Osyrol 50 mg 124071/A3
20170328B,	Osyrol 50 mg 124071/A3
20170807A,	Osyrol 50 mg 154501/A2
20180419D,	Osyrol 50 mg 154501/A2
20180720B,	Spironolacton Hexal 50 mg HX4993
20190322A,	Spironolacton Hexal 50 mg JP9670
20200220B,	Spironolacton Hexal 50 mg JY3667

Duration of treatment
3 weeks

Blinding
Double-blind

Criteria for evaluation
Primary endpoint
The primary endpoint is change in working memory performance assessed by the n-back test (2-back level, relative hit rate) before and after the intervention period.

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Secondary endpoints

- Secondary endpoints include the change after the intervention period in the remaining n-back test results (relative hit rates, error rates, and reaction times) and the change after the follow-up period in n-back performance and in other cognitive functions:
- The verbal declarative memory assessed by the German version of the Rey Auditory Verbal Learning Test (Verbaler Lern-und Merkfähigkeitstest, VLMT),
- The complex visual scanning, motor speed, the ability to shift strategies assessed by the Trail-Making-Test (TMT-A and TMT-B),
- Measures of sustained and selective attention assessed by d2-attention test,
- Positive and Negative Syndrome Scale (PANSS),
- Frequency of remitters according to the Andreasen criteria,
- Calgary Depression Scale for Schizophrenia (CDSS),
- Disease severity using the Clinical Global Impression scale (CGI),
- General functioning using the Global Assessment of Functioning scale (GAF),
- Differences between both active study groups in all outcome measures are assessed,
- Pooled data of both spironolactone groups vs. placebo for selected outcomes.
- Secondary endpoints are assessed directly after the intervention and after the naturalistic follow-up.

Safety assessments
Safety measures include physical examination, electrocardiography (ECG), study laboratory, blood pressure, heart rate as well as height, body weight and body mass index (BMI). The Simpson-Angus scale (SiAS) was used to rate extrapyramidal side effects. Due to the specific side-effect profile of spironolactone special attention was drawn to potassium levels and creatinine levels (to be assessed every 2 – 3 days during the intervention period). 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). 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.

Statistical methods
Population for analysis

Intention-to-Treat (ITT) Population: All randomized patients who received at least one dose of IMP

Per-protocol Population (PP): All subjects evaluable for the primary endpoint without major protocol deviations

Safety population (SP): The safety analysis set consists of all patients who entered the trial and was used for conducting all safety analyses (corresponds to the ITT population)

Statistical analysis
All statistical analyses were determined and prespecified prior to unblinding in a statistical analyses plan (SAP). An interim analysis was not planned. The statistician remained blinded until data-base hard-lock.

Primary endpoint
Normality assumption was checked with a Kolmogorow-Smirnow-Test and if this assumption was violated, a Rankit-transformation (Bliss, 1967, Bishara und Hittner 2012) was performed. For the intention-to-treat population, primary and secondary outcomes were analyzed with a linear mixed model analysis, nonrestrictely assuming an unstructured covariance matrix. Group (100 mg, 200

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mg, placebo) was defined as fixed-factor and time (V1, V10) as within-subject factor. The statistic analyzed for significance was the interaction between time of measurement and group, indicating whether the change of the primary outcome variable over time differed between groups.

Secondary endpoints
Secondary endpoints were analysed in the same manner where appropriate. Here, we focussed on the analyses of all timepoints with available data unless otherwise indicated. If there were significant deviations from normality assumptions, a Rankit trandformation was performed. In cases where despite the Rankit transformation the normality assumption was not fulfilled, non-parametric tests were used: Kruskal-Wallis-Tests (3-groups) or Mann-Whitney U-Tests (2-groups) for between group comparisons. Categorical variables were analyzed using Chi²-Tests or adapted tests where needed. Where indicated, a correction for multiple comparisons was performed with the Sidak procedure. AEs were summarized by MedDRA Preferred Term and System Organ Class using absolute and relative frequencies. Serious AEs and AEs which are causally related to study medication were tabulated separately.

Summary Results, Conclusions

Patient demographics and patient disposition
FPFV: 08.07.2015; **LPI:** 25.05.2020; **LPLV:** 11.08.2020

Only adults between 18 and 65 years were included. The median age was 36.50 (20.00 to 62.00) years in the spironolactone 100 mg group, 35.50 (19.00 to 57.00) years in the spironolactone 200 mg group and 35.50 (18.00 to 58.00) years in the placebo group. There were 23 female and 61 male participants.

Table 1 shows the demographics of the ITT-population. Apart from a significant difference in the variable height, no differences across all study groups could be detected. No differences between groups for the duration of illness, the number of hospitalizations and psychopathological measures could be detected at baseline.

	Spiro 100 mg							Spiro 200 mg							Placebo							Group comparison		
	number							number							number							LR	df	p
Center (LMU / Regensburg / TMU)	24 / 3 / 3							23 / 1 / 4							22 / 1 / 3							1,48	4	0,830
Gender (no. male / no. female)	21 / 9							19 / 9							21 / 5							1,34	2	0,511
Course of the disease (no. continuous / no. episodic)	13 / 16							7 / 21							9 / 17							2,49	2	0,288
	Spiro 100 mg							Spiro 200 mg							Placebo							Group comparison		
	n	m	sd	median	min	max	range	n	m	sd	median	min	max	range	m	m	sd	median	min	max	range	F	df	p
Age (years)	30	37,93	12,00	36,50	20,00	62,00	42,00	28	35,61	10,62	35,50	19,00	57,00	38,00	26	37,96	11,25	35,50	18,00	58,00	40,00	0,4	2, 81	0,673
Age at first hospitalisation (years)	29	28,38	10,30	25,00	17,00	56,00	39,00	28	25,61	7,63	24,00	17,00	44,00	27,00	26	27,15	8,65	26,00	16,00	48,00	32,00	0,68	2, 80	0,507
Duration of Illness (months)	29	113,48	104,59	72,00	7,00	432,00	425,00	28	120,75	89,75	114,00	8,00	324,00	316,00	26	129,65	114,70	114,00	11,00	456,00	445,00	0,17	2, 80	0,845
number of hospitalizations	28	4,96	6,00	3,00	1,00	30,00	29,00	28	4,43	4,69	2,00	1,00	20,00	19,00	25	6,00	6,68	3,00	1,00	30,00	29,00	0,49	2, 78	0,612
Duration of School education (years)	29	10,84	2,14	10,00	8,00	15,00	7,00	28	11,61	1,81	12,00	9,00	17,00	8,00	26	11,29	2,09	11,00	8,00	17,00	9,00	1,03	2, 80	0,363
Duration of School Education + Vocational Training (years)	28	13,39	3,70	13,00	8,00	23,00	15,00	27	15,52	4,73	15,00	9,00	26,00	17,00	26	14,10	3,63	13,00	9,00	23,00	14,00	1,95	2, 78	0,149
blood pressure (sys) baseline	30	122,43	14,27	120,50	101,00	164,00	63,00	28	124,57	13,12	124,50	103,00	160,00	57,00	26	125,62	11,61	125,50	96,00	145,00	49,00	0,43	2, 81	0,649
blood pressure (dia) baseline	30	80,77	10,63	79,50	62,00	103,00	41,00	28	81,39	9,62	83,00	62,00	102,00	40,00	26	80,77	9,19	82,50	57,00	96,00	39,00	0,04	2, 81	0,963
Heart Frequence	30	80,07	11,38	80,50	61,00	101,00	40,00	28	84,04	14,55	83,00	55,00	120,00	65,00	26	84,35	13,23	85,50	64,00	105,00	41,00	0,96	2, 81	0,387
Weight	30	79,66	15,54	79,10	54,00	114,00	60,00	28	83,90	16,92	87,45	50,30	116,00	65,70	26	89,69	20,14	88,00	59,00	157,00	98,00	2,29	2, 81	0,108
Height	30	171,97	9,74	172,00	153,00	193,00	40,00	28	177,64	8,22	178,50	162,00	191,00	29,00	25	177,28	9,97	179,00	158,00	193,00	35,00	3,35	2, 80	**0,049**
BMI	30	26,90	4,82	26,50	17,90	40,40	22,50	28	26,50	4,91	26,40	18,40	38,60	20,20	25	28,25	5,90	28,10	20,90	44,10	23,20	0,81	2, 80	0,447
PANSS positive score baseline	30	11,97	3,68	11,50	7,00	19,00	12,00	28	11,96	3,12	12,00	7,00	20,00	13,00	26	12,42	3,43	12,00	7,00	20,00	13,00	0,16	2, 81	0,852
PANSS negative score baseline	30	14,27	4,31	14,50	7,00	24,00	17,00	28	14,32	4,16	13,00	8,00	25,00	17,00	26	14,96	3,28	15,00	8,00	22,00	14,00	0,26	2, 81	0,775
PANSS general score baseline	30	27,13	6,25	26,50	18,00	43,00	25,00	28	25,11	5,28	24,00	16,00	35,00	19,00	26	27,12	5,85	27,00	16,00	38,00	22,00	1,23	2, 81	0,331
PANSS total score baseline	30	53,37	11,45	50,50	36,00	72,00	36,00	28	51,39	10,79	51,50	32,00	75,00	43,00	26	54,50	10,71	53,50	33,00	71,00	38,00	0,56	2, 81	0,576

Table 1: Demographic data of the intention-to-treat population

Table 2 shows the demographics of the PP-population. No differences across all study groups could be detected. No significant differences between groups for the duration of illness, the number of hospitalizations and psychopathological measures could be detected at baseline.

	Spiro 100 mg							Spiro 200 mg							Placebo							Group comparison		
	number							number							number							LR	df	p
Center (LMU / Regensburg / TMU)	21 / 2 / 3							22 / 1 / 3							17 / 1 / 3							0,49	4	0,975
Gender (no. male / no. female)	19 / 7							18 / 8							17 / 4							0.87	2	0.647
Course of the disease (no. continuous / no. episodic)	11 / 14							5 / 21							7 / 14							3.72	2	0.156
	Spiro 100 mg							Spiro 200 mg							Placebo							Group comparison		
	n	m	sd	median	min	max	range	n	m	sd	median	min	max	range	m	m	sd	median	min	max	range	F	df	p
Age (years)	26	38,00	12,02	36,5	20	62	42	26	34,46	10,12	34,0	19	57	38	21	37,71	11,95	35,0	18	58	40	0,759	2, 70	0,472
Age at first hospitalisation (years)	25	28,88	10,63	27,0	17	56	39	26	25,19	7,58	24,0	17	44	27	21	26,90	8,97	25,0	16	48	32	1,04	2, 69	0,359
Duration of Illness (months)	25	108,16	108,84	72,0	7	432	425	26	112,23	85,95	108,0	8	324	316	21	129,57	117,88	108,0	11	456	445	0,267	2, 69	0,767
number of hospitalizations	24	5,13	6,32	3,0	1	30	29	26	4,62	4,82	2,5	1	20	19	20	6,05	7,08	3,0	1	30	29	0,321	2, 67	0,767
Duration of School education (years)	25	10,82	2,16	10,0	8	15	7	26	11,62	1,83	12,0	9	17	8	21	11,12	2,10	11,0	8	17	9	1,00	2, 69	0,374
Duration of School Education + Vocational Training (years)	24	13,50	3,89	12,5	8	23	15	25	15,60	4,81	15,0	9	26	17	21	13,81	3,58	13,0	9	23	14	1,809	2, 67	0,172
blood pressure (sys) baseline	26	122,69	14,02	120,5	105	164	59	26	122,00	9,46	123,0	103	140	37	21	126,10	10,40	125,0	106	145	39	0,814	2, 70	0,447
blood pressure (dia) baseline	26	80,46	9,95	79,5	62	103	41	26	80,00	8,44	82,0	62	92	30	21	81,52	8,08	82,0	66	96	30	0,175	2, 70	0,870
Heart Frequence	26	79,77	12,11	80,5	61	101	40	26	83,96	14,80	83,0	55	120	65	21	83,57	13,20	83,0	64	105	41	0,754	2, 70	0,474
Weight	26	81,40	15,56	83,9	55,0	114,0	59,0	26	82,43	16,26	85,5	50,3	107,0	56,7	21	90,04	22,05	90,0	59,0	157,0	98,0	1,567	2, 70	0,216
Height	26	172,73	9,14	173,0	157,0	193,0	36,0	26	177,50	8,39	178,5	162,0	191,0	29,0	20	176,05	8,89	178,5	158,0	190,0	32,0	1,989	2, 69	0,145
BMI	26	27,28	5,01	27,1	17,9	40,4	22,5	26	26,04	4,47	25,8	18,4	32,9	14,5	20	28,62	6,31	28,6	20,9	44,1	23,2	1,383	2, 69	0,258
PANSS positive score baseline	26	11,81	3,37	11,5	7	19	12	26	12,04	3,12	12,0	7	20	13	21	11,67	2,82	11,0	7	18	11	0,086	2, 70	0,918
PANSS negative score baseline	26	14,31	4,34	14,5	7	24	17	26	14,50	4,19	13,0	8	25	17	21	15,05	3,25	15,0	8	22	14	0,209	2, 70	0,812
PANSS general score baseline	26	27,27	6,28	26,5	18	43	25	26	25,35	5,40	24,0	16	35	19	21	26,24	5,90	27,0	16	38	22	0,698	2, 70	0,501
PANSS total score baseline	26	53,38	10,94	50,5	36	70	34	26	51,88	10,88	51,5	32	75	43	21	52,95	10,14	52,0	33	69	36	0,134	2, 70	0,874

Table 2: Demographic data of the per-protocol population

Concomitant therapy during the study

All patients received the routine care treatment in the respective participating study centres including pharmacotherapy, psychotherapy, and psychosocial treatments in accordance with the defined inclusion and exclusion criteria.

Compliance

There were five violations of inclusion or exclusion criteria. In subject 121, one inclusion criterion was violated (substance dependency with substance free interval of only four instead of six months). In subject 124, antipsychotic medication was stable for less than seven days. In subject 138, a syncope was retrospectively detected in the patient chart. In subject 157, the cumulative CPZ dose was exceeded. In patient 303, the signature of a MD not involved in the study, was made after the begin of the intervention. All these violations were rated as major protocol violations without being a risk for patient safety or data integrity.

In total, **90 patients** were included (signed informed consent). **4 patients** were not randomized, and **2 patients** were randomized, but did not receive an IMP. Thus, a total of **84 patients** were included in the ITT set. **7 patients did not reach V10**. **11 patients** were excluded from the ITT Population due to major protocol deviations resulting in a total of **73 patients** for the PP population.

Regarding EOS (V12): 5 patients discontinued the study due to an AE, 6 patients discontinued the study due to protocol violations, 18 patients discontinued the study due to lost-to-follow-up, four patient withdrew consent and three patients had other reasons for discontinuing the study. 0 patients stopped treatment due to death or due to a worsening of symptoms.

Protocol Violation (PV)

154 PV were reported in 69 out of 90 patients. 14 protocol violations in 11 patients were rated as major and the remaining protocol deviations were rated as minor. 86 out of 140 minor protocol violations were due to visits scheduled at other visit timepoints or not-performed visits. 23 out of 140 PV were due to uncomplete assessment of questionnaires or other items (e.g. laboratory data, ecg). 31 minor PV were due to other reasons.

Study medication

6 patients left the study before intake of any IMP. Further 7 patients received IMP but did not reach visit 10 (V10). From these 7 patients, 5 were randomized to placebo and two to spironolactone 200 mg.

Safety Assessments (all patients included)

Annual Safety Reports have been provided to PEI and EC for the following periods:
DSUR 1: 23.02.2015 – 22.02.2016
DSUR 2: 23.02.2016 – 22.02.2017
DSUR 3: 23.02.2017 – 22.02.2018
DSUR 4: 23.02.2018 – 22.02.2019
DSUR 5: 23.02.2019 – 22.02.2019
DSUR 6: 23.02.2020 – 11.08.2020

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Adverse Events (AE) / Non-serious AE

Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4.0 and coded according to MedDRA V. 23.1 English. A total of 154 AEs were reported in 84 patients (see Supplementary Tables 1 and 2). In the ITT sample 152 AEs appeared. **Table 3** shows the distribution of AEs across study groups. While not reaching significance (p=0.088), numeric distribution indicates that in both study groups more AEs occurred with no significant differences across these two groups compared to the placebo group.

Crosstab

			Patients_with_AEs		Total
			no	yes	
group	Spiro 100	Count	7	23	30
		% within group	23.3%	76.7%	100.0%
	Spiro 200	Count	6	22	28
		% within group	21.4%	78.6%	100.0%
	Placebo	Count	12	14	26
		% within group	46.2%	53.8%	100.0%
Total		Count	25	59	84
		% within group	29.8%	70.2%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.865[a]	2	0.088
Likelihood Ratio	4.702	2	0.095
Linear-by-Linear Association	3.246	1	0.072
N of Valid Cases	84		

Table 3: Distribution of AEs (number of patients with AE) across study groups

The relation to treatment administered (AR) is displayed in **Table 4**. Table 4 shows significant differences in the distribution of relationships across groups (p = 0.043). In general, it can be described that more relationships between AE and active IMP were observed than with placebo.

Crosstab

			AE causal relations					
			definite	probable	possible	not known	not applicable	Total
group	Spiro 100	Count	0	8	11	6	33	58
		% within group	0.0%	13.8%	19.0%	10.3%	56.9%	100.0%
	Spiro 200	Count	5	3	12	10	32	62
		% within group	8.1%	4.8%	19.4%	16.1%	51.6%	100.0%
	Placebo	Count	0	0	8	7	17	32
		% within group	0.0%	0.0%	25.0%	21.9%	53.1%	100.0%
Total		Count	5	11	31	23	82	152
		% within group	3.3%	7.2%	20.4%	15.1%	53.9%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15.976[a]	8	0.043
Likelihood Ratio	19.308	8	0.013
Linear-by-Linear Association	0.256	1	0.613
N of Valid Cases	152		

Table 4: AE relatedness

121 AE were rated Grade 1 (mild), 27 Grade 2 (moderate), 4 Grade 3 (severe), 0 Grade 4 (life-threatening), 0 Grade 5 (death). No significant differences could be observed across study groups (p = 0.164) (**see Table 5**)

Crosstab

			Intensity			
			mild	moderate	severe	Total
group	Spiro 100	Count	41	16	1	58
		% within group	70.7%	27.6%	1.7%	100.0%
	Spiro 200	Count	52	8	2	62
		% within group	83.9%	12.9%	3.2%	100.0%
	Placebo	Count	28	3	1	32
		% within group	87.5%	9.4%	3.1%	100.0%
Total		Count	121	27	4	152
		% within group	79.6%	17.8%	2.6%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.508[a]	4	0.164
Likelihood Ratio	6.434	4	0.169
Linear-by-Linear Association	2.484	1	0.115
N of Valid Cases	152		

Table 5: AE intensity

Table 6 displays the outcome of AE showing no between-group differences (p = 0.575)

Crosstab

			Outcome				
			Recovered	Ongoing	Recovered with Sequelae	Unknown	Total
group	Spiro 100	Count	44	12	1	2	59
		% within group	74.6%	20.3%	1.7%	3.4%	100.0%
	Spiro 200	Count	47	12	0	3	62
		% within group	75.8%	19.4%	0.0%	4.8%	100.0%
	Placebo	Count	22	10	0	0	32
		% within group	68.8%	31.3%	0.0%	0.0%	100.0%
Total		Count	113	34	1	5	153
		% within group	73.9%	22.2%	0.7%	3.3%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.756[a]	6	0.575
Likelihood Ratio	5.936	6	0.430
Linear-by-Linear Association	0.203	1	0.652
N of Valid Cases	153		

Table 6: AE outcome distribution

Table 7 displays the action taken in relation to AE and again no between-group differences could be observed (p = 0.290)

Crosstab

			Action Taken			
			none	medication	other	Total
group	Spiro 100	Count	36	7	15	58
		% within group	62.1%	12.1%	25.9%	100.0%
	Spiro 200	Count	34	13	15	62
		% within group	54.8%	21.0%	24.2%	100.0%
	Placebo	Count	24	4	4	32
		% within group	75.0%	12.5%	12.5%	100.0%
Total		Count	94	24	34	152
		% within group	61.8%	15.8%	22.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.971[a]	4	0.290
Likelihood Ratio	5.146	4	0.273
Linear-by-Linear Association	1.452	1	0.228
N of Valid Cases	152		

Table 7: Action taken due to AE

Table 8 displays the total number of cumulative AE across study groups. No significant differences could be observed across study groups ($Chi^2_{(20)} = 6.212$, p = 0.999)

Crosstab

			AE Nr.										
			1	2	3	4	5	6	7	8	9	10	11	Total
group	Spiro 100	Count	23	15	10	4	2	2	1	1	0	0	0	58
		% within group	39.7%	25.9%	17.2%	6.9%	3.4%	3.4%	1.7%	1.7%	0.0%	0.0%	0.0%	100.0%
	Spiro 200	Count	22	16	9	6	2	2	1	1	1	1	1	62
		% within group	35.5%	25.8%	14.5%	9.7%	3.2%	3.2%	1.6%	1.6%	1.6%	1.6%	1.6%	100.0%
	Placebo	Count	14	8	4	3	1	1	1	0	0	0	0	32
		% within group	43.8%	25.0%	12.5%	9.4%	3.1%	3.1%	3.1%	0.0%	0.0%	0.0%	0.0%	100.0%
Total		Count	59	39	23	13	5	5	3	2	1	1	1	152
		% within group	38.8%	25.7%	15.1%	8.6%	3.3%	3.3%	2.0%	1.3%	0.7%	0.7%	0.7%	100.0%

Table 8: Cumulative number of AE

Serious AE (SAE)

A total of 2 SAE (2 terms) were reported in 2 patients (see **Table 9** and Supplementary Tables 3, 4 and 5). No significant differences could be observed across groups (p = 0.565).

Crosstab

			Patients_with_SAEs		
			no	yes	Total
group	Spiro 100	Count	30	0	30
		% within group	100.0%	0.0%	100.0%
	Spiro 200	Count	27	1	28
		% within group	96.4%	3.6%	100.0%
	Placebo	Count	25	1	26
		% within group	96.2%	3.8%	100.0%
Total		Count	82	2	84
		% within group	97.6%	2.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.143[a]	2	0.565
Likelihood Ratio	1.797	2	0.407
Linear-by-Linear Association	0.914	1	0.339
N of Valid Cases	84		

Table 9: Number and distribution of AE

Suspected Serious Adverse Reactions (SARs)

No SAE were deemed related (SARs).

Suspected Unexpected Serious Adverse Reactions (SUSAR)

No SUSARs were reported in the study.

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Primary Endpoint

The primary endpoint analyses in the ITT-population could not establish a significant time x group interaction for the comparison of the three study groups between V1 and V10 ($F_{(2, 74.882)}$ = 0.606, p = 0.548). While the descriptive data as shown in figure 3 indicate a numerical improvement in both intervention groups (100/200 mg spironolactone), this could not be confirmed in the respective statistical analyses. Table 10 shows the LMM outcome for the primary endpoint analyses. **Figure 3** shows the relative N-back hits (2-Back) across groups and the respective data after Rankit transformation (data presented for all three time points, please see also secondary endpoints).

Based on these analyses, the trial must be considered as a negative trial. Against our assumptions, the add-on treatment with spironolactone did not result in a significantly improved cognitive performance according to the relative 2-back hit rate.

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	74.456	0.253	0.616
Time	1	75.061	14.092	0.000
Group	2	74.736	0.078	0.925
Gender	1	74.595	0.664	0.418
Center	2	76.467	1.167	0.317
Age	1	75.040	8.472	0.005
School_years	1	74.814	6.174	0.015
Time * Group	2	74.882	0.606	0.548

Table 10: LMM outcome for the primary endpoint analyses (performed on Rankit transformed data)

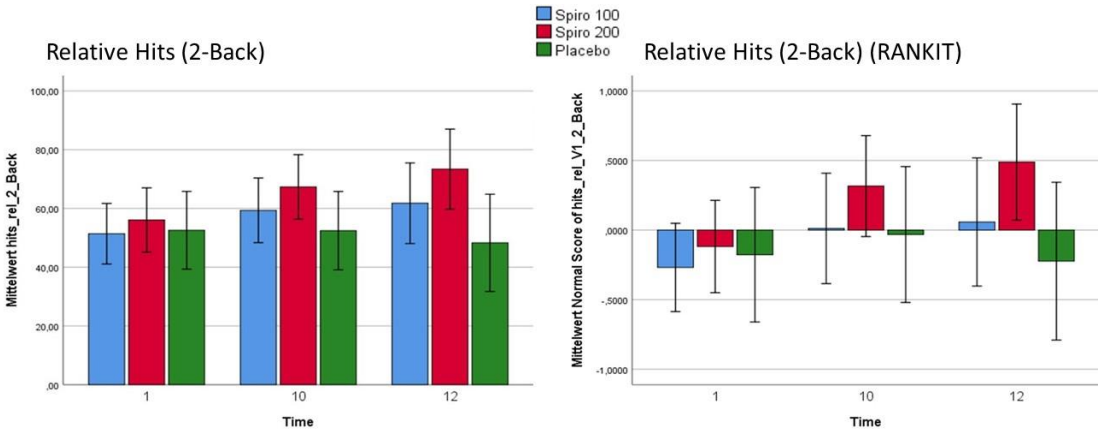

Figure 3: Visualisation of 2-back outcome data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Secondary Endpoints

In agreement with the primary endpoint analyses, the LMM of 1-back and 0-back did also not show a significant time x group interaction ($F_{(2, 76.810)}$ = 0.539, p = 0.586; $F_{(2, 75.473)}$ = 0.034 p = 0.967). While for 1-back, a significant effect of time (p = 0.002; improved for V10 vs. V1) could be observed, this was not detected for 0-back (p = 0.173). Extending the 2-back analyses to all three visits (V1, V10 and V12) in the ITT-population there was again no significant time x group interaction (p = 0.593). While the descriptive data indicates - as shown in **Figure 3** - an

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improvement in both intervention groups (100/200 mg spironolactone), this could not be confirmed in the respective statistical analyses (see **Table 11**).

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Konstanter Term	1	71.897	0.093	0.761
Time	2	59.993	9.079	0.000
Group	2	75.601	0.354	0.703
Gender	1	75.622	0.732	0.395
Center	2	69.790	0.811	0.449
Age	1	75.023	7.572	0.007
School_years	1	72.294	5.113	0.027
Time * Group	4	59.906	0.703	0.593

Table 11: LMM analyses for 2-Back, relative hits across all three timepoints (performed on Rankit transformed data)

In agreement with the 2-Back analyses, also the 1-Back (p=0.607) and 0-Back (p=0.643) condition showed no time x group interactions using the Rankit-transformed data as shown in **Tables 12 and 13**.

Apart from the variables VLMT WF, CDSS and CGI all secondary clinical outcome variables were normally distributed or fulfilled this assumption after Rankit transformation. **Tables 12 and 13** show the descriptive data and the time x group interaction for the comparison V1 vs. V10 (Table 12) and V1 vs. V10 vs. V12 (Table 13). For those variables that did not fulfil the requirements for LMM, non-parameteric analyses are displayed separately (see page 14).

All LMM analyses detailed below showed - apart from a significant time x group interaction for GAF - no significant effect. A detailed analysis of GAF is shown below.

Item	V1			V10			Time x Group Interaction		
	100	200	PLC	100	200	PLC	Df	F	p
2-Back relative hits	51.39±27.63	56.05±28.23	52.56±32.78	59.35±29.48	67.34±27.77	52.43±29.33	2, 74.882	0.606	0.548
1-Back relative hits	64.74±29.80	70.01±31.34	65.19±34.09	71.15±28.24	79.68±25.08	68.62±28.45	2, 76.810	0.539	0.586
0-Back relative hits	89.09±19.42	96.39±4.99	91.76±15.62	93.73±9.10	95.50±12.28	96.03±4.69	2, 75.473	0.034	0.967
VLMT 5th trial	11.20±2.310	11.64 ± 2.93	10.32±2.81	11.37±2.74	11.30±3.28	11.09±2.76	2, 74.870	1.014	0.368
VLMT 7th trial	8.43±3.24	9.86±4.08	8.08±3.43	8.33±3.89	9.54±4.00	8.45±3.74	2, 75.016	0.377	0.687
VLMT trial 5 minus 7	2.80±2.34	1.79±1.97	2.20±1.71	3.07±2.64	1.81±1.67	2.68±2.19	2, 76.428	0.086	0.918
VLMT trial 1 to 5	45.43±9.76	49.86±14.34	42.36±13.02	46.73±10.19	49.67±14.13	46.82±12.40	2, 75.771	0.989	0.412
VLMT recognition	11.23±3.72	12.39±3.34	10.68±4.39	10.40±4.26	10.63±5.44	9.86±5.05	See nonparametric results		
TMT A [sec]	39.57±19.04	36.07±15.63	34.69±13.59	32.97±12.86	29.56±11.40	31.32±10.50	2, 77.136	0.823	0.443
TMT B [sec]	100.13±67.09	87.82±41.83	107.08±57.16	93.83±48.23	74.48±35.22	96.68±47.77	2, 75.744	0.985	0.378
TMT B-A [sec]	60.57±58.11	51.75±33.58	72.38±46.09	60.87±38.74	44.93±26.58	65.55±41.14	2, 76.591	1.692	0.191
d2 total signs	393.48±111.8	431.25±91.93	395.44±118.1	408.69±115.1	466.30±90.14	429.57±100.3	2, 72.358	1.794	0.174
d2 failures	23.97±20.62	26.11±18.10	28.04±35.13	19.62±14.02	22.07±15.31	20.62±19.45	2, 72.944	0.032	0.969
d2 failure %	6.28±6.42	6.07±4.92	6.45±7.13	5.02±4.20	4.83±3.33	5.13±5.69	2, 72.116	0.032	0.969
d2 total minus failures	366.07±105.0	409.07±84.32	364.48±106.6	388.90±114.6	444.56±89.8	408.95±102.2	2, 72.200	1.201	0.307
d2 concentration score	141.97±47.20	156.25±42.46	139.88±61.24	157.52±48.30	176.67±43.88	152.19±60.73	2, 72.988	0.435	0.649
GAF	56.90±9.04	61.75±10.47	57.96±7.37	63.30±10.93	63.70±11.49	59.45±9.76	2, 75.078	5.619	0.005*
CDSS	3.82±3.30	2.07±3.07	2.81±2.19	3.10±2.87	2.15±2.80	3.68±4.67	See nonparametric results		
CGI	3.97±0.67	3.75±0.70	4.00±0.63	3.73±0.74	3.56±0.80	3.91±0.68	See nonparametric results		

Table 12: LMM analyses for main secondary outcome variables (V1 vs V10). Data is presented as mean ± SD

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Item	V1			V10			V12			Time x Group Interaction		
	100	200	PLC	100	200	PLC	100	200	PLC	Df	F	p
2-Back relative hits	51.39±27.63	56.05±28.23	52.56±32.78	59.35±29.48	67.34±27.77	52.43±29.33	61.77±28.48	73.38±27.40	48.29±27.40	4, 59.906	0.703	0.593
1-Back relative hits	64.74±29.80	70.01±31.34	65.19±34.09	71.15±28.24	79.68±25.08	68.62±28.45	72.94±27.66	83.97±21.92	61.93±29.71	4, 59.829	0.682	0.607
0-Back relative hits	89.09±19.42	96.39±4.99	91.76±15.62	93.73±9.10	95.50±12.28	96.03±4.69	93.17±12.84	98.35±4.15	94.41±9.02	4, 60.417	0.63	0.643
VLMT 5th trial	11.20±2.310	11.64 ± 2.93	10.32±2.81	11.37±2.74	11.30±3.28	11.09±2.76	11.00±2.87	11.11±3.16	9.38±3.23	4, 58.312	0.668	0.617
VLMT 7th trial	8.43±3.24	9.86±4.08	8.08±3.43	8.33±3.89	9.54±4.00	8.45±3.74	7.75±3.93	9.22±4.85	6.54±2.88	4, 59.768	0.463	0.762
VLMT trial 5 minus 7	2.80±2.34	1.79±1.97	2.20±1.71	3.07±2.64	1.81±1.67	2.68±2.19	3.55±2.24	1.89±2.03	2.85±2.19	4, 63.729	0.235	0.918
VLMT trial 1 to 5	45.43±9.76	49.86±14.34	42.36±13.02	46.73±10.19	49.67±14.13	46.82±12.40	44.40±12.92	48.28±13.99	39.77±12.48	4, 57.,614	0.695	0.598
VLMT recognition	11.23±3.72	12.39±3.34	10.68±4.39	10.40±4.26	10.63±5.44	9.86±5.05	10.00±4.81	11.61±3.01	7.17±5.24	See nonparametric results		
TMT A [sec]	39.57±19.04	36.07±15.63	34.69±13.59	32.97±12.86	29.56±11.40	31.32±10.50	33.00±12.04	26.61±9.66	33.92±9.74	4, 61.333	1.292	0.283
TMT B [sec]	100.13±67.09	87.82±41.83	107.08±57.16	93.83±48.23	74.48±35.22	96.68±47.77	90.75±52.70	68.56±46.59	100.00±38.72	4, 61.057	1.327	0.27
TMT B-A [sec]	60.57±58.11	51.75±33.58	72.38±46.09	60.87±38.74	44.93±26.58	65.55±41.14	57.75±45.27	41.94±40.36	66.08±30.36	4, 62.680	1.632	0.177
d2 total signs	393.48±111.8	431.25±91.93	395.44±118.1	408.69±115.1	466.30±90.14	429.57±100.3	424.25±113.9	487.11±96.25	419.00±119.9	4, 56.802	0.886	0.478
d2 failures	23.97±20.62	26.11±18.10	28.04±35.13	19.62±14.02	22.07±15.31	20.62±19.45	20.35±13.83	15.00±12.56	28.67±31.91	4, 61.911	1.866	0.128
d2 failure %	6.28±6.42	6.07±4.92	6.45±7.13	5.02±4.20	4.83±3.33	5.13±5.69	4.84±3.27	3.18±2.54	7.03±8.96	4, 65.359	1.364	0.256
d2 total minus errors	366.07±105.0	409.07±84.32	364.48±106.6	388.90±114.6	444.56±89.8	408.95±102.2	413.90±120.2	466.61±96.38	390.33±117.9	4, 56.730	0.878	0.483
d2 concentration	141.97±47.20	156.25±42.46	139.88±61.24	157.52±48.30	176.67±43.88	152.19±60.73	158.45±49.24	190.89±45.84	147.42±55.64	4, 50.064	0.873	0.487
GAF	56.90±9.04	61.75±10.47	57.96±7.37	63.30±10.93	63.70±11.49	59.45±9.76	64.10±10.37	67.00±11.42	62.43±11.34	4, 60.225	2.973	0.026*
CDSS	3.82±3.30	2.07±3.07	2.81±2.19	3.10±2.87	2.15±2.80	3.68±4.67	2.35±3.34	1.68±2.60	3.47±3.80	See nonparametric results		
CGI	3.97±0.67	3.75±0.70	4.00±0.63	3.73±0.74	3.56±0.80	3.91±0.68	3.90±0.79	3.37±0.89	3.47±0.99	See nonparametric results		

Table 13: LMM analyses for main secondary outcome variables (V1 to V12). Data is presented as mean ± SD

***GAF analyses**:* GAF analyses show - apart from the time x group interactions (V1 vs. V10: p = 0.005; V1 vs V10 vs. V12: p = 0.026) - a significant effect of time (all p<0.001). The interaction is mainly driven by a subtle improvement in the spironolactone 100 mg group (V1 vs. V10), but as the mean increase in GAF is below 10 points, this effect can be considered to be not clinically relevant. The mean GAF values are presented in the Tables 12 and 13 and a visualization can be found in Figure 4.

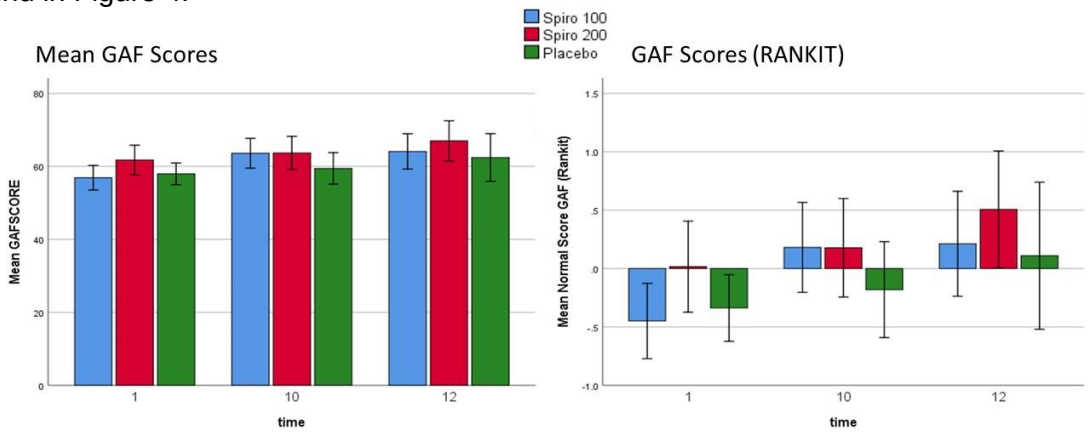

Figure 4: Visualisation of GAF outcome data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

From the analysis of remaining neuropsychologic tests, we received no significant time x group interactions for VLMT (all p> 0.368), for TMT (all p> 0.191) and for d2 test (all p> 0.174) for the V1 vs. V10 comparison, nor for the V1 vs. V10 vs. V12 comparison (VLMT: all p> 0.598, TMT: all p> 0.177, d2 test: all p> 0.128) (see tables 12 and 13). For VLMT recognition, nonparametric Kruskal-Wallis tests revealed no significant group differences at V1, V10 or V12 (all p > 0.058). For CGI severity score, from Kruskal-Wallis tests there were no significant group effects at any visit (all p > 0.119). For CDSS Kruskal-Wallis tests showed significant group effects only at V1 (p = 0.024), following Mann-Whitney U-tests resulted in a significantly larger CDSS score in the Spironolactone 100 compared to the Spironolactone 200 group (Sidak-corrected p = 0.036).

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Remission rates: Based on PANSS (see detailed analyses below), the RSWG remission criteria (Andreasen criteria) were calculated. The RSWG criteria link DSM-IV symptoms of schizophrenia with items of the Positive and Negative Syndrome Scale (PANSS): Here, three symptom clusters need to be considered: (1) psychoticism/reality distortion (PANSS items: delusions, unusual thought content and hallucinatory behaviour), (2) disorganisation (PANSS items: conceptual disorganisation and mannerisms/posturing), and (3) negative symptoms (PANSS items: blunted affect, social withdrawal, lack of spontaneity). According to the RSWG criteria, the symptomatic criterion states that to achieve symptomatic remission all items (P1, G9, P3, P2, G5, N1, N4 and N6) must be rated as absent or present only to a mild degree (PANSS value ≤ 3). We tested the frequency of symptomatic remission according to this criterion at V10 ($Chi^2_{(2)}$=1.169, p = 0.557) and V12 ($Chi^2_{(2)}$=3.632, p = 0.163), but could not detect significant differences across different groups (see **Table 14**).

Crosstab

			Gruppe			
			Spiro 100	Spiro 200	Placebo	Total
Andreasen Criterium V10	nein	Count	8	9	9	26
		% within Gruppe	26.7%	33.3%	40.9%	32.9%
	ja	Count	22	18	13	53
		% within Gruppe	73.3%	66.7%	59.1%	67.1%
Total		Count	30	27	22	79
		% within Gruppe	100.0%	100.0%	100.0%	100.0%

Crosstab

			Gruppe			
			Spiro 100	Spiro 200	Placebo	Total
Andreasen Criterium V12	nein	Count	7	2	5	14
		% within Gruppe	35.0%	10.5%	33.3%	25.9%
	ja	Count	13	17	10	40
		% within Gruppe	65.0%	89.5%	66.7%	74.1%
Total		Count	20	19	15	54
		% within Gruppe	100.0%	100.0%	100.0%	100.0%

Table 14: Distribution of remission status at V10 (top table) and V12 (lower table)

PANSS analyses: We used the Positive and Negative Syndrome Scale (PANSS) to measure psychopathology in our schizophrenia patients at several timepoints of the study. PANSS is a 30-item rating scale that has been developed to investigate the severity of psychopathology in schizophrenia patients. The scale is composed of three subscales (positive, negative, general) and one total scale. As PANSS was assessed more frequently during the study course than the aforementioned secondary endpoints, PANSS outcomes are presented separately.

Please see **Figure 5** for the course of the PANSS subscales and the visualisation of the Rankit transformed data. For all PANSS analyses no significant time x group interaction could be observed in the LMM analyses:

- **$PANSS_{Positive}$** $F_{(12, 72.495)}$ = 1.100, p = 0.374
- **$PANSS_{Negative}$** $F_{(12, 71.851)}$ = 1.015, p = 0.445
- **$PANSS_{General}$** $F_{(12, 67.873)}$ = 1.097, p = 0.377
- **$PANSS_{Total}$** $F_{(12, 72.261)}$ = 1.518, p = 0.138

In general, a subtle decrease in all PANSS values over the trial period was observed. This pattern did not show any differences across groups and can be expected in such trials as being in a trial provides social and emotional support for study patients by the research teams resulting in a secondary improvement of psychopathology.

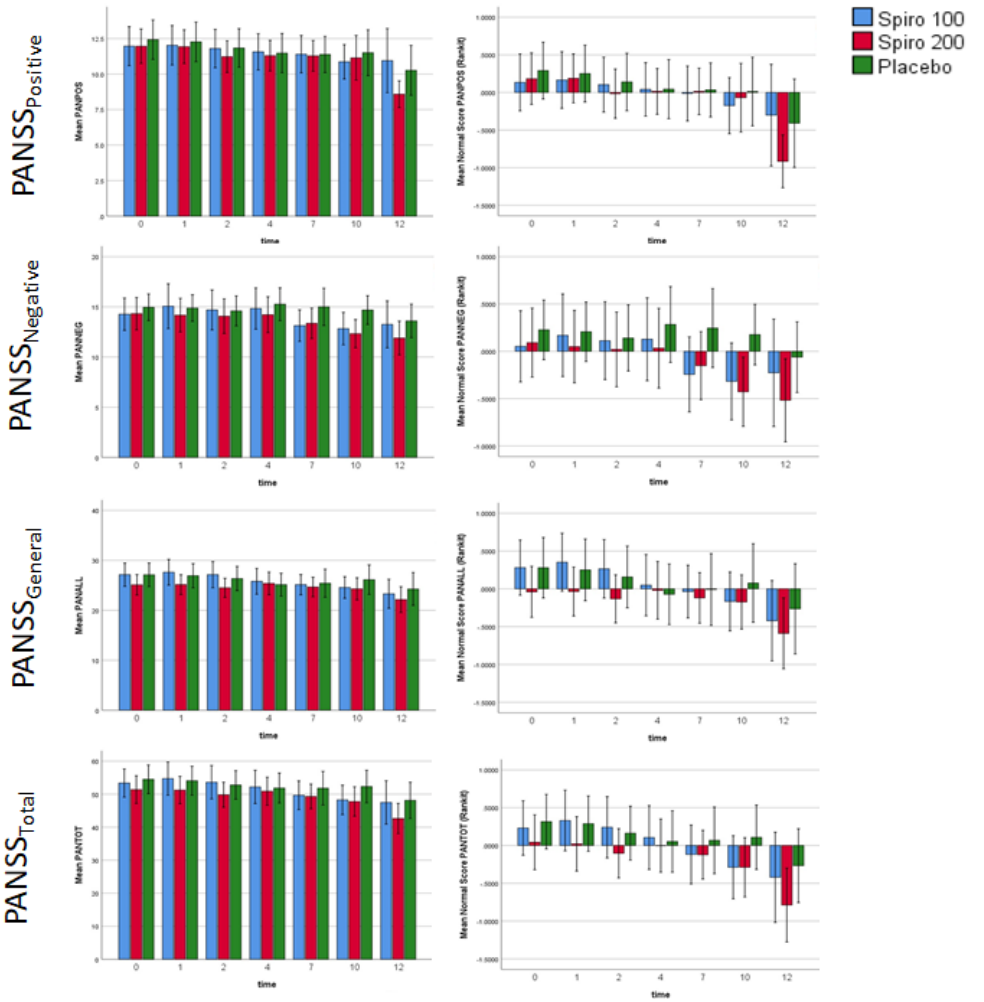

Figure 5: Visualisation of PANSS outcome data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

All spironolactone patients vs placebo group: As a further secondary analysis, we performed a LMM for the primary endpoint analysis (relative hits from 2-Back test) comparing all patients who were randomized to spironolactone (100 mg and 200 mg as a group) versus placebo. Again, LMM did not show a significant time x group interaction for the comparisons V1 vs V10 ($F_{(1, 76.709)}$ = 0.602, p = 0.440) and V1 vs. V10 vs. V12 ($F_{(2, 61.859)}$ = 0.872, p = 0.423). Both analyses showed a group unspecific effect of time (p=0.002; p=0.004) indicating intervention-independent learning effects of the working-memory task.

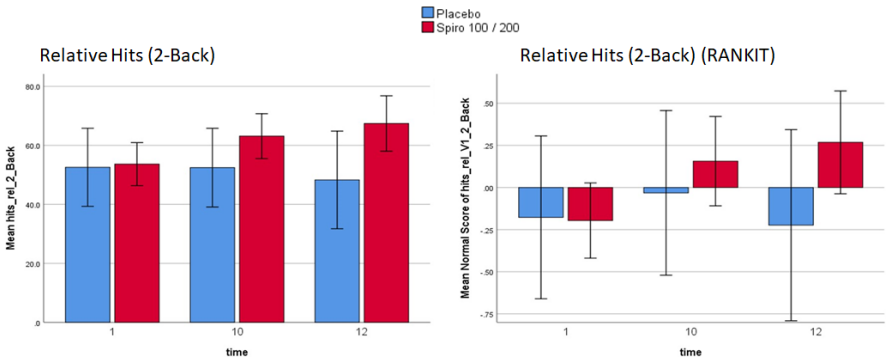

Figure 6: Visualisation of 2-back outcome data (both spironolactone groups vs. placebo) (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

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Sensitivity analyses restricted to patients from the Ludwig Maximilian University (LMU): As most patients (71 of 84 from the ITT population) were recruited at one centre, we repeated the primary endpoint analysis and the 2-back analysis across all three timepoints exclusively for patients recruited from the center LMU Munich. Again, no significant time x group interactions (V1 vs V10: $F_{(2, 63.099)} = 0.500$, $p = 0.609$; V1 vs V10 vs V12: $F_{(4, 48.029)} = 0.592$, $p = 0.670$) were observed.

Laboratory measures (potassium, sodium, creatinine)
As electrolyte abnormalities are known and an effect of spironolactone was expected, special attention was paid to the courses of sodium (Na) and potassium (KAL) and the creatinine (KREA) values. As expected, we were able to observe an increase in potassium levels and a decrease in sodium levels during the intervention period that normalized after the end of the intervention. These analyses are presented for all available timepoints. LMM showed a significant time x group interaction ($p = 0.005$) and several other expected effects for the potassium (KAL) level analyses. **Figure 7** shows the course of potassium levels over time (visit 1 to 12) with raw and Rankit transformed values. Please see **Table 15** for the respective analyses.

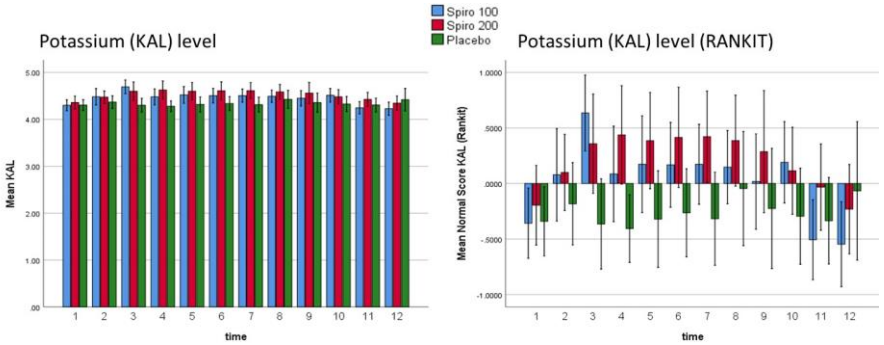

Figure 7: Visualisation of potassium levels data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	68.076	0.786	0.378
Time	11	68.208	4.955	0.000
Gruppe	2	71.832	4.795	0.011
Gender	1	72.833	2.418	0.124
Center	2	65.563	7.764	0.001
Age	1	68.418	4.789	0.032
School_Years	1	66.539	0.145	0.704
Time * Gruppe	22	69.712	2.256	0.005

Table 15: LMM outcome for the potassium analyses (performed on Rankit transformed data)

Despite Rankit transformation, the assumption of normality was not met for the sodium analyses. Thus, non-parametric tests were used. Kruskal-Wallis tests showed significant between-group differences for visits V4 ($p = 0.003$), V5 ($p = 0.002$), V6 ($p = 0.005$), V7 ($p = 0.003$) and V8 ($p = 0.015$). All other visits showed no between-group differences (all $p > 0.098$). In all visits with significant between-group differences the spironolactone groups showed significant differences or were on trend level in the Sidak-corrected Mann-Whitney U-tests compared to placebo (all p between 0.056 and 0.003), but not between each other (all $p > 0.686$). Please see **Figure 8** for the visualization of the sodium level course and the Rankit transformed data for the visualisation of between group differences.

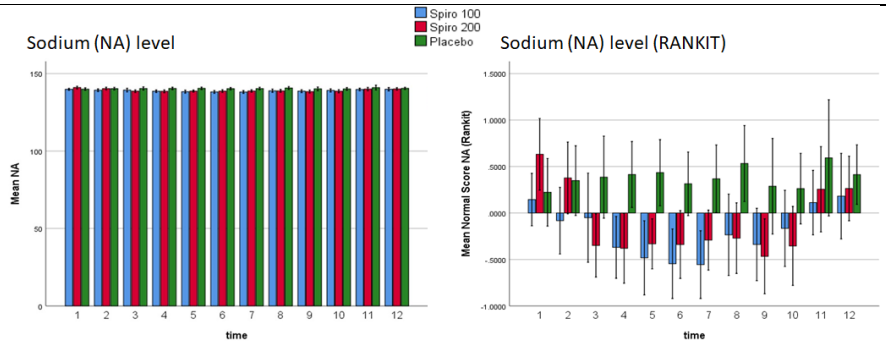

Figure 8: Visualisation of sodium data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Despite Rankit transformation, the assumption of normality was not met for the creatinine analyses. Thus, non-parametric tests were used. Kruskal-Wallis tests showed significant between-group differences for visits V5 (p = 0.042) and V9 (p = 0.039). All other visits showed non-significant between-group differences (all p > 0.056). In visit V5 a significant difference in creatinine between the spironolactone 200mg and the placebo group (p = 0.036) was shown using Sidak-corrected Mann-Whitney U-Tests. In visit V9 the same pattern could be observed (p = 0.033). Please see **Figure 9** for the visualization of the sodium level course and the Rankit transformed data for the visualisation of between-group differences.

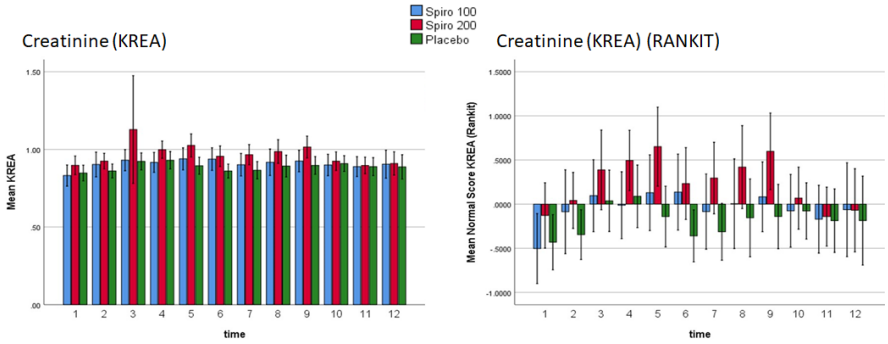

Figure 9: Visualisation of creatinine data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Blood pressure and heart rate

Including data of all points in time LMM did not show significant time x group interactions for systolic ($F_{(14, 70.847)}$ = 0.512, p = 0.919) and diastolic blood pressure values ($F_{(14, 70.444)}$ = 0.756, p = 0.712). However, for systolic blood pressure a significant (p = 0.027) and for diastolic blood pressure a trend (p = 0.052) was observed for within subject-fator time. This can be explained by the expected effect of a blood pressure-lowering effect of spironolactone during the intervention period. Please see **Figures 10 and 11** for a presentation of the course of blood pressure (BP).

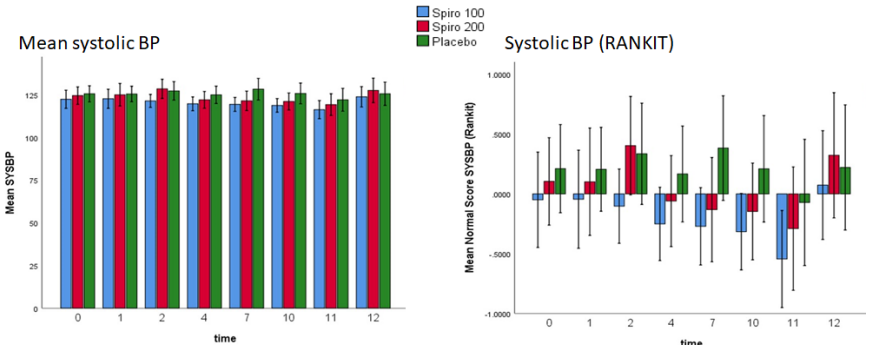

Figure 10: Visualisation of systolic blood pressure (BP) data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

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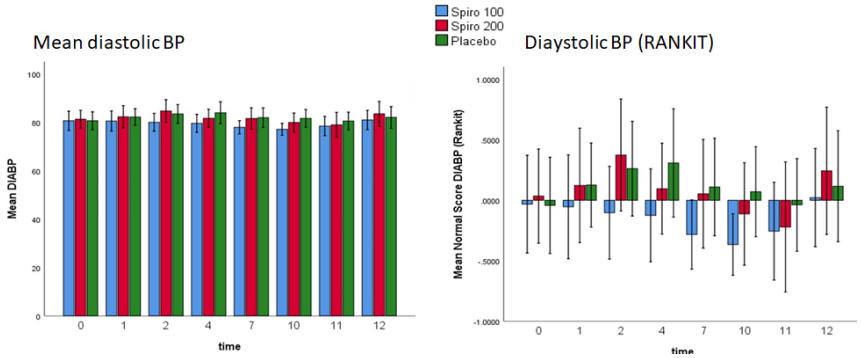

Figure 11: Visualisation of diasystolic blood pressure (BP) data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

For heart rate, no significant time x group interaction (p = 0.713) and no significant effect of time (0.071) was observed. Please see **Figure 12** for a detailed presentation of the course of heart rate values over time.

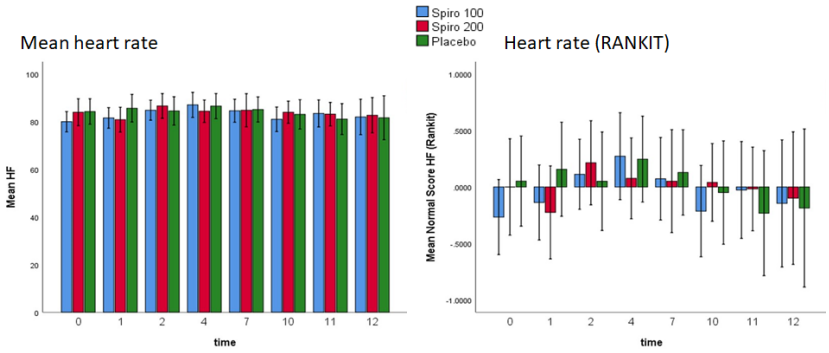

Figure 12: Visualisation of heart rate data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Body mass index (BMI)
For BMI, no significant time x group interaction (p = 0.540) and no significant effect of time (0.143) was observed. Please see **Figure 13** for a presentation of the course of BMI.

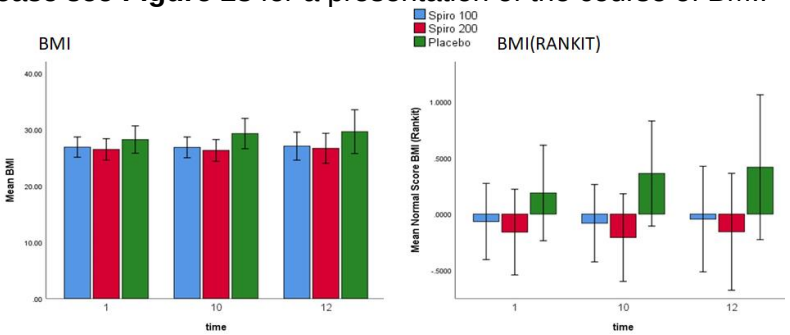

Figure 13: Visualisation of BMI data (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

For the Simpson-Angus scale (SiAS), Kruskal-Wallis tests revealed no significant group differences for V1, V10 or V12 (all p > 0.214).

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Additional analyses

As indicated above, this trial had two optional investigations: TMS measures and mRNA measures from peripheral blood. These measures were defined as exploratory biological measures and the results are not available yet.

Per Protocol analyses

As predefined in our protocol and the statistical analyses plan (SAP), ITT-analyses presented above are the main analyses for this study. However, we also performed analyses on the per-protocol population.

For the primary endpoint analyses, a repeated-measures ANCOVA with the same covariates used in the LMM was applied. These analyses confirmed the negative finding from the LMM analyses in the intention-to-treat-population. Again, no time x group interaction was observed for the V1 vs V10 contrast ($F_{(2, 60)}$ = 0.141, p = 0.869).The effect size of this interaction it *partial η²* = 0.005 (related to f = 0.07). Please see **Figure 14** for the presentation of the primary outcome in the per protocol population.

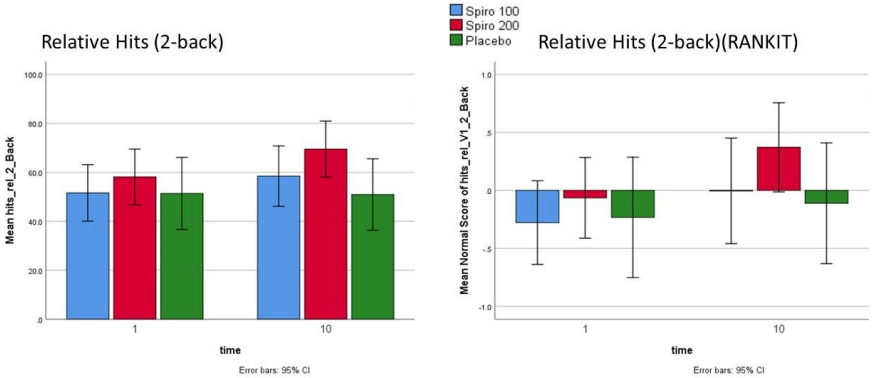

Figure 14: Visualisation of 2-back outcome data (primary endpoint in the per protocol analysis) (left: mean values; right: Rankit transformed data). Error bars refer to 95%CI

Due to the negative outcome of the study with no relevant between group-differences for any of the outcome or safety variables, we focussed the per protocol analyses for this report on the primary endpoint analyses. All other per protocol analyses did not reveal any relevant differences compared to the ITT-population regarding efficacy or safety outcomes.

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Overall Conclusion

This trial was negative regarding the primary endpoint. Against our assumptions, the add-on treatment with spironolactone did not result in a significantly improved cognitive performance according to the relative 2-back hit rate.

In detail, we were not able to establish a significant superiority of add-on spironolactone 100 mg or 200mg compared to placebo in improving working memory function according to the 2-Back relative hit rate in patients with schizophrenia. The same pattern was observed in the per protocol analyses and in one respective sensitivity analysis. While the numeric data indicates an effect of spironolactone (especially 200 mg), this could not be confirmed by any of the presented analyses. This can be explained by the relevant variance of the data as shown in the error bars of the respective figures.

All secondary efficacy endpoint analyses, apart from a subtle, but clinical not relevant effect on GAF measurement, were also negative.

The safety profile was in accordance with the previously reported safety profile of spironolactone. No new aspects of safety could be observed. As expected, spironolactone resulted in a decrease of sodium (Na) and an increase of potassium (K) in the spironolactone groups. These effects were observed during the intervention phase, but as expected not during the follow-up phase.

Two SAEs and a total of 154 AEs were reported in 84 patients. Disease-related adverse events, such as worsening of psychotic symptoms or hospitalization were not related to the treatment according to the assessment made by the investigators. No treatment-related severe adverse events, death or SUSAR were reported in this study. No fatal outcomes during the trial were observed.

Appendix

Supplementary Table 1: Cumulative Summary Tabulation of Adverse Events (German Language)

MedDRA System Organ Class. SOC / Preferred Term. PT	Ergebnis (N)	%
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	**16**	**10.39**
Asthenie	1	
Durst	1	
Ermuedung	10	
Grippeaehnliche Erkrankung	1	
Oedem peripher	1	
Schmerz	1	
Traegheit	1	
Augenerkrankungen	**1**	**0.65**
Blepharospasmus	1	
Chirurgische und medizinische Eingriffe	**2**	**1.3**
Krankenhausaufenthalt	1	
Varizenoperation	1	
Erkrankungen der Geschlechtsorgane und der Brustdruese	**4**	**2.6**
Amenorrhoe	2	
Dysmenorrhoe	1	
Hodenschmerz	1	
Erkrankungen der Haut und des Unterhautgewebes	**3**	**1.95**
Ausschlag	1	
Ekzem	1	
Hyperhidrosis	1	
Erkrankungen der Nieren und Harnwege	**10**	**6.49**
Dranginkontinenz	2	
Dysurie	1	
Harndrang	2	
Nierenschmerz	1	
Pollakisurie	4	
Erkrankungen des Blutes und des Lymphsystems	**5**	**3.25**
Leukozytose	3	
Lymphadenopathie	1	
Thrombozytose	1	
MedDRA System Organ Class. SOC preferred term. pt	**Ergebnis**	**%**
Erkrankungen des Gastrointestinaltrakts	**11**	**7.14**
Abdominaler Druckschmerz	1	
Abdominalschmerz	2	
Diarrhoe	2	
Dyspepsie	1	
Gastrooesophageale Refluxerkrankung	1	
Hypersalivation	1	
Obstipation	1	
Uebelkeit	2	
Erkrankungen des Nervensystems	**29**	**18.83**
Akathisie	1	
Dysmetrie	1	
Kopfschmerzen	5	
Psychomotorische Hyperaktivitaet	1	
Schwindel orthostatisch	2	
Schwindelgefuehl	11	
Schwindelgefuehl bei Belastung	1	
Somnolenz	1	
Syndrom der ruhelosen Beine	1	
Tremor	5	
Gefaesserkrankungen	**4**	**2.6**
Hypertonie	1	
Hypotonie	1	
Periphere Venenerkrankung	1	
Varizen	1	
Herzerkrankungen	**8**	**5.19**
Arrhythmie	1	
Bradykardie	1	
Palpitationen	1	
Supraventrikulaere Extrasystolen	1	
Tachykardie	3	
Ventrikulaere Extrasystolen	1	
Infektionen und parasitaere Erkrankungen	**10**	**6.49**
Bakterielle Infektion	1	

Febrile Infektion	1	
Infektion	1	
Infektion der oberen Atemwege	1	
Nasopharyngitis	3	
Picorna-Virusinfektion	1	
Subkutaner Abszess	1	
Virusinfektion	1	
Psychiatrische Erkrankungen	**23**	**14.94**
Affekterkrankung	1	
Angst	1	
MedDRA System Organ Class. SOC preferred term. pt	**Ergebnis**	**%**
Apathie	3	
Depression	1	
Eingeschraenkter Affekt	1	
Halluzination	1	
Psychose	6	
Schlaflosigkeit	1	
Schlafstoerung	3	
Suizidgedanken	1	
Unruhe	4	
Skelettmuskulatur-. Bindegewebs- und Knochenerkrankungen	**6**	**3.9**
Arthralgie	1	
Muskelspasmen	2	
Muskuloskelettale Steifigkeit	2	
Schmerzen des Muskel- und Skelettsystems	1	
Stoffwechsel- und Ernaehrungsstoerungen	**16**	**10.39**
Appetit vermindert	2	
Folatmangel	1	
Hyperkaliaemie	13	
Untersuchungen	**6**	**3.9**
C-reaktives Protein erhoeht	1	
Gewicht erhoeht	1	
Kalium im Blut erhoeht	3	
Kreatinin im Blut erhoeht	1	
Gesamtergebnis	**154**	**100**

Supplementary Table 2: Cumulative Summary Tabulation of Adverse Events (Englisch Language)

MedDRA System Organ Class. SOC Preferred Term. PT	**Results (N)**	**%**
General disorders and administration site conditions	**16**	**10.39**
Asthenia	1	
Thirst	1	
Fatigue	10	
Flu-like illness	1	
Edema peripheral	1	
Pain	1	
Lethargy	1	
Eye disorders	**1**	**0.65**
Blepharospasm	1	
Surgical and medical procedures	**2**	**1.3**
Hospitalization	1	
Varicose vein operation	1	
Reproductive system and breast disorders	**4**	**2.6**
Amenorrhea	2	
Dysmenorrhea	1	
Testicular pain	1	
Skin and subcutaneous tissue disorders	**3**	**1.95**
Rash	1	
Eczema	1	
Hyperhidrosis	1	
Renal und urinary disorders	**10**	**6.49**
Urge incontinence	2	
Dysuria	1	
Urgency urination	2	
Kidney pain	1	
Pollakisuria	4	
Blood and lymphatic system disorders	**5**	**3.25**
Leukocytosis	3	
Lymphadenopathy	1	

Thrombocytosis		1	
Gastrointestinal disorders		**11**	**7.14**
Abdominal tenderness		1	
Abdominal pain		2	
Diarrhea		2	
Dyspepsia		1	
Gastroesophageal reflux disease		1	
Hypersalivation		1	
Obstipation		1	
Nausea		2	
Nervous system disorders		**29**	**18.83**
Akathisia		1	
Dysmetria		1	
MedDRA System Organ Class. SOC	**preferred term. pt**	**Results**	**%**
Headache		5	
Psychomotor hyperactivity		1	
Orthostatic dizziness		2	
Dizziness		11	
Dizziness exertional		1	
Somnolence		1	
Restless leg syndrome		1	
Tremor		5	
Vascular disorders		**4**	**2.6**
Hypertension		1	
Hypotension		1	
Peripheral venous disease		1	
Varicose veins of lower extremities		1	
Cardiac disorders		**8**	**5.19**
Arrhythmia		1	
Bradykardia		1	
Palpitations		1	
Supraventricular extrasystoles		1	
Tachykardia		3	
Ventricular extrasystoles		1	
Infections and infestations		**10**	**6.49**
Bacterial infection		1	
Febrile infection		1	
Infection		1	
Upper respiratory tract infection		1	
Nasopharyngitis		3	
Picornavirus infection		1	
Subcutaneous abscess		1	
Viral infection		1	
Psychiatric disoders		**23**	**14.94**
Affective disorder		1	
Fear		1	
Apathy		3	
Depression		1	
Affect lack		1	
Hallucinations		1	
Psychosis		6	
Insomnia		1	
Sleep disorder		3	
Suicidal ideation		1	
Restlessness		4	
Musculoskeletal and connective tissue disorders		**6**	**3.9**
Arthralgia		1	
Muscle spasms		2	
MedDRA System Organ Class. SOC	**preferred term. pt**	**Results**	**%**
Musculoskeletal stiffness		2	
Musculoskeletal pain		1	
Metabolism and nutrition disorders		**16**	**10.39**
Decreased appetite		2	
Folate dificiency		1	
Hyperkalemia		13	
Investigations		**6**	**3.9**
C-reactive protein increased		1	
Weight increased		1	
Blood potassium increased		3	
Blood creatinine increased		1	
Overall Result		**154**	**100**

Supplementary Table 3: CIOMS II Summary Tabulation

Study Short Name: SPIRO-TREAT / EudraCT: 2014-001968-35

Cumulative Summary Tabulation of all serious Adverse Events

System Organ Class Preferred Term	Number of events Total up to 04.08.2020
Cardiac disorders	**1**
Tachycardia	1
Investigations	**1**
Antipsychotic drug level below therapeutic	1
Psychiatric disorders	**3**
Psychotic disorder	2
Restlessness	1

Supplementary Table 4: Serious Adverse Events overview

SAE Overview SPIRO-TREAT / EudraCT: 2014-001968-35

Onset Date	SAE_Nr	PatientNr	Pat.Age	Sex	SAE-Type	Status	First Received	Expected ?	Relationship to IMP?	SUSAR
CenterNr: 001	**München, Klinikum der LMU**								**Number of SAEs: 2**	
14.12.2018	001-049-01	049	31	male	initial + follow-up	closed	14.12.2018	not done	not related	no
Reaction: re-hospitalization due to worsening of psychotic symptoms					SAE-Criteria: Involved or prolonged inpatient hospitalization			Outcome: Recovered		
31.01.2019	001-052-01	052	49	female	initial	closed	16.07.2019	not done	not related	no
Reaction: worsening of psychotic symptoms because of stopping taking antipsychotics					SAE-Criteria: Involved or prolonged inpatient hospitalization			Outcome: Recovered		

Total Number of SAEs: 2

Supplementary Table 5: Serious Adverse Events Safety Review

Sub-ID	Age	Sex	Reaction description	Onset Date	Resolved Date	Severity	Relation Drug	Outcome
001-049-01	31	male	re-hospitalization due to worsening of psychotic symptoms	14-Dez-18	27-Feb-19	moderate	not related	Recovered
001-052-01	49	female	worsening of psychotic symptoms because of stopping taking antipsychotics	31-Jan-19	01-Feb-19	moderate	not related	Recovered

Supplementary Table 6: List of Adverse Reactions (in German Language)

Site	Label	AE Beschreibung	Startdatum	NK	Stoppdatum	NK	SAE	Intensität	Kausalzusammenhang	Änderung Prüfsubstanz	Gegenmaßnahmen	andere Gegenmaßnahmen	Ausgang
lmu01	101	Schwindel	15.07.2015		17.07.2015		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	110	leichte Hyperkaliämie: 5,1mmol/l	09.03.2016		11.03.2016		nein	mild	wahrscheinlich	keine	andere	Pat.über reichliche Flüssigkeitszufuhr und K.arme Diät aufgeklärt.Keine klin.Symptome.Kontrolle.	wiederhergestellt
lmu01	112	Hypotoner RR	01.06.2016		06.06.2016		nein	mässig	wahrscheinlich	keine	andere	3xtgl RR Trinkmenge erhöhen	wiederhergestellt
lmu01	112	intermitt.Schwindel	11.06.2016		17.06.2016		nein	mild	wahrscheinlich	keine	andere	Trinkmenge erhöhen	wiederhergestellt
lmu01	112	Kopfschmerz	14.06.2016		17.06.2016		nein	mässig	wahrscheinlich	keine	andere	Trinkmenge erhöhen	wiederhergestellt
lmu01	115	Schwindel	14.07.2016		19.07.2016		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	121	Übelkeit	23.01.2017		23.01.2017		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	122	Kaliumerhöhung	13.02.2017		14.02.2017		nein	mässig	sicher	keine	andere	Kaliumarme Diät	wiederhergestellt
lmu01	122	Kaliumerhöhung	17.02.2017		20.02.2017		nein	mässig	sicher	keine	andere	Kaiumarme Diät	wiederhergestellt
lmu01	122	Hautexanthem	22.02.2017		24.02.2017		nein	mild	möglich	Unterbrechung	keine		wiederhergestellt
lmu01	122	Kaliumerhöhung	22.02.2017		24.02.2017		nein	mässig	sicher	Unterbrechung	andere	Kaliumarme Diät	wiederhergestellt
lmu01	124	Schwindel	23.03.2017		23.03.2017		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	130	Harndrang	15.09.2017	day NK	15.09.2017	day NK	nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	134	Hyperkaliämie	15.01.2018		16.01.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	136	Hyperkalemia I°	21.02.2018		22.02.2018		nein	mild	sicher	keine	andere	Kontrolle	wiederhergestellt
lmu01	136	Hyperkalemia I°	28.02.2018		02.03.2018		nein	mild	sicher	keine	andere	Kontrolle	wiederhergestellt
lmu01	137	häufiges Wasserlassen	23.03.2018		02.04.2018		nein	mild	wahrscheinlich	keine	keine		wiederhergestellt
lmu01	137	Hyperkaliamämie	26.03.2018		27.03.2018		nein	mild	möglich	keine	andere	Kontrolle am 27.3. opB	wiederhergestellt
lmu01	140	Schwindelgefühle	02.05.2018		02.05.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	142	Kopfschmerzen	02.06.2018		06.06.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	144	Problemat. Wasserlassen	15.08.2018	day NK	30.08.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	144	vermehrter Durst	21.08.2018		30.08.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	146	häufiges Wasserlassen	09.10.2018		15.10.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	150	Hyperkaliämie	12.12.2018		13.12.2018		nein	mässig	wahrscheinlich	keine	andere	erneute Laborkontrolle am 13.12.18	wiederhergestellt
lmu01	151	Häufiges Wasserlassen	01.02.2019		06.02.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	153	Schwindel	23.04.2019		29.04.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	158	Orthostase Schwindel	17.07.2019		19.07.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	158	orthostat. Schwindel	29.07.2019		02.08.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	162	häufiges Wasserlassen	09.10.2019		21.10.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	167	Hyperkaliämie Grad II	13.11.2019		14.11.2019		nein	mässig	wahrscheinlich	Unterbrechung	andere	Kontrolle 14.11.2019	wiederhergestellt
lmu01	167	Hyperkaliämie Grad I	14.11.2019		18.11.2019		nein	mild	wahrscheinlich	Unterbrechung	andere	Kontrolle 18.11.	wiederhergestellt
lmu01	170	Hyperkaliämie	17.02.2020		21.02.2020		nein	mild	möglich	nicht anwendbar	andere	Kontrolle bei V11	wiederhergestellt
lmu01	171	Hyperkaliämie Grad I	03.02.2020		05.02.2020		nein	mild	wahrscheinlich	keine	andere	kaliumarme Kost weiter	wiederhergestellt
tum02	204	Fatigue	19.01.2017		02.02.2017		nein	mild	möglich	keine	keine		wiederhergestellt
tum02	205	Hyperkaliämie	03.02.2017		06.02.2017		nein	mässig	wahrscheinlich	Unterbrechung	medikamentöse Behandlung	z-CPS-Pulver + Bifiteral + Kontrolle	wiederhergestellt
tum02	211	Hyperkaliämie	18.03.2019		19.03.2019		nein	mild	möglich	Unterbrechung	keine		wiederhergestellt
reg03	301	leichter Schwindel	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Appetitlosigkeit	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Schweißausbrüche	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Schwindel	27.09.2017		28.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	302	leichte affektive Herabstimmung	02.10.2017			date NK	nein	mild	möglich	keine	keine		unbekannt
reg03	302	leichte Verschlechterung des Antriebs	02.10.2017			date NK	nein	mild	möglich	keine	keine		unbekannt
reg03	303	leichter Schwindel	12.02.2018		19.02.2018		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	305	erhöhter Harndrang	05.11.2018		09.11.2018		nein	mild	möglich	keine	keine		wiederhergestellt

Supplementary Table 6: List of Adverse Events (in German Language)

Site	Label	AE Beschreibung	Startdatum	NK	Stoppdatum	NK	SAE	Intensität	Kausalzusammenhang	Änderung Prüfsubstanz	Gegenmaßnahmen	andere Gegenmaßnahmen	Ausgang
lmu01	101	Schwindel	15.07.2015		17.07.2015		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	102	Ekzem, Brustbereich li	17.07.2015		20.07.2015		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	106	Zunahme psych.Erleben	21.01.2016		16.02.2016		nein	schwer	kein Zusammenhang	keine	medikamentöse Behandlung		wiederhergestellt
lmu01	108	Bauchkrämpfe	15.03.2016		15.03.2016		nein	mässig	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	108	elektive Varizen-OP	03.05.2016		05.05.2016		nein	mässig	kein Zusammenhang	nicht anwendbar	andere	OP	wiederhergestellt mit Folgesymptomen
lmu01	108	Zunahme psychot.Erlebens	09.05.2016				nein	mässig	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		unbekannt
lmu01	108	Bradykardie		Date NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	108	chron.venöse Insuffizienz		Date NK			nein	mässig	kein Zusammenhang	keine	keine		anhaltend
lmu01	108	Reflux (GERD I°)		Date NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	108	US-Varizen		Date NK			nein	mässig	kein Zusammenhang	keine	keine		anhaltend
lmu01	108	Drang-Inkontinenz		Date NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	110	leichte Hyperkaliämie: 5,1mmol/l	09.03.2016		11.03.2016		nein	mild	wahrscheinlich	keine	andere	Pat.über reichliche Flüssigkeitszufuhr und K.arme Diät aufgeklärt.Keine klin.Symptome.Kontrolle.	wiederhergestellt
lmu01	110	Zunahme psychot.Sympt.	14.03.2016		16.03.2016		nein	mild	unwahrscheinlich	keine	medikamentöse Behandlung		wiederhergestellt
lmu01	110	Norovirusinfektion	22.03.2016		27.03.2016		nein	mässig	kein Zusammenhang	keine	andere	Isolation bei v.a.Norovirus Infektion + Steigerung der Trinkmenge + regelmässig Vitalparameter	wiederhergestellt
lmu01	111	Unruhe	28.05.2016		29.05.2016		nein	mild	kein Zusammenhang	keine	andere	Reduktion AP	wiederhergestellt
lmu01	111	Ängste	28.05.2016		29.05.2016		nein	mild	kein Zusammenhang	keine	andere	Reduktion AP	wiederhergestellt
lmu01	112	Hypotoner RR	01.06.2016		06.06.2016		nein	mässig	wahrscheinlich	keine	andere	3xtgl RR Trinkmenge erhöhen	wiederhergestellt
lmu01	112	intermitt.Schwindel	11.06.2016		17.06.2016		nein	mild	wahrscheinlich	keine	andere	Trinkmenge erhöhen	wiederhergestellt
lmu01	112	Kopfschmerz	14.06.2016		17.06.2016		nein	mässig	wahrscheinlich	keine	andere	Trinkmenge erhöhen	wiederhergestellt
lmu01	114	Herzklopfen abends	14.07.2016		15.07.2016		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	115	vergrößerter Lymphknoten subman.links	07.07.2016		11.07.2016		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	115	Schwindel	14.07.2016		19.07.2016		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	115	Schlafstörung	01.09.2016		19.09.2016		nein	mässig	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		wiederhergestellt
lmu01	117	Tremor re. Hand	15.06.2016	day+month NK			nein	mild	kein Zusammenhang	nicht anwendbar	andere	Anpassung Begleitmedikation erfolgt	anhaltend
lmu01	117	Abdominaler Druckschmerz	14.11.2016		16.11.2016		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	120	Supraventrikuläre Extrasystolen im EKG	02.12.2016		22.12.2016		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	120	Unregelmäßiger Herzrythmus	02.12.2016		22.12.2016		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	120	Müdigkeit tagsüber	03.12.2016		05.12.2016		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	120	Ventrikuläre Extrasystole	21.02.2017		21.02.2017		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	121	Dysmetrie bei Koordinationsprüfng unter Extremitäten	23.01.2017		25.01.2017		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	121	Übelkeit	23.01.2017		23.01.2017		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	121	Appetitminderung	27.01.2017		14.02.2017		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	121	Niedergedrücktes Affekt	06.02.2017		16.02.2017		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	122	Kaliumerhöhung	13.02.2017		14.02.2017		nein	mässig	sicher	keine	andere	Kaliumarme Diät	wiederhergestellt
lmu01	122	Kaliumerhöhung	17.02.2017		20.02.2017		nein	mässig	sicher	keine	andere	Kaiumarme Diät	wiederhergestellt
lmu01	122	Kaliumerhöhung	22.02.2017		24.02.2017		nein	mässig	sicher	Unterbrechung	andere	Kaliumarme Diät	wiederhergestellt
lmu01	122	Hautexanthem	22.02.2017		24.02.2017		nein	mild	möglich	Unterbrechung	keine		wiederhergestellt
lmu01	123	Infekt obere Atemwege	09.03.2017		12.03.2017		nein	mässig	kein Zusammenhang	keine	andere	Bettruhe	wiederhergestellt
lmu01	123	Schwindel bei Sprint	14.03.2017		14.03.2017		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	124	Müdigkeit	15.03.2017	day NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend

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lmu01	124	Schwindel	23.03.2017		23.03.2017		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	124	Abzess Rücken	29.03.2017				nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung	celuroxim	anhaltend
lmu01	125	Periphere Ödeme	15.06.2015	day+month NK			nein	mässig	kein Zusammenhang	nicht anwendbar	andere	Pt. vormediziert mit Torasemid	anhaltend
lmu01	125	Amenorrhoe	15.06.2016	day+month NK			nein	mässig	kein Zusammenhang	nicht anwendbar	andere	amb. Vorstellung Gynökologie	anhaltend
lmu01	125	CRP - Erhöhung	15.06.2016	day+month NK			nein	mild	kein Zusammenhang	nicht anwendbar	andere	Kontrolle i.V.	anhaltend
lmu01	126	Antriebslosigkeit	15.02.2017	day NK	15.05.2017	day NK	nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung	Aripiprazol	wiederhergestellt
lmu01	126	Kraftlosigkeit	15.02.2017	day NK	15.05.2017	day NK	nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	127	Müdigkeit	15.05.2017	day NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	127	Tremor bds.	15.05.2017	day NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	127	Schlundkrampf	01.06.2017		02.06.2017		nein	mässig	unwahrscheinlich	Unterbrechung	medikamentöse Behandlung		wiederhergestellt
lmu01	128	Tagesmüdigkeit	29.07.2017				nein	mild	unwahrscheinlich	keine	keine		anhaltend
lmu01	129	gel. Tremor	15.02.2017	day NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	129	Gewichtszunahme	15.04.2017	day NK			nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung		anhaltend
lmu01	129	Steifigkeit	15.07.2017	day NK	15.09.2017	day NK	nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung	Biperiden	wiederhergestellt
lmu01	129	Kopfschmerzen	15.10.2017	day NK	15.10.2017	day NK	nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung	Tomapyrin	wiederhergestellt
lmu01	130	Kopfschmerzen	15.06.2016	day+month NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend
lmu01	130	Trägheit	15.01.2017	day NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend
lmu01	130	Benommenheit	15.05.2017	day NK	15.09.2017	day NK	nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	130	leichte Steifigkeit	15.06.2017	day NK	15.09.2017	day NK	nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	130	Hüftschmerzen	15.08.2017	day NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend
lmu01	130	Harndrang	15.09.2017	day NK	15.09.2017	day NK	nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	130	reduzierter Antrieb	15.09.2017	day NK	15.09.2017	day NK	nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	131	Bauchschmerzen	29.10.2017		29.10.2017		nein	mild	unwahrscheinlich	nicht anwendbar	keine		wiederhergestellt
lmu01	131	Erkältungssymptome, Halsschmerzen Rachenrötung, Müdigkeit, Husten mit Auswurf	05.02.2018		13.02.2018		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	133	Unruhe d. Beine	15.06.2015	day+month NK	15.01.2018	day NK	nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	133	Tagesmüdigkeit	15.06.2017	day+month NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend
lmu01	133	Folsäuremangel	15.10.2017	day NK	15.12.2017	day NK	nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung	Folsäure oral	wiederhergestellt
lmu01	133	Übelkeit b. Schlucken	15.10.2017	day NK			nein	mild	kein Zusammenhang	nicht anwendbar	keine		anhaltend
lmu01	133	fieberhafter Infekt	21.11.2017		15.12.2017	day NK	nein	mässig	unwahrscheinlich	keine	andere	Beurlaubung von Therapie	wiederhergestellt
lmu01	133	Durchfall	26.11.2017		26.11.2017		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	134	Tachykardie	15.06.2016	day+month NK			nein	mässig	kein Zusammenhang	keine	medikamentöse Behandlung	Bisoprolol	anhaltend
lmu01	134	Erschöpfung	04.10.2017				nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	134	Schlafprobleme	15.10.2017	day NK	15.01.2018	day NK	nein	mässig	kein Zusammenhang	keine	medikamentöse Behandlung	Mitrazapin	wiederhergestellt
lmu01	134	Hyperkaliämie	15.01.2018		16.01.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	134	Erkältung: upfen, rhimitis	22.01.2018		01.02.2018		nein	mild	kein Zusammenhang	keine	andere	konservativ körperl. Ruhe, Flüssigkeitseinnahme	wiederhergestellt
lmu01	134	Rücken. und Kopfschmerzen bei infekt	22.01.2018		01.02.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	135	erhöhter Speichelfluss	15.12.2017	day NK	15.01.2018	day NK	nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	135	Tremor re>li	15.12.2017	day NK	15.01.2018	day NK	nein	mässig	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	135	Tagesmüdigkeit	15.01.2018	day NK	15.01.2018	day NK	nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	136	Hyperkalemia I°	21.02.2018		22.02.2018		nein	mild	sicher	keine	andere	Kontrolle	wiederhergestellt
lmu01	136	Hyperkalemia I°	28.02.2018		02.03.2018		nein	mild	sicher	keine	andere	Kontrolle	wiederhergestellt

lmu01	136	unklarer bakterieller Infekt	09.03.2018		13.03.2018		nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		wiederhergestellt
lmu01	136	Urge-Inkontinenz	15.06.2018	day+month NK			nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		anhaltend
lmu01	137	häufiges Wasserlassen	23.03.2018		02.04.2018		nein	mild	wahrscheinlich	keine	keine		wiederhergestellt
lmu01	137	Hyperkaliämie	26.03.2018		27.03.2018		nein	mild	möglich	keine	andere	Kontrolle am 27.3. opB	wiederhergestellt
lmu01	139	leichter Schwindel	05.04.2018		09.04.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	140	Schwindelgefühle	02.05.2018		02.05.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	140	Hodenschmerzen	09.05.2018		11.05.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	140	Erschöpfung	15.05.2018	day NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	140	Psychomotorische Unruhe	15.06.2018	day+month NK			nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	142	Thrombozytose	01.06.2018				nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	142	Kopfschmerzen	02.06.2018		06.06.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	144	Problemat. Wasserlassen	15.08.2018	day NK	30.08.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	144	Regelschmerzen	17.08.2018		19.08.2018		nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung		wiederhergestellt
lmu01	144	vermehrter Durst	21.08.2018		30.08.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	145	Müdigkeit	03.08.2018		15.10.2018	day NK	nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	145	Psychopathologische Verschlechterung, Halluzinationen	04.09.2018		15.10.2018	day NK	nein	schwer	unwahrscheinlich	keine	andere	stat. Aufnahme, Bedarfsmedikation	wiederhergestellt
lmu01	146	häufiges Wasserlassen	09.10.2018		15.10.2018		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	146	Verstopfung	19.10.2018				nein	mild	unwahrscheinlich	keine	keine		anhaltend
lmu01	147	Zunahme psychotisches Erleben	02.11.2018		05.11.2018		nein	mässig	unwahrscheinlich	keine	andere	Hospitalisation	wiederhergestellt
lmu01	148	Zwinkern d. Augenlider bds.	12.11.2018				nein	mild	unwahrscheinlich	keine	medikamentöse Behandlung		anhaltend
lmu01	149	Kopfschmerzen	07.12.2018		07.12.2018		nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung		wiederhergestellt
lmu01	149	Leukozytose	10.12.2018		12.12.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	149	Unruhe	14.12.2018		20.02.2019		nein	mild	kein Zusammenhang	keine	andere	Rehospitalisierung	wiederhergestellt
lmu01	149	Tachykardie	14.12.2018		18.12.2018		nein	mild	kein Zusammenhang	keine	andere	Rehospitalisierung	wiederhergestellt
lmu01	149	Hypertonie	14.12.2018		18.12.2018		nein	mässig	kein Zusammenhang	keine	andere	Rehospitalisierung	wiederhergestellt
lmu01	149	Hospitalization due to worsening of psychosis	14.12.2018		27.02.2019		ja	mässig	kein Zusammenhang	keine	andere	rehospitalization	wiederhergestellt
lmu01	149	Leukozytose	19.12.2018		21.12.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	149	Sodbrennen	26.12.2018				nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		anhaltend
lmu01	149	Muskel-/Knochenschmerzen inkomitt.	12.01.2019		20.02.2019		nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		wiederhergestellt
lmu01	149	Akathisie	18.02.2019				nein	mild	kein Zusammenhang	nicht anwendbar	medikamentöse Behandlung		anhaltend
lmu01	150	Unruhe	11.12.2018		14.12.2018		nein	mässig	kein Zusammenhang	keine	medikamentöse Behandlung	Reduktion von Cariprazin = Begleitmedikation Nr.2	wiederhergestellt
lmu01	150	Hyperkaliämie	12.12.2018		13.12.2018		nein	mässig	wahrscheinlich	keine	andere	erneute Laborkontrolle am 13.12.18	wiederhergestellt
lmu01	150	Schlafstörungen	29.01.2019		27.02.2019		nein	mild	kein Zusammenhang	nicht anwendbar	keine		wiederhergestellt
lmu01	151	Häufiges Wasserlassen	01.02.2019		06.02.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	152	Tachykardie (120 BPM)	29.01.2019		15.01.2019	day NK	nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
lmu01	152	Exazerbation psychotischer Symptome - stat.Aufnahme	31.01.2019		01.02.2019		ja	mässig	kein Zusammenhang	keine	andere	stat.Aufnahme+ med.Behandl, Studienabbruch	wiederhergestellt
lmu01	153	Schwindel	23.04.2019		29.04.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	154	Depressives Syndrom	15.05.2019		16.05.2019		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	154	Leukozytose	23.05.2019				nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	155	innere Unruhe	21.05.2019				nein	mild	kein Zusammenhang	keine	keine		anhaltend
lmu01	155	Schlaflosigkeit	21.05.2019				nein	mild	kein Zusammenhang	keine	keine		unbekannt
lmu01	156	Erkältung	05.07.2019		06.07.2019		nein	mild	kein Zusammenhang	keine	medikamentöse Behandlung		wiederhergestellt
lmu01	158	Orthostase Schwindel	17.07.2019		19.07.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	158	orthostat. Schwindel	29.07.2019		02.08.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	162	Krea-Anstieg 1,1-1,4, zu wenig Flüssigkeit	07.10.2019		21.10.2019		nein	mild	unwahrscheinlich	keine	andere		wiederhergestellt
lmu01	162	häufiges Wasserlassen	09.10.2019		21.10.2019		nein	mild	möglich	keine	keine		wiederhergestellt
lmu01	163	Ausfall Periode	07.10.2019		09.10.2019		nein	mild	unwahrscheinlich	keine	keine		wiederhergestellt
lmu01	167	Hyperkaliämie Grad II	13.11.2019		14.11.2019		nein	mässig	wahrscheinlich	Unterbrechung	andere	Kontrolle 14.11.2019	wiederhergestellt
lmu01	167	Hyperkaliämie Grad I	14.11.2019		18.11.2019		nein	mild	wahrscheinlich	Unterbrechung	andere	Kontrolle 18.11.	wiederhergestellt

lmu01	170	Hyperkaliämie	17.02.2020		21.02.2020		nein	mild	möglich	nicht anwendbar	andere	Kontrolle bei V11	wiederhergestellt
lmu01	171	Hyperkaliämie Grad I	03.02.2020		05.02.2020		nein	mild	wahrscheinlich	keine	andere	kaliumarme Kost weiter	wiederhergestellt
lmu01	172	Diarrhoe	24.02.2020		28.02.2020		nein	mild	unwahrscheinlich	keine	andere	Bettruhe	wiederhergestellt
lmu01	173	Suizidalität	15.06.2020		16.06.2020		nein	mässig	unwahrscheinlich	nicht anwendbar	andere	stationäre Weiterbahndlung	wiederhergestellt
lmu01	173	stat. psychiatrische Behandlung	23.07.2020				nein	schwer	unwahrscheinlich	nicht anwendbar	keine		unbekannt
tum02	204	Flu like Symptoms	15.01.2017		18.01.2017		nein	schwer	kein Zusammenhang	keine	keine		wiederhergestellt
tum02	204	Fatigue	19.01.2017		02.02.2017		nein	mild	möglich	keine	keine		wiederhergestellt
tum02	205	Hyperkaliämie	03.02.2017		06.02.2017		nein	mässig	wahrscheinlich	Unterbrechung	medikamentöse Behandlung	z-CPS-Pulver + Bifiteral + Kontrolle	wiederhergestellt
tum02	205	Nierenschmerz	06.02.2017		08.02.2017		nein	mild	unwahrscheinlich	Unterbrechung	keine		wiederhergestellt
tum02	211	Hyperkaliämie	18.03.2019		19.03.2019		nein	mild	möglich	Unterbrechung	keine		wiederhergestellt
reg03	301	leichter Schwindel	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Appetitlosigkeit	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Schweißausbrüche	20.09.2017		23.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	301	Schwindel	27.09.2017		28.09.2017		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	302	leichte affektive Herabstimmung	02.10.2017			date NK	nein	mild	möglich	keine	keine		unbekannt
reg03	302	leichte Verschlechterung des Antriebs	02.10.2017			date NK	nein	mild	möglich	keine	keine		unbekannt
reg03	303	leichter Schwindel	12.02.2018		19.02.2018		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	304	Wadenkrampf	02.03.2018		02.03.2018		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt
reg03	305	erhöhter Harndrang	05.11.2018		09.11.2018		nein	mild	möglich	keine	keine		wiederhergestellt
reg03	305	Grippaler Infekt	15.01.2019	day NK	23.01.2019		nein	mild	kein Zusammenhang	keine	keine		wiederhergestellt

Literatur:

Bishara A. J., Hittner J. B. (2012). Testing the significance of a correlation with non-normal data: Comparison of Pearson, Spearman, transformation, and resampling approaches. Psychological Methods, 17, 399-417.

Bliss, C.I.: Statistics in Biology. Statistical Methods for Research in the Natural Sciences. Vol. 1. McGraw-Hill Book Company, New York 1967.

Hasan A, Roeh A, Leucht S, Langguth B, Hansbauer M, Oviedo-Salcedo T, Kirchner SK, Papazova I, Löhrs L, Wagner E, Maurus I, Strube W, Rossner MJ, Wehr MC, Bauer I, Heres S, Leucht C, Kreuzer PM, Zimmermann S, Schneider-Axmann T, Görlitz T, Karch S, Egert-Schwender S, Schossow B, Rothe P, Falkai P (2020). Add-on spironolactone as antagonist of the NRG1-ERBB4 signaling pathway for the treatment of schizophrenia: Study design and methodology of a multicenter randomized, placebo-controlled trial. Contemp Clin Trials Commun. 2020 Jan 28;17:100537. doi: 10.1016/j.conctc.2020.100537. eCollection 2020 Mar.