



Clinical trial results:

Multimodal Prevention of First Psychotic Episode – a 2x2-Factorial Randomized Trial investigating the efficacy of Acetylcysteine (ACC) and Integrated Preventive Psychological Intervention (IPPI) in Subjects Clinically at High Risk for Psychosis

Summary

EudraCT number	2014-003076-22
Trial protocol	DE
Global end of trial date	26 January 2021

Results information

Result version number	v1 (current)
This version publication date	01 April 2026
First version publication date	01 April 2026

Trial information

Trial identification

Sponsor protocol code	PSY-201401_ESPRIT
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03149107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zentralinstitut für Seelische Gesundheit
Sponsor organisation address	J5, Mannheim, Germany, 68159
Public contact	Dr. rer. nat. Christine Fuhrmann, Studienzentrale des Studienzentrum Bonn (SZB), 0049 22816046, Studienzentrale-SZB@ukbonn.de
Scientific contact	Dr. rer. nat. Christine Fuhrmann, Studienzentrale des Studienzentrum Bonn (SZB), 0049 22816046, Studienzentrale-SZB@ukbonn.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	23 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2021
Global end of trial reached?	Yes
Global end of trial date	26 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate individual and combined preventive effects of a pharmaceutical intervention with glutamatergic, neuroprotective and anti-inflammatory capabilities (ACC) and an integrated preventive psychological intervention (IPPI) on transition rates to psychosis, on progression of symptoms and on improvement of social functioning.

Protection of trial subjects:

N-Acetylcysteine is already well known as a safe and well-tolerable agent.

The integrated psychological preventive intervention (IPPI) developed for this study considers the heterogeneous demands of subjects clinically at risk for psychosis by targeting three major needs: stress management, symptom management and social cognition. Thus, besides effects on symptomatic risk indicators and a significant lowering of transition rates, an improvement of psychosocial functioning can be expected. The control condition, Psychological Stress Management (PSM), offers another treatment approach based on the vulnerability-stress-coping model of psychosis development, one of the leading concepts in the field of schizophrenia research (Gispén-de Wied & Jansen, 2002). Thus, even in the control condition, a useful treatment is offered.

Background therapy: -

Evidence for comparator:

Regarding psychological treatments, cognitive behavioral therapy (CBT) has been compared in five studies to a supportive treatment (standard counseling (PSM)) as usual (PMID: 17440198). Three of these studies reported significant reductions of TR, one (presumably underpowered) study a trend, one suffered from methodological problems hampering the discrimination of preventive effects. The most successful relative reduction was achieved in a trial conducted by Cologne, Bonn, Düsseldorf and Munich. This randomized trial compared a 12-month manual-based psychological intervention with a supportive counseling. TR was reduced by 81% to 3.2% during the intervention period. However, unfortunately, this TR showed not to be stable: 12 months after stopping the intervention (i.e. 24 months after baseline), it nearly doubled to 6.3%, equaling a nearly two-hundred times higher incidence rate than observed in the general population. Furthermore, it was an open-label study and the treatment period was too long with regard to convenience: more than a third of the participants took part in less than 50% of the sessions. Thus, an advancing of this approach is required with regard to (i) long-term sustainability of preventive effects beyond the phase of active intervention, (ii) methodology and (iii) convenience.

Actual start date of recruitment	15 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 46 months at 11 sites in Germany

First patient in to last patient out: 52 months

Participants were recruited via the center's early detection facilities and either self-referred or referred via practitioners in stationary or ambulant settings.

Pre-assignment

Screening details:

Participants were recruited via the center's early detection facilities and either self-referred or referred via practitioners in stationary or ambulant settings. Further details on inclusion and exclusion criteria, as well as trial design and recruitment, can be found in the publication (see tab "more information").

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NAC + IPPI

Arm description:

Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks

+

IPPI (Intergrated Preventive Psychological Intervention): IPPI has been applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.

Arm type	Experimental
Investigational medicinal product name	N-Acetylcysteine
Investigational medicinal product code	NAC
Other name	ACC
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID

Arm title	PLC + PSM
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Arm description:

Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks

+

PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.

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

Dosage and administration details:

2 x 2 capsules/day

Arm title	PLC + IPPI
Arm description: Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks + IPPI (Integrated Preventive Psychological Intervention): IPPI was applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	PLC
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details: 2 x 2 capsules/day	
Arm title	NAC + PSM

Arm description:

N-Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks

+

PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	PLC
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details: 2 x 2 capsules/day	

Number of subjects in period 1	NAC + IPPI	PLC + PSM	PLC + IPPI
Started	11	11	13
Completed	11	11	13

Number of subjects in period 1	NAC + PSM
Started	11
Completed	11

Baseline characteristics

Reporting groups

Reporting group title	NAC + IPPI
Reporting group description:	
Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks	
+	
IPPI (Integrated Preventive Psychological Intervention): IPPI has been applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.	
Reporting group title	PLC + PSM
Reporting group description:	
Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks	
+	
PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.	
Reporting group title	PLC + IPPI
Reporting group description:	
Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks	
+	
IPPI (Integrated Preventive Psychological Intervention): IPPI was applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.	
Reporting group title	NAC + PSM
Reporting group description:	
N-Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks	
+	
PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.	

Reporting group values	NAC + IPPI	PLC + PSM	PLC + IPPI
Number of subjects	11	11	13
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)	11	11	13
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	25.1	20.9	23.8
standard deviation	± 4.5	± 3.9	± 6.2

Gender categorical Units: Subjects			
Female	3	5	6
Male	8	6	7
Employment Units: Subjects			
unemployed	0	1	1
employed	11	10	12
Marital status Units: Subjects			
marital status (single)	8	7	8
marital status (not single)	3	4	5
Living situation Units: Subjects			
alone	2	2	2
not alone	9	9	11
Social Connections Units: Subjects			
min. 1/week	10	9	11
none	1	2	2
Weight Units: kg			
arithmetic mean	76.3	69.1	67.3
standard deviation	± 19.5	± 14.8	± 14.8
Height Units: cm			
arithmetic mean	176.8	175.5	172.8
standard deviation	± 9.8	± 8.9	± 8.2
BMI Units: none			
arithmetic mean	24.4	22.4	22.4
standard deviation	± 5.6	± 5.0	± 3.7
Education Units: Years			
arithmetic mean	12.3	11.5	12.0
standard deviation	± 1.3	± 1.2	± 1.2
Population density Units: per square km			
arithmetic mean	2112.4	1518.8	1791.1
standard deviation	± 1358.3	± 1512.1	± 1461.6

Reporting group values	NAC + PSM	Total	
Number of subjects	11	46	
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)	11	46	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	27.1		
standard deviation	± 5.9	-	
Gender categorical			
Units: Subjects			
Female	4	18	
Male	7	28	
Employment			
Units: Subjects			
unemployed	3	5	
employed	8	41	
Marital status			
Units: Subjects			
marital status (single)	5	28	
marital status (not single)	6	18	
Living situation			
Units: Subjects			
alone	2	8	
not alone	9	38	
Social Connections			
Units: Subjects			
min. 1/week	8	38	
none	3	8	
Weight			
Units: kg			
arithmetic mean	79.2		
standard deviation	± 25.5	-	
Height			
Units: cm			
arithmetic mean	174.2		
standard deviation	± 11.3	-	
BMI			
Units: none			
arithmetic mean	25.9		
standard deviation	± 7.4	-	
Education			
Units: Years			
arithmetic mean	11.5		
standard deviation	± 1.9	-	
Population density			
Units: per square km			
arithmetic mean	2243.8		
standard deviation	± 1518.8	-	

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary analysis set was based on the full analysis set, as derived from the intention-to-treat (IIT) principle. All randomized patients were included. Patients who withdraw or showed protocol violations were included in the IIT population. Data of drop outs was analyzed using all available data.

Reporting group values	Full analysis		
Number of subjects	46		
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)	46		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	24.2		
standard deviation	± 5.6		
Gender categorical Units: Subjects			
Female	18		
Male	28		
Employment Units: Subjects			
unemployed	5		
employed	41		
Marital status Units: Subjects			
marital status (single)	28		
marital status (not single)	18		
Living situation Units: Subjects			
alone	8		
not alone	38		
Social Connections Units: Subjects			
min. 1/week	38		
none	8		
Weight Units: kg			
arithmetic mean	72.8		
standard deviation	± 19.1		
Height			

Units: cm arithmetic mean standard deviation	174.8 ± 9.4		
BMI Units: none arithmetic mean standard deviation	23.7 ± 5.6		
Education Units: Years arithmetic mean standard deviation	11.8 ± 1.4		
Population density Units: per square km arithmetic mean standard deviation	1938.4 ± 1472.6		

End points

End points reporting groups

Reporting group title	NAC + IPPI
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Reporting group description:

Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks

+

IPPI (Integrated Preventive Psychological Intervention): IPPI has been applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.

Reporting group title	PLC + PSM
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Reporting group description:

Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks

+

PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.

Reporting group title	PLC + IPPI
-----------------------	------------

Reporting group description:

Placebo (PLC), Dose: 4 (2 x 2) capsules/day, Mode of Application: oral intake, 2 capsules BID, Duration of Treatment: 26 weeks

+

IPPI (Integrated Preventive Psychological Intervention): IPPI was applied weekly for the first 20 weeks (sessions 1 to 20, weeks 0 to 19), a booster and closure session (session 21) have taken place at week 24.

Reporting group title	NAC + PSM
-----------------------	-----------

Reporting group description:

N-Acetylcysteine 500 mg capsules, Dose: 2000 mg/d (2 x 2 capsules/day), Mode of application: oral intake, 1000 mg (2 capsules) BID, Duration of treatment: 26 weeks

+

PSM (Psychological Stress Management) has been applied bi-weekly (sessions 1 to 10, weeks 0 to 18), a booster and closure session (session 11) have taken place at week 24.

Subject analysis set title	Full analysis
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Primary analysis set was based on the full analysis set, as derived from the intention-to-treat (IIT) principle. All randomized patients were included. Patients who withdraw or showed protocol violations were included in the IIT population. Data of drop outs was analyzed using all available data.

Primary: Overall Event free survival - combined intervention

End point title	Overall Event free survival - combined intervention
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End point description:

event = transition to psychosis - Details see attached publication Wasserthal et al. 2024, doi 10.1093

End point type	Primary
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End point timeframe:

after 18 Months (after treatment and follow Up phase)

End point values	NAC + IPPI	PLC + PSM	PLC + IPPI	NAC + PSM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	13	11
Units: %				
arithmetic mean (standard deviation)				
Overall Event free survival - combined interventio	72.7 (± 13.4)	39.0 (± 17.4)	56.1 (± 15.3)	72.7 (± 13.4)

Statistical analyses

Statistical analysis title	event free survival probability after 18 months
Statistical analysis description: NAC+IPPI vs. PLC+PSM	
Comparison groups	PLC + PSM v NAC + IPPI
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	3.549

Statistical analysis title	event free survival probability after 18 months
Statistical analysis description: NAC+PSM vs. PLC+PSM	
Comparison groups	NAC + PSM v PLC + PSM
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.785
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.197
upper limit	3.119

Statistical analysis title	event free survival probability after 18 months
Statistical analysis description: PLC+IPPI vs. PLC+PSM	
Comparison groups	PLC + IPPI v PLC + PSM
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.814
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.815
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	4.457

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	1 IPPI+ACC
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Reporting group description: -

Reporting group title	2 IPPI+PLC
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Reporting group description: -

Reporting group title	3 PSM+ACC
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Reporting group description: -

Reporting group title	4 PSM+PLC
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Reporting group description: -

Serious adverse events	1 IPPI+ACC	2 IPPI+PLC	3 PSM+ACC
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Disease prodromal stage	Additional description: Disease prodromal stage		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute stress disorder	Additional description: Acute stress disorder		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	4 PSM+PLC		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Disease prodromal stage	Additional description: Disease prodromal stage		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute stress disorder	Additional description: Acute stress disorder		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	1 IPPI+ACC	2 IPPI+PLC	3 PSM+ACC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	8 / 13 (61.54%)	4 / 11 (36.36%)
Vascular disorders			
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Adverse drug reaction	Additional description: Adverse drug reaction		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Asthenia	Additional description: Asthenia		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0

Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dry throat	Additional description: Dry throat		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	2 / 11 (18.18%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Attention deficit hyperactivity disorder	Additional description: Attention deficit hyperactivity disorder		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Depressive symptom	Additional description: Depressive symptom		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Indifference	Additional description: Indifference		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Libido increased	Additional description: Libido increased		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Restlessness	Additional description: Restlessness		
subjects affected / exposed	1 / 11 (9.09%)	2 / 13 (15.38%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Tension	Additional description: Tension		

subjects affected / exposed	2 / 11 (18.18%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Terminal insomnia	Additional description: Terminal insomnia		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Thinking abnormal	Additional description: Thinking abnormal		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Blood cannabinoids increased	Additional description: Blood cannabinoids increased		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Urine cannabinoids increased	Additional description: Urine cannabinoids increased		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Advanced sleep phase	Additional description: Advanced sleep phase		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Dizziness postural	Additional description: Dizziness postural		

subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Headache	Additional description: Headache		
subjects affected / exposed	2 / 11 (18.18%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Mental impairment	Additional description: Mental impairment		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sedation	Additional description: Sedation		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tension headache	Additional description: Tension headache		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Accommodation disorder	Additional description: Accommodation disorder		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Aptyalism	Additional description: Aptyalism		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dyspepsia	Additional description: Dyspepsia		

subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastroesophageal reflux disease	Additional description: Gastroesophageal reflux disease		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Saliva altered	Additional description: Saliva altered		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pigmentation disorder	Additional description: Pigmentation disorder		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pruritus	Additional description: Pruritus		
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rash	Additional description: Rash		
subjects affected / exposed	0 / 11 (0.00%)	2 / 13 (15.38%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Micturition disorder	Additional description: Micturition disorder		
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Influenza subjects affected / exposed occurrences (all)	Additional description: Influenza		
	1 / 11 (9.09%) 1	0 / 13 (0.00%) 0	0 / 11 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis		
	0 / 11 (0.00%) 0	0 / 13 (0.00%) 0	1 / 11 (9.09%) 1
Norovirus infection subjects affected / exposed occurrences (all)	Additional description: Norovirus infection		
	0 / 11 (0.00%) 0	1 / 13 (7.69%) 1	0 / 11 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	Additional description: Pneumonia		
	0 / 11 (0.00%) 0	1 / 13 (7.69%) 1	0 / 11 (0.00%) 0
Skin candida subjects affected / exposed occurrences (all)	Additional description: Skin candida		
	0 / 11 (0.00%) 0	1 / 13 (7.69%) 1	0 / 11 (0.00%) 0

Non-serious adverse events	4 PSM+PLC		
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 11 (45.45%)		
Vascular disorders Circulatory collapse subjects affected / exposed occurrences (all)	Additional description: Circulatory collapse		
	0 / 11 (0.00%) 0		
General disorders and administration site conditions Adverse drug reaction subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	Additional description: Adverse drug reaction		
	0 / 11 (0.00%) 0		
	Additional description: Asthenia		
	1 / 11 (9.09%) 1		
	Additional description: Fatigue		
	1 / 11 (9.09%) 2		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	Additional description: Seasonal allergy		
	0 / 11 (0.00%) 0		

Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dry throat	Additional description: Dry throat		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Attention deficit hyperactivity disorder	Additional description: Attention deficit hyperactivity disorder		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Depressive symptom	Additional description: Depressive symptom		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Indifference	Additional description: Indifference		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Libido increased	Additional description: Libido increased		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Restlessness	Additional description: Restlessness		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Tension	Additional description: Tension		

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Terminal insomnia	Additional description: Terminal insomnia		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Thinking abnormal	Additional description: Thinking abnormal		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Investigations			
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood cannabinoids increased	Additional description: Blood cannabinoids increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urine cannabinoids increased	Additional description: Urine cannabinoids increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			
Advanced sleep phase	Additional description: Advanced sleep phase		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dizziness postural	Additional description: Dizziness postural		

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache	Additional description: Headache		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Mental impairment	Additional description: Mental impairment		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sedation	Additional description: Sedation		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Tension headache	Additional description: Tension headache		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Eye disorders			
Accommodation disorder	Additional description: Accommodation disorder		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Aptyalism	Additional description: Aptyalism		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspepsia	Additional description: Dyspepsia		

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Saliva altered	Additional description: Saliva altered		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pigmentation disorder	Additional description: Pigmentation disorder		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash	Additional description: Rash		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Micturition disorder	Additional description: Micturition disorder		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			

Influenza subjects affected / exposed occurrences (all)	Additional description: Influenza	
	0 / 11 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis	
	1 / 11 (9.09%) 1	
Norovirus infection subjects affected / exposed occurrences (all)	Additional description: Norovirus infection	
	0 / 11 (0.00%) 0	
Pneumonia subjects affected / exposed occurrences (all)	Additional description: Pneumonia	
	0 / 11 (0.00%) 0	
Skin candida subjects affected / exposed occurrences (all)	Additional description: Skin candida	
	0 / 11 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2016	Amendment 1: update from initially approved protocol version 3 to version 4. Changes: Correction of an error in the list of stress training sessions/laboratory assessments now max. 28 days old instead of 3 months
04 April 2017	Amendment 3: approval of protocol version 6, changes from version 4 to version 5: details of new PIs/deputy PIs added, changes from version 5 to 6: deletion of 3 inclusion criteria, Pregnancy tests now explicitly permitted through blood tests .
15 August 2017	Amendment 4: protocol version 6 to version 7: changes of PIs
18 July 2018	Amendment 5: protocol version 7 to version 8: Deletion of various test procedures that were not previously evaluated in the eCRF / Adjustments to visits / Deletions and changes to exclusion criteria
23 July 2019	Amendment 6: protocol version 9 submitted, protocol version 10 approved. Changes from version 8 to 9: Follow-up Phase now only optional for 12 months / Introduction of a futility parameter / Addition of inclusion criterion 5 / Adjustment of the end date as part of the cost-neutral extension change of PIs Changes from version 9 to 10: Additions at the suggestion of the BfArM: only the DSMB has access to unblinded data after futility analysis, early termination date corrected to June 30, 2019.
18 February 2020	Amendment 7: protocol version 10 to version 11, changes: Change to an exclusion criterion, change of sponsor representative adjustment of trial medication label

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/30784233>

<http://www.ncbi.nlm.nih.gov/pubmed/39144108>