Clinical trial results:
Prevent: Secondary Prevention of Schizophrenia. A randomized controlled trial.

Summary

EudraCT number	2007-001573-28
Trial protocol	DE
Global end of trial date	26 January 2015

Results information

Result version number	v1 (current)
This version publication date	02 November 2022
First version publication date	02 November 2022

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-320

Additional study identifiers

ISRCTN number	ISRCTN02658871
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Koeln, Germany, 50923
Public contact	Gruppe Lebenswissenschaften 2, Deutsche Forschungsgemeinschaft, hendrik.mueller@uk-koeln.de
Scientific contact	Gruppe Lebenswissenschaften 2, Deutsche Forschungsgemeinschaft, hendrik.mueller@uk-koeln.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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2014
Global end of trial reached?	Yes
Global end of trial date	26 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study addresses the following principal research questions (PRQ):
(1) Are clinical management and aripiprazole combined (CM+ARI) more effective in PAR than CM and placebo combined (CM+PL)?
(2) Is CBT more effective in PAR than CM+PL?
(3) Is CBT not less effective in PAR than CM+ARI?

If PRQ 1-3 will be answered positively, there will be substantial empirical evidence for the prevention of first-episode psychosis.

The major motivation for the study is to answer PRQ 1, 2 and 3 regarding the primary aim of prevention of first-episode psychosis, the "delay or prevention of transition to psychosis".

Protection of trial subjects:

Assessment of safety: death, suicidal behaviour and severe depressive symptom exacerbation, pharmacological side effects

Background therapy:

Citalopram or escitalopram were the preferred antidepressive drugs. Lorazepam (maximum 7,5mg/d), zopiclon (maximum 15
mg/d), and chloral hydrate (maximum 1000 mg/d) were allowed to use for agitation and/or insomnia. Propranalol hydrochloride was allowed to treat akathisia. Biperiden up to 6 mg/day, was allowed to treat extrapyramidal symptoms.

Evidence for comparator:

Many authors claimed a need for methodological sound collaborative large scale randomized controlled trials (RCTs) in the clinical high risk for first episode psychosis population (CHR) involving strategies which have been found to have preventive potential in CHR (e. g. Heinssen et al., 2003; McGorry et al., 2004; Marshall and Lockwood, 2004; Olsen and Rosenbaum, 2005).

Aripiprazole (ARI) was chosen as antipsychotic agent because of its partial dopamine D2 and 5-HT1A receptor agonist and 5-HT2A receptor antagonist activity, which was postulated to be effective on schizophrenia positive and negative symptoms as well as on cognitive deficits while at the same time causing little extrapyramidal side effects, prolactin plasma level elevations and weight gain. The efficacy of ARI has been evaluated with regard to negative symptoms and depression as well as to positive symptoms. ARI is as effective as other antipsychotics combined with good tolerability, especially with regard to hyperprolactinaemia, sedation, weight gain, for diabetes mellitus, electrocardiographic disturbances and extrapyramidal symptoms (Lieberman, 2004; El-Sayeh and Morganti, 2006). First pilot evaluations in CHR demonstrated a good efficacy and tolerability of the compound (Woods 2006).

Cognitive Behavioral Therapy (CBT): There are two reasons to include this condition in the study: (a) evidence for superiority of antipsychotic agents and CBT when compared with unspecific conditions is equivocal so far. (b) CBT in PAR may have ethical, acceptance and compliance advantages.

Actual start date of recruitment	01 April 2008
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: 280
Worldwide total number of subjects	280
EEA total number of subjects	280

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)	280
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 01.04.2008 and ended on 31.10.2013.
The trial was conducted at eleven early detection and intervention centers located at the departments of psychiatry and psychotherapy of the Universities of Cologne, Aachen, Berlin, Bochum, Bonn, Dresden, Düsseldorf, Göttingen, Hamburg, Heidelberg (Medical Faculty Mannheim), and Munich.

Pre-assignment

Screening details:

3004 help-seeking individuals were screened with a checklist. Those who met the threshold checklist criteria and fulfilled no exclusion criteria underwent an assessment in terms of inclusion criteria: 18-49 years old, verbal IQ >70 meeting: Ultra high risk for psychosis criteria and/or basic symptoms cognitive disturbances criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Clinical management (CM) and aripiprazole (ARI)

Arm description:

Clinical management and low dose of aripiprazole.

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

Dosage and administration details:

The initial dose of aripiprazole was 2 mg in the first week, 2–5 mg in the second week, and 2–10 mg in the third week. After that, it could be dosed to a maximum of 15 mg. Bristol-Meyers Squibb USA manufactured the aripiprazole and matching placebo.

Arm title	Clinical management (CM) and placebo (PL)

Arm description:

Clinical management and placebo. The placebo was matching aripiprazole.

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

Dosage and administration details:

The packaging, appearance, color, and taste of the aripiprazole and placebo tablets were identical to verum.

Arm title	Cognitive Behavioral Therapy (CBT)

Arm description:

Cognitive behavioral therapy adapted to the needs of individuals at clinical high risk for first-episode

psychosis as detailed by a manual developed by Bechdolf et al.

Arm type	Experimental
Investigational medicinal product name	Cognitive behavioral therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Other use

Dosage and administration details:

CBT included a maximum of 30 individual sessions of up to 50 minutes over 52 weeks and was provided using a manual developed by Bechdolf et al.

Number of subjects in period 1	Clinical management (CM) and aripiprazole (ARI)	Clinical management (CM) and placebo (PL)	Cognitive Behavioral Therapy (CBT)
Started	96	55	129
Completed	21	14	53
Not completed	75	41	76
Lost to follow-up	56	34	55
Transition to psychosis	19	7	21

Baseline characteristics

Reporting groups

Reporting group title	Randomization

Reporting group description: -

Reporting group values	Randomization	Total	
Number of subjects	280	280	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age in years at randomization.			
Units: years			
arithmetic mean	24.4		
standard deviation	± 5.1	-	
Gender categorical Units: Subjects			
Female	98	98	
Male	182	182	

Subject analysis sets

Subject analysis set title	Subject analysis set: ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Following the intention-to-treat (ITT) principle, all randomized subjects were included in the analysis.

Reporting group values	Subject analysis set: ITT		
Number of subjects	280		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years at randomization.			
Units: years arithmetic mean standard deviation	 24.4 ±		
Gender categorical Units: Subjects			
Female Male	98 182		

End points

End points reporting groups

Reporting group title	Clinical management (CM) and aripiprazole (ARI)

Reporting group description:

Clinical management and low dose of aripiprazole.

Reporting group title	Clinical management (CM) and placebo (PL)

Reporting group description:

Clinical management and placebo. The placebo was matching aripiprazole.

Reporting group title	Cognitive Behavioral Therapy (CBT)

Reporting group description:

Cognitive behavioral therapy adapted to the needs of individuals at clinical high risk for first-episode psychosis as detailed by a manual developed by Bechdolf et al.

Subject analysis set title	Subject analysis set: ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Following the intention-to-treat (ITT) principle, all randomized subjects were included in the analysis.

Primary: Transition to psychosis

End point title	Transition to psychosis[1]

End point description:

Transition to psychosis at 12 months defined as one or more of the five positive scales of the Structured Interview for Prodromal Symptoms (SIPS) and its companion Scale of Prodromal Symptoms (SOPS), rated with a score of 6 and lasting longer than seven days, is reported as the primary outcome.

End point type	Primary

End point timeframe:

The primary endpoint was assessed by blinded raters at weeks 0, 4, 8, 12, 16, 20, 28, 36, 44, and 52.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: We present the pairwise comparisons.

End point values	Clinical management (CM) and aripiprazole (ARI)	Clinical management (CM) and placebo (PL)	Subject analysis set: ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	96	55	280	
Units: Transitions	19	7	151	

Statistical analyses

Statistical analysis title	CM+ARI vs. CM+PL

Statistical analysis description:

Clinical management plus aripiprazole (CM+ARI) compared to clinical management plus placebo (CM+PLC).
SIPS-P at baseline as covariate.

Comparison groups	Clinical management (CM) and aripiprazole (ARI) v Clinical management (CM) and placebo (PL) v Subject analysis set: ITT

Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Regression, Cox
Parameter estimate	Log hazard ratio
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	0.49

Primary: Transition to psychosis

End point title	Transition to psychosis[2]

End point description:

Transition to psychosis at 12 months defined as one or more of the five positive scales of the Structured Interview for Prodromal Symptoms (SIPS) and its companion Scale of Prodromal Symptoms (SOPS), rated with a score of 6 and lasting longer than seven days, is reported as the primary outcome.

End point type	Primary

End point timeframe:

The primary endpoint was assessed by blinded raters at weeks 0, 4, 8, 12, 16, 20, 28, 36, 44, and 52.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: We present the pairwise comparisons.

End point values	Clinical management (CM) and placebo (PL)	Cognitive Behavioral Therapy (CBT)	Subject analysis set: ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	55	129	184	
Units: Transitions	7	21	184	

Statistical analyses

Statistical analysis title	CBT vs. CM+PL

Statistical analysis description:

Cognitive-behavioral therapy (CBT) compared to clinical management plus placebo (CM+PLC).

Comparison groups	Clinical management (CM) and placebo (PL) v Cognitive Behavioral Therapy (CBT)

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	0.482

Primary: Transition to psychosis

End point title	Transition to psychosis[3]

End point description:

Transition to psychosis at 12 months defined as one or more of the five positive scales of the Structured Interview for Prodromal Symptoms (SIPS) and its companion Scale of Prodromal Symptoms (SOPS), rated with a score of 6 and lasting longer than seven days, is reported as the primary outcome.

End point type	Primary

End point timeframe:

The primary endpoint was assessed by blinded raters at weeks 0, 4, 8, 12, 16, 20, 28, 36, 44, and 52.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: We present the pairwise comparisons.

End point values	Clinical management (CM) and aripiprazole (ARI)	Cognitive Behavioral Therapy (CBT)	Subject analysis set: ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	96	129	225[4]	
Units: Transitions	19	21	225	

Notes:

[4] - We present the pairwise comparisons

Statistical analyses

Statistical analysis title	CBT vs. CM+ARI

Statistical analysis description:

Cognitive-behavioral therapy (CBT) compared to Clinical management plus aripiprazole (CM+ARI). SIPS-P at baseline as covariate.

Comparison groups	Cognitive Behavioral Therapy (CBT) v Clinical management (CM) and aripiprazole (ARI)

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.065
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.548
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.326

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the trial and the following 30 days (04.2008 to 11.2014)

Assessment type	Systematic

Dictionary used

Dictionary name	non
Dictionary version	0

Reporting groups

Reporting group title	Clinical management (CM) and aripiprazole (ARI)

Reporting group description:

CM was provided in addition to ARI or PLC and comprised a maximum of 21 sessions in the treatment phase of 52 weeks: weekly in the first four weeks, biweekly in the next 20 weeks and every fourth week over the following 28 weeks. The initial session lasted up to 60 minutes; the following sessions ranged from 20 to 30 minutes.
The initial dose of Aripiprazole (ARI) was 2 mg in the first week, 2-5 mg in the second week, and 2-10 mg in the third week, which could be dosed to a maximum of 15 mg thereafter. In accordance with the literature on people at risk, the overall dose range is lower (from 5 to 15 milligrams per day) as compared to first episode psychosis patients.

Reporting group title	Clinical management (CM) and placebo (PL)

Reporting group description:

CM was provided in addition to ARI or PLC and comprised a maximum of 21 sessions in the treatment phase of 52 weeks: weekly in the first four weeks, biweekly in the next 20 weeks and every fourth week over the following 28 weeks. The initial session lasted up to 60 minutes; the following sessions ranged from 20 to 30 minutes.
Aripiprazole matching placebo.

Reporting group title	Cognitive Behavioral Therapy (CBT)

Reporting group description:

CBT included a total maximum of 30 individual sessions up to 50 minutes in 12 months. CBT started with weekly appointments for the first four months, fortnightly over the next six months and monthly over the last two months. However, the frequency and duration of the sessions were flexible depending on the arrangement made between the individual clients and the therapists as well as on the mental state of individual clients. CBT was provided by a manual developed by Bechdolf et al.

Serious adverse events	Clinical management (CM) and aripiprazole (ARI)	Clinical management (CM) and placebo (PL)	Cognitive Behavioral Therapy (CBT)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 75 (12.00%)	0 / 43 (0.00%)	7 / 117 (5.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Leg fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
myocardial infarction			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epileptic seizure			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abnormal EEG			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Orthostatic dysregulation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinnitus			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	3 / 117 (2.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			

subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inner restlessness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggressive behavoir			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Self harm			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Digit inflammation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess incision			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Clinical management (CM) and aripiprazole (ARI)	Clinical management (CM) and placebo (PL)	Cognitive Behavioral Therapy (CBT)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 75 (60.00%)	20 / 43 (46.51%)	36 / 117 (30.77%)
Injury, poisoning and procedural complications			
Injuries			
subjects affected / exposed	1 / 75 (1.33%)	2 / 43 (4.65%)	2 / 117 (1.71%)
occurrences (all)	1	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 75 (5.33%)	1 / 43 (2.33%)	1 / 117 (0.85%)
occurrences (all)	12	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	2 / 117 (1.71%)
occurrences (all)	1	0	3
Nervous system disorders			
Inner restlessness			
subjects affected / exposed	16 / 75 (21.33%)	2 / 43 (4.65%)	2 / 117 (1.71%)
occurrences (all)	21	4	2
Motor disturbances (Rigor, Tremor, Extrapyramidal syndrome , Dyskinesia)			
subjects affected / exposed	9 / 75 (12.00%)	1 / 43 (2.33%)	0 / 117 (0.00%)
occurrences (all)	34	1	0
Daytime sleepiness			
subjects affected / exposed	6 / 75 (8.00%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences (all)	8	0	0
Sleep disorder			
subjects affected / exposed	9 / 75 (12.00%)	6 / 43 (13.95%)	6 / 117 (5.13%)
occurrences (all)	20	7	16
Perspiration			
subjects affected / exposed	1 / 75 (1.33%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences (all)	1	0	2
Pain			
subjects affected / exposed	13 / 75 (17.33%)	2 / 43 (4.65%)	9 / 117 (7.69%)
occurrences (all)	19	5	76
Blood and lymphatic system disorders			

Blood count other			
subjects affected / exposed	7 / 75 (9.33%)	6 / 43 (13.95%)	7 / 117 (5.98%)
occurrences (all)	16	10	7
Ear and labyrinth disorders			
Orthostatic dysregulation			
subjects affected / exposed	3 / 75 (4.00%)	0 / 43 (0.00%)	2 / 117 (1.71%)
occurrences (all)	3	0	2
Eye disorders			
Sight disorder			
subjects affected / exposed	3 / 75 (4.00%)	0 / 43 (0.00%)	0 / 117 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	7 / 75 (9.33%)	2 / 43 (4.65%)	3 / 117 (2.56%)
occurrences (all)	9	2	8
Hepatobiliary disorders			
Elevated Liver Function Tests			
subjects affected / exposed	3 / 75 (4.00%)	5 / 43 (11.63%)	1 / 117 (0.85%)
occurrences (all)	3	3	1
Psychiatric disorders			
Self-harm			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	3 / 117 (2.56%)
occurrences (all)	0	0	4
Suicidal ideation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 43 (0.00%)	1 / 117 (0.85%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	7 / 75 (9.33%)	3 / 43 (6.98%)	7 / 117 (5.98%)
occurrences (all)	11	6	7
Anxiety			
subjects affected / exposed	1 / 75 (1.33%)	2 / 43 (4.65%)	0 / 117 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Mild infection			
subjects affected / exposed	5 / 75 (6.67%)	3 / 43 (6.98%)	17 / 117 (14.53%)
occurrences (all)	7	4	23
Metabolism and nutrition disorders			

Elevated blood lipids subjects affected / exposed occurrences (all)	13 / 75 (17.33%) 7	11 / 43 (25.58%) 4	6 / 117 (5.13%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2007	Amendment 01 approved by the Ethics Committee of the University of Cologne: The ethics committee of the University of Cologne made the following conditions for the initial approval of the trial protocol: 1. Addition to the exclusion criteria: intended pregnancy during the study. 2. Cardiovascular diseases should be included in the exclusion criteria, as hypersensitivity to aripiprazole administration must be expected. 3. Exclusion criteria should be expanded to: The person concerned has not been committed to an institution by virtue of an order issued by judicial or administrative authorities. 4. The wording concerning the termination of the study in the case of suicide or SAEs should be clarified (e.g. by stating rates) or deleted, as this is already included under "safety reasons". 5. Correct that during the visits, not only adverse Reactions but also adverse events are documented. 6. Even if allergic reactions to placebo cannot be ruled out, they should not be considered "expected" but treated as SUSAR if necessary. 7. We assume that by and large patients will be in the normal range of laboratory parameters. Therefore, any change of these parameters outside of the norm or changes in vital signs, (ECG), and changes that are otherwise considered clinically relevant by the investigator should be documented as an adverse event. 8. On page 112, 'initials' should be deleted, since according to Section 4.6.6 a patient ID is assigned without initials, and the use of initials must be considered inadmissible under data protection law.
02 October 2008	Amendment 02, Protocol version 6.1 approved by the Ethics Committee of the University of Cologne: Based on the experience gathered since the start of the PREVENT trial, the following changes were necessary to improve the feasibility of the study and increase its practicability. There was no change in the primary endpoints; the secondary endpoints were expanded. 1. Physical examinations (ECG and laboratory parameters) were reduced to improved feasibility. 2. Specifications of how blood samples are to be taken, processed and stored were added. 3. Inclusion of the additional secondary endpoint "neurotrophic factors and oxidative stress as an add on to the study.

03 November 2011	Amendment 03 Protocol version 8.0 approved by the Ethics Committee of the University of Cologne: 1. Four additional centres were added to speed up recruitment. 2. Change of principal investigator in Düsseldorf was documented. 3. Inclusion criteria were revised from 40 to 49 years to accelerate recruitment. 4. Exclusion criteria were made more specific for better comprehensibility or were narrowed down in some points in order to include a larger group of patients (exclusion criterium: "current or past antipsychotic treatment for longer than 1 week: current or past antipsychotic treatment shorter than 1 week without a washout phase of at least 4 weeks "was changed to: "current or past antipsychotic treatment without a washout phase of at least 4 weeks. " 5. As the trial fell short of its recruitment goals, the time schedule was extended. 6. Contact details of principal investigators were updated. 7. Due to delays in the inclusion diagnostics, imaging (MRT) should be alternatively performed by CT. 8. The assessment frequency of the "Social Adjustment Scale" was reduced, since the scale refers to the period of the last three months on the one hand, and the survey dates were assessed as sufficient by the study director on the other.
07 May 2014	Amendment 04 Protocol version 3.0 approved by the Ethics Committee of the University of Cologne: 1. The trial did not meet its recruitment milestones. Thus, the power calculation was revised. The number of subjects to be included was reduced from 380 to 300. 2. Declining event rates were reported by studies in the field. Thus the primary endpoint "transition to psychosis" was expanded to "progression to psychosis". 3. In order to improve recruitment, two recruiting centres were added to the study. 4. Contact details were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported