



Clinical trial results: Optimization of Treatment and Management of Schizophrenia in Europe Summary

EudraCT number	2010-020185-19
Trial protocol	DE GB ES NL CZ DK AT BE IT BG RO
Global end of trial date	01 November 2017

Results information

Result version number	v1 (current)
This version publication date	24 August 2019
First version publication date	24 August 2019
Summary attachment (see zip file)	Summary (Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	KP7242114
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01248195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 XC
Public contact	Inge Winter-van Rossum, University Medical Center Utrecht, i.winter@umcutrecht.nl
Scientific contact	Inge Winter-van Rossum, University Medical Center Utrecht, i.winter@umcutrecht.nl

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	28 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2017
Global end of trial reached?	Yes
Global end of trial date	01 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test guideline recommendation that non-responders to an antipsychotic drug benefit from a switch to an antipsychotic with a different receptor binding profile.

Protection of trial subjects:

No interventions were expected to cause pain or distress.

Background therapy:

None.

Evidence for comparator:

The three antipsychotics used are repeatedly found to be among the most effective of antipsychotics.

Actual start date of recruitment	15 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	16 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Denmark: 42
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Israel: 71
Country: Number of subjects enrolled	Switzerland: 11
Worldwide total number of subjects	446
EEA total number of subjects	364

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)	446
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started may 2011 and ended april 2016.

Not all subjects who did not meet remission criteria at the end of the phase continued into the next phase, due to various reasons. These numbers could not be included as drop out anywhere in these forms.

Pre-assignment

Screening details:

Eligible patients were aged 18–40 years and met criteria of the DSM-IV for schizophrenia, schizophreniform disorder, or schizoaffective disorder; diagnoses were confirmed by the Mini International Neuropsychiatric Interview plus. Antipsychotic exposure was limited to max 14 days.

Period 1

Period 1 title	Phase 1, 4-week open label amisulpride
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Amisulpride
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Arm description:

All patients started with 4-week open label amisulpride treatment.

Arm type	Single, open label treatment
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

flexible dose between 200-800, target dose 400 mg

Number of subjects in period 1	Amisulpride
Started	446
Completed	371
Not completed	75
Consent withdrawn by subject	28
Physician decision	7
Adverse event, non-fatal	18
Involuntary hospital admission	5
Lost to follow-up	8
Protocol deviation	9

Period 2	
Period 2 title	Phase 2, double blind treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Arms	
Are arms mutually exclusive?	Yes
Arm title	Amisulpride
Arm description: Flexible dose, 200-800 mg amisulpride	
Arm type	Active comparator
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Flexible dose, 5-20 mg olanzapine	
Arm title	Olanzapine double blind
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	2
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 5-20 mg per day	

Number of subjects in period 2^[1]	Amisulpride	Olanzapine double blind
Started	47	46
Completed	33	39
Not completed	14	7
Consent withdrawn by subject	2	4
Adverse event, non-fatal	6	1
Lost to follow-up	1	1
Lack of efficacy	1	1
Protocol deviation	4	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In between treatment phases, subjects withdrew consent for various reasons, mainly due to not wanting to switch medication or avoid the medication in the subsequent phase. These 'drop outs' cannot be entered at any location in the system.

Period 3

Period 3 title	Phase 3, open label clozapine
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Clozapine 12-week open label
Arm description: -	
Arm type	Active treatment
Investigational medicinal product name	Clozapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dose, 100-900 mg clozapine

Number of subjects in period 3^[2]	Clozapine 12-week open label
Started	28
Completed	18
Not completed	10
Consent withdrawn by subject	2
Adverse event, non-fatal	4
subjects refused safety blood draws	2
Lost to follow-up	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In between treatment phases, subjects withdrew consent for various reasons, mainly due to not wanting to switch medication or avoid the medication in the subsequent phase. These 'drop outs' cannot be entered at any location in the system.

Baseline characteristics

Reporting groups

Reporting group title	Phase 1, 4-week open label amisulpride
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Reporting group description: -

Reporting group values	Phase 1, 4-week open label amisulpride	Total	
Number of subjects	446	446	
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 continuous measure, allowed age was 18-40 years			
Units: years			
arithmetic mean	26.0		
standard deviation	± 6.0	-	
Gender categorical			
Units: Subjects			
Female	134	134	
Male	312	312	

Subject analysis sets

Subject analysis set title	Intention To Treat phase 1
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.

Subject analysis set title	Intention To Treat phase 2
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients who were randomised at the start of phase 2 were included in this analyses.

Subject analysis set title	Intention To Treat phase 3
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients who received study medication at the beginning of phase 3 were included in this analyses.

Reporting group values	Intention To Treat phase 1	Intention To Treat phase 2	Intention To Treat phase 3
Number of subjects	446	93	28
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 continuous measure, allowed age was 18-40 years			
Units: years			
arithmetic mean	26.0	25.2	26.3
standard deviation	± 6.0	± 5.4	± 6.5
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Amisulpride
Reporting group description: All patients started with 4-week open label amisulpride treatment.	
Reporting group title	Amisulpride
Reporting group description: Flexible dose, 200-800 mg amisulpride	
Reporting group title	Olanzapine double blind
Reporting group description: -	
Reporting group title	Clozapine 12-week open label
Reporting group description: -	
Subject analysis set title	Intention To Treat phase 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.	
Subject analysis set title	Intention To Treat phase 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were randomised at the start of phase 2 were included in this analyses.	
Subject analysis set title	Intention To Treat phase 3
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who received study medication at the beginning of phase 3 were included in this analyses.	

Primary: Remission end of phase 2

End point title	Remission end of phase 2
End point description:	
End point type	Primary
End point timeframe: Duration of treatment phase, covering 6 weeks.	

End point values	Amisulpride	Olanzapine double blind	Intention To Treat phase 2	Intention To Treat phase 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	47	46	47	46
Units: 0 or 1 number (not applicable)				
No remission	33	29	33	29
Remission	14	17	14	17

Statistical analyses

Statistical analysis title	Comparing remission rates between treatment arms
Statistical analysis description:	
Remission, assessed at the final visit of each phase, was first summarised as patient counts and percentages. Subsequently, remission at each visit was analysed using a generalised linear mixed model (GLMM), with a logistic link and binomial error distribution. A comparison was made between the amisulpride and olanzapine groups, by including the treatment group as a factor in the GLMM.	
Comparison groups	Olanzapine double blind v Amisulpride
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were reported up until 30 days after the study medication was completed or discontinued.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Phase 1 amisulpride 4 week open label
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Reporting group description: -

Reporting group title	Phase 2 double blind 6 week treatment with amisulpride
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Reporting group description: -

Reporting group title	Phase 2 double blind 6 week treatment with olanzapine
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Reporting group description: -

Reporting group title	Phase 3 clozapine 12 week treatment
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Reporting group description: -

Serious adverse events	Phase 1 amisulpride 4 week open label	Phase 2 double blind 6 week treatment with amisulpride	Phase 2 double blind 6 week treatment with olanzapine
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 446 (9.42%)	2 / 47 (4.26%)	1 / 46 (2.17%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Dystonia	Additional description: Acute dystonia of such severity that patient needed to be hospitalized.		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Akathesia	Additional description: Akathesia of such severity that the patient needed to be hospitalized.		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Sedation	Additional description: Severe sedation, required hospitalisation		
subjects affected / exposed	0 / 446 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epileptic seizure	Additional description: Epileptic seizure of such severity, it required hospitalisation		
subjects affected / exposed	2 / 446 (0.45%)	0 / 47 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder	Additional description: Extrapyramidal disorder of such severity that hospitalisation was required		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Glioma cerebellum			
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Blood and lymphatic system disorders			
Leukocytopenia	Additional description: Required hospitalisation		
subjects affected / exposed	0 / 446 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pregnancy			
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Hepatobiliary disorders			
Acute hepatopathy	Additional description: Required hospitalisation		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Psychiatric disorders			
Exacerbation of psychotic symptoms			
subjects affected / exposed	29 / 446 (6.50%)	2 / 47 (4.26%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 29	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation	Additional description: Suicidal ideation of such severity that hospitalisation is required.		
subjects affected / exposed	2 / 446 (0.45%)	0 / 47 (0.00%)	0 / 46 (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
Depression	Additional description: Depression of such severity, hospitalisation was required		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Hospitalisation due to social circumstances			
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Hospitalisation due to drug use			
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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
Renal and urinary disorders			
Rabdomiolysis	Additional description: Required hospitalisation		
subjects affected / exposed	1 / 446 (0.22%)	0 / 47 (0.00%)	0 / 46 (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

Serious adverse events	Phase 3 clozapine 12 week treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Dystonia	Additional description: Acute dystonia of such severity that patient needed to be hospitalized.		

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Akathesia	Additional description: Akathesia of such severity that the patient needed to be hospitalized.		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sedation	Additional description: Severe sedation, required hospitalisation		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epileptic seizure	Additional description: Epileptic seizure of such severity, it required hospitalisation		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Extrapyramidal disorder	Additional description: Extrapyramidal disorder of such severity that hospitalisation was required		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glioma cerebellum			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytopenia	Additional description: Required hospitalisation		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pregnancy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Acute hepatopathy	Additional description: Required hospitalisation		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Exacerbation of psychotic symptoms			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation	Additional description: Suicidal ideation of such severity that hospitalisation is required.		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression	Additional description: Depression of such severity, hospitalisation was required		
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hospitalisation due to social circumstances			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hospitalisation due to drug use			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Rabdomiolyis	Additional description: Required hospitalisation		

subjects affected / exposed	0 / 28 (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	Phase 1 amisulpride 4 week open label	Phase 2 double blind 6 week treatment with amisulpride	Phase 2 double blind 6 week treatment with olanzapine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	223 / 446 (50.00%)	11 / 47 (23.40%)	24 / 46 (52.17%)
Investigations			
Weight gain	Additional description: Significant weight gain, i.e. 7% or more compared to baseline of the applicable treatment phase		
subjects affected / exposed	70 / 446 (15.70%)	5 / 47 (10.64%)	10 / 46 (21.74%)
occurrences (all)	70	5	10
Nervous system disorders			
Dystonia			
subjects affected / exposed	58 / 446 (13.00%)	1 / 47 (2.13%)	4 / 46 (8.70%)
occurrences (all)	58	1	4
Rigidity			
subjects affected / exposed	83 / 446 (18.61%)	3 / 47 (6.38%)	9 / 46 (19.57%)
occurrences (all)	83	3	9
Tremor			
subjects affected / exposed	92 / 446 (20.63%)	3 / 47 (6.38%)	10 / 46 (21.74%)
occurrences (all)	92	3	10
Akathesia			
subjects affected / exposed	105 / 446 (23.54%)	1 / 47 (2.13%)	5 / 46 (10.87%)
occurrences (all)	105	1	5

Non-serious adverse events	Phase 3 clozapine 12 week treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 28 (50.00%)		
Investigations			
Weight gain	Additional description: Significant weight gain, i.e. 7% or more compared to baseline of the applicable treatment phase		
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Nervous system disorders			

Dystonia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Rigidity			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Akathesia			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2011	<ul style="list-style-type: none">• follow-up visits at 48 weeks (remission criteria assessment, for phase III non-remitters only) and 72 (remission criteria assessment) were added to enable long term follow-up of participants.• contraceptive use as inclusion criteria was added on request of regulatory authorities.• inclusion criteria regarding the onset of illness was changed from 'a maximum of 2 years since onset of positive symptoms' to 'a maximum of 2 years since onset of psychosis'. Many patients have experienced vague symptoms in their childhood, but the onset of psychosis was regarded a more relevant starting point.• For patients using clozapine, leucocyte checks need to be continued for at least 4 weeks when a patient discontinues clozapine.• Several reasons for withdrawal of participants were added: 1) The nature of the patients treatment is changed to coercive treatment (based on judicial ruling); 2) In contrast to the patient's status at enrollment, the patient is now represented by a legal guardian or under legal custody; 3) Emergence of one or more contraindications against any of the study drugs as mentioned in the Summaries of Product Characteristics (refer to Appendix B). In particular, clozapine use needs to be discontinued when one or more of the following adverse events occur: severe leucopenia (leucocyte count <3000/mm³ or 3.0x10⁹/l) or neutropenia (count <1500/mm³ or 1.5x10⁹/l), myocarditis or cardiac arrhythmias; 4) Patient becomes pregnant or initiates lactation
01 July 2011	<ul style="list-style-type: none">• the recommended tapering schedule of study medication was adjusted to slow down the dose increase in order to decrease the chance on and severity of extrapyramidal symptoms, as the first patient who entered the study suffered from severe EPS.• on request of the participating centers, a titration recommendation for the transfer from phase I to phase II, and from phase II to phase III study medication was included.• target dose of 400 mg/day amisulpride was added, in line with findings from the EUFEST study. However, clinicians could deviate from the target dose as well as the titration scheme if deemed necessary.
04 July 2012	<ul style="list-style-type: none">• the eligibility for entering the Psychosocial Intervention component after the pharmaco-therapeutic component was no longer limited to patients meeting remission criteria, but also for drop outs and patients not meeting remission criteria, as they could also benefit from this intervention.• It was found that 'Schizophreniform disorder' could not be completely assessed through the M.I.N.I. diagnostic interview. Therefore the confirmation of this diagnosis was rephrased as follows: Schizophreniform disorder is assessed through a M.I.N.I. diagnosis of psychosis NOS complemented by a diagnosis of schizophreniform disorder according to DSM-IV criteria.• a clinical diagnosis was added to the long term f/u visit 22 (74 weeks) to gain insight into the stability of the diagnosis of participants at baseline.

15 November 2013	<ul style="list-style-type: none"> closure of one participating center, addition of a new participating center. increase of patient sample from 350 to 500, due to the high remission rate in phase I. a third MRS scan was added, 10 weeks after baseline, providing a longer term follow up of the timing of any glutamate changes, and investigating any differential effects of amisulpride versus olanzapine on glutamate changes. changes in Serious Adverse Event reporting were implemented: 1) pregnancy is no longer reported as SAE but rather an AE; 2) hospitalisation due to psychiatric exacerbation is reported only in the annual line listings, due to the high frequency of occurrence at this early stage of the illness and the fact that immediate reporting does not have added value.
07 May 2015	<ul style="list-style-type: none"> recalculation of power analyses for MRS. following changes in the amisulpride SPC, a safety procedure was added: if female patients have a history of breast cancer, and/or a first degree relative with a (history of) breast cancer, prolactin levels should be assessed at the local lab, at visit 2 and visit 5. a blood count assessment was added to the biomarker blood draws, in order to support epigenetic analyses.
06 July 2015	The generic amisulpride used for the study thus far, was no longer commercially available, therefore a switch to another generic amisulpride was required.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 July 2015	Due to final substantial amendment - there was a short interruption in study meds supply so the recruitment was on hold for a while.	30 September 2015

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30115598>