Clinical trial results:
OCTUMI-4: Evaluation of Mirtazapine and Folic Acid for Schizophrenia: A randomised, double-blind, 2x2 factorial trial

Summary

EudraCT number	2009-014469-19
Trial protocol	GB FI IT
Global end of trial date	18 August 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	RECOVERY[OCTUMI-4]

Additional study identifiers

ISRCTN number	ISRCTN32434568
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Wellington Square, Oxford, United Kingdom, OX1 2JD
Public contact	Professor John Geddes, University of Oxford Department of Psychiatry, =44 Email address, john.geddes@psych.ox.ac.uk
Scientific contact	Professor John Geddes, University of Oxford Department of Psychiatry, +44 1865 226451, john.geddes@psych.ox.ac.uk

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	11 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2014
Global end of trial reached?	Yes
Global end of trial date	18 August 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Principal research question: Is mirtazapine as add-on therapy to antipsychotic treatment more effective than placebo for treatment of positive and negative symptoms of schizophrenia?
Current treatments for schizophrenia, primarily antipsychotic drugs, are not fully effective. There is some evidence that treatment with mirtazapine plus an antipsychotic may be more effective than an antipsychotic alone ((Berk, Ichim & Brook 2001; Joffe et al. 2009; Zoccali et al. 2004)). OCTUMI-4 is designed to evaluate the effects of mirtazapine as add-on therapy to antipsychotic treatment in patients with schizophrenia who are currently experiencing active psychotic symptoms. OCTUMI-4 will be a double-blind placebo controlled randomised trial.

References
Berk, Ichim & Brook 2001. Int.Clin.Psychopharmacol, vol. 16, no. 2, pp. 87-92.
Joffe et al. 2009. Schizophr.Res., vol. 108, no. 1-3, pp. 245-251.
Zoccali et al. 2004. Int.Clin.Psychopharmacol, vol. 19, no. 2, pp. 71-76.

Protection of trial subjects:

If participants had difficulty concentrating during trial visits or became distressed the visit could be stopped and continued on another day.

Background therapy:

The eligibility criteria required participants to be on an effective dose of an antipsychotic medicine. (Effective was defined as the range given in the British National Formulary for maintenance treatment.)

Evidence for comparator:

Both IMPs (mirtazapine and folic acid) were compared to matched placebos. Participants were already being prescribed standard therapy for psychotic symptoms and the IMPs were prescribed as adjunctive treatment. There were no standard adjunctive treatments to use as comparators.

Actual start date of recruitment	01 January 2011
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	Finland: 9
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	52
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant was randomised on 13/4/2011 and last participant was randomised on 23/7/2013 across seven UK sites (Berkshire, Humber, Leeds, Lothian, Coventry/Warwick, Oxford, SW York), one Italy site and one Finland site.

Pre-assignment

Screening details:

Participants were enrolled into a 7 to 14 day run-in phase prior to randomisation.
During which, the antipsychotic treatment were prescribed for the duration of
the randomised phase was established. No trial drugs or placebos
were given during this phase. After the run-in phase, participants were assessed for eligibility for randomisation.

Pre-assignment period milestones

Number of subjects started	64[1]
Number of subjects completed	53

Pre-assignment subject non-completion reasons

Reason: Number of subjects	PANSS score < 60: 11

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 11 particpants were no longer eligible for randomisation after the run-un

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This is a placebo blind study

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirtazapine + Folic Acid

Arm description:

Mirtazapine + Folic Acid

Arm type	Experimental + Experimental
Investigational medicinal product name	Mirtazapine
Investigational medicinal product code	N06AX11
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mirtazapine: 30mg/day for 12 weeks followed by a 2-week tapering period of 30mg every other day.

Investigational medicinal product name	Folic acid
Investigational medicinal product code	A11E
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Folic acid: 500microg/day for 12 weeks.

Arm title	Mirtazapine + Folic Acid placebo

Arm description:

Mirtazapine + Folic Acid Placebo

Arm type	Experimental + Placebo

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine + No Folic Acid

Arm description:

Mirtazapine + No Folic Acid

Arm type	Experimental + No intervention

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine Placebo + Folic Acid

Arm description:

Mirtazapine Placebo + Folic Acid

Arm type	Placebo + Experimental

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine Placebo + Folic Acid placebo

Arm description:

Mirtazapine Placebo + Folic Acid placebo

Arm type	Placebo + Placebo

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine Placebo + No Folic Acid

Arm description:

Mirtazapine Placebo + No Folic Acid

Arm type	Placebo + No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid
Started	14	12	1
Completed	14	12	1

Number of subjects in period 1	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid placebo	Mirtazapine Placebo + No Folic Acid
Started	12	13	1
Completed	12	13	1

Period 2	
Period 2 title	Week 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Mirtazapine + Folic Acid
Arm description: Mirtazapine Placebo + Folic Acid	
Arm type	Experimental + Experimental
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine + Folic Acid placebo
Arm description: Mirtazapine Placebo + Folic Acid Placebo	
Arm type	Experimental + Placebo
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine + No Folic Acid
Arm description: Mirtazapine + No Folic Acid	
Arm type	Experimental + No intervention
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine Placebo + Folic Acid
Arm description: Mirtazapine Placebo + Folic Acid	
Arm type	Placebo + Experimental
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine Placebo + Folic Acid Placebo
Arm description: Mirtazapine Placebo + Folic Acid Placebo	
Arm type	Placebo + Placebo
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine Placebo + No Folic Acid
Arm description: Mirtazapine Placebo + No Folic Acid	
Arm type	Placebo + No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2[2]	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid
Started	13	12	1
Completed	13	10	1
Not completed	0	2	0
Consent withdrawn by subject	-	-	-

Trial terminated	-	1	-
Lost to follow-up	-	1	-

Number of subjects in period 2[2]	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid
Started	12	13	1
Completed	10	12	1
Not completed	2	1	0
Consent withdrawn by subject	1	-	-
Trial terminated	-	1	-
Lost to follow-up	1	-	-

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: Participants excluded due to attrition

Period 3

Period 3 title	Week 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirtazapine + Folic Acid

Arm description:

Mirtazapine + Folic Acid

Arm type	Experimental + Experimental

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine + Folic Acid placebo

Arm description:

Mirtazapine + Folic Acid placebo

Arm type	Experimental + Placebo

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine + No Folic Acid

Arm description:

Mirtazapine + No Folic Acid

Arm type	Experimental + No intervention

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine Placebo + Folic Acid

Arm description:

Mirtazapine Placebo + Folic Acid

Arm type	Placebo + Experimental

No investigational medicinal product assigned in this arm

Arm title	Mirtazapine Placebo + Folic Acid

Arm description:

Mirtazapine Placebo + Folic Acid

Arm type	Placebo + Experimental
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine Placebo + No Folic Acid
Arm description: Mirtazapine Placebo + No Folic Acid	
Arm type	Placebo + No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid
Started	13	10	1
Completed	13	10	1

Number of subjects in period 3	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + No Folic Acid
Started	10	12	1
Completed	10	12	1

Period 4	
Period 4 title	Week 12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator
Arms	
Are arms mutually exclusive?	Yes
Arm title	Mirtazapine + Folic Acid
Arm description: Mirtazapine + Folic Acid	
Arm type	Experimental + Experimental
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine + Folic Acid Placebo
Arm description: Mirtazapine Placebo + Folic Acid Placebo	
Arm type	Experimental + Placebo
No investigational medicinal product assigned in this arm	
Arm title	Mirtazapine + No Folic Acid
Arm description: Mirtazapine Placebo + No Folic Acid	
Arm type	Experimental + No intervention
No investigational medicinal product assigned in this arm	

Arm title	Mirtazapine Placebo + Folic Acid
Arm description: Mirtazapine Placebo + Folic Acid	
Arm type	Placebo + Experimental
No investigational medicinal product assigned in this arm	

Arm title	Mirtazapine Placebo + Folic Acid Placebo
Arm description: Mirtazapine Placebo + Folic Acid Placebo	
Arm type	Placebo + Placebo
No investigational medicinal product assigned in this arm	

Arm title	Mirtazapine Placebo + No Folic Acid
Arm description: Mirtazapine Placebo + No Folic Acid	
Arm type	Placebo + No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4[3]	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid
Started	13	9	1
Completed	13	9	1
Not completed	0	0	0
Unknown	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 4[3]	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid
Started	10	12	1
Completed	10	11	0
Not completed	0	1	1
Unknown	-	-	1
Protocol deviation	-	1	-

Notes:

[3] - 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: Particpants excluded due to attrition

Baseline characteristics

Reporting groups	
Reporting group title	Mirtazapine + Folic Acid
Reporting group description: Mirtazapine + Folic Acid	
Reporting group title	Mirtazapine + Folic Acid placebo
Reporting group description: Mirtazapine + Folic Acid Placebo	
Reporting group title	Mirtazapine + No Folic Acid
Reporting group description: Mirtazapine + No Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description: Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid placebo
Reporting group description: Mirtazapine Placebo + Folic Acid placebo	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description: Mirtazapine Placebo + No Folic Acid	

Reporting group values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid
Number of subjects	14	12	1
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)	13	12	1
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	48.9	42.5	20.7
standard deviation	± 11.8	± 8.7	± 0
Gender categorical Units: Subjects			
Female	4	2	0
Male	10	10	1
PANSS negative score Units: Subjects			
0-2	4	9	1
3-7	10	3	0

PANSS Score Units: Subjects			
< 75	5	5	1
>=75	9	7	0
Duration of illness Units: Subjects			
< 1 year	0	0	0
1-5 years	1	1	0
>=5 years	13	11	1
Benzodiazepines Units: Subjects			
Not prescribed/not taken	10	11	1
Prescribed/taken	4	1	0
Mood stabilisers Units: Subjects			
Missing	0	1	0
No	11	9	1
Yes	3	2	0
Antipschotics Units: Subjects			
FGA only	3	2	0
SGA only	10	9	1
Both	1	1	0
Calgary Depression Scale Units: Subjects			
< 6	10	8	0
>=6	4	4	1
Global Clinical Assessment of Akathisia Units: Subjects			
Absent	7	1	1
Questionable	3	9	0
Mild Akathisia	3	2	0
Moderate Akathisia	0	0	0
Marked Akathisia	1	0	0
Severe Akathisia	0	0	0
PANSS Score Units: point			
arithmetic mean	83.5	76.9	69
standard deviation	± 16.5	± 9.2	± 0
Barnes Akathisia Scale Units: Point			
arithmetic mean	1.4	2.2	0
standard deviation	± 1.9	± 1.3	± 0
Simpson-Angus Extrapyramidal Scale Units: point			
arithmetic mean	4.6	3.2	0
standard deviation	± 1.3	± 1.7	± 0

Reporting group values	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid placebo	Mirtazapine Placebo + No Folic Acid
Number of subjects	12	13	1

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)	12	13	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.4	44.4	42.2
standard deviation	± 11.7	± 8.7	± 0
Gender categorical Units: Subjects			
Female	4	2	1
Male	8	11	0
PANSS negative score Units: Subjects			
0-2	8	5	0
3-7	4	8	1
PANSS Score Units: Subjects			
< 75	5	6	0
>=75	7	7	1
Duration of illness Units: Subjects			
< 1 year	0	0	0
1-5 years	2	3	0
>=5 years	10	10	1
Benzodiazepines Units: Subjects			
Not prescribed/not taken	9	9	1
Prescribed/taken	3	4	0
Mood stabilisers Units: Subjects			
Missing	0	1	0
No	12	12	1
Yes	0	0	0
Antipschotics Units: Subjects			
FGA only	2	2	0
SGA only	6	8	1
Both	4	3	0
Calgary Depression Scale Units: Subjects			
< 6	8	11	0
>=6	4	2	1

Global Clinical Assessment of Akathisia Units: Subjects			
Absent	5	8	1
Questionable	3	1	0
Mild Akathisia	4	2	0
Moderate Akathisia	0	1	0
Marked Akathisia	0	1	0
Severe Akathisia	0	0	0
PANSS Score Units: point			
arithmetic mean	76.5	84.2	85
standard deviation	± 10.2	± 23	± 0
Barnes Akathisia Scale Units: Point			
arithmetic mean	1.4	2.2	1
standard deviation	± 1.7	± 1.3	± 0
Simpson-Angus Extrapyramidal Scale Units: point			
arithmetic mean	4.2	1.7	1
standard deviation	± 1.3	± 1.7	± 0

Reporting group values	Total		
Number of subjects	53		
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)	52		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	13		
Male	40		
PANSS negative score Units: Subjects			
0-2	27		
3-7	26		
PANSS Score Units: Subjects			
< 75	22		
>=75	31		

Duration of illness Units: Subjects			
< 1 year	0		
1-5 years	7		
>=5 years	46		
Benzodiazepines Units: Subjects			
Not prescribed/not taken	41		
Prescribed/taken	12		
Mood stabilisers Units: Subjects			
Missing	2		
No	46		
Yes	5		
Antipschotics Units: Subjects			
FGA only	9		
SGA only	35		
Both	9		
Calgary Depression Scale Units: Subjects			
< 6	37		
>=6	16		
Global Clinical Assessment of Akathisia Units: Subjects			
Absent	23		
Questionable	16		
Mild Akathisia	11		
Moderate Akathisia	1		
Marked Akathisia	2		
Severe Akathisia	0		
PANSS Score Units: point arithmetic mean standard deviation	 -		
Barnes Akathisia Scale Units: Point arithmetic mean standard deviation	 -		
Simpson-Angus Extrapyramidal Scale Units: point arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Mirtazapine + Folic Acid
Reporting group description: Mirtazapine + Folic Acid	
Reporting group title	Mirtazapine + Folic Acid placebo
Reporting group description: Mirtazapine + Folic Acid Placebo	
Reporting group title	Mirtazapine + No Folic Acid
Reporting group description: Mirtazapine + No Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description: Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid placebo
Reporting group description: Mirtazapine Placebo + Folic Acid placebo	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description: Mirtazapine Placebo + No Folic Acid	
Reporting group title	Mirtazapine + Folic Acid
Reporting group description: Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine + Folic Acid placebo
Reporting group description: Mirtazapine Placebo + Folic Acid Placebo	
Reporting group title	Mirtazapine + No Folic Acid
Reporting group description: Mirtazapine + No Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description: Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid Placebo
Reporting group description: Mirtazapine Placebo + Folic Acid Placebo	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description: Mirtazapine Placebo + No Folic Acid	
Reporting group title	Mirtazapine + Folic Acid
Reporting group description: Mirtazapine + Folic Acid	
Reporting group title	Mirtazapine + Folic Acid placebo
Reporting group description: Mirtazapine + Folic Acid placebo	
Reporting group title	Mirtazapine + No Folic Acid
Reporting group description: Mirtazapine + No Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid

Reporting group description:	
Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description:	
Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description:	
Mirtazapine Placebo + No Folic Acid	
Reporting group title	Mirtazapine + Folic Acid
Reporting group description:	
Mirtazapine + Folic Acid	
Reporting group title	Mirtazapine + Folic Acid Placebo
Reporting group description:	
Mirtazapine Placebo + Folic Acid Placebo	
Reporting group title	Mirtazapine + No Folic Acid
Reporting group description:	
Mirtazapine Placebo + No Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description:	
Mirtazapine Placebo + Folic Acid	
Reporting group title	Mirtazapine Placebo + Folic Acid Placebo
Reporting group description:	
Mirtazapine Placebo + Folic Acid Placebo	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description:	
Mirtazapine Placebo + No Folic Acid	

Primary: PANSS score

End point title	PANSS score[1]
End point description:	
End point type	Primary
End point timeframe:	
12 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Trial terminated early and sample size too small to make any interference. Descriptive statistics were presented as per SAP

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	75.2 (± 22.9)	61.9 (± 11.6)	47 (± 0)	69.8 (± 9)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[2]		
Units: point				
arithmetic mean (standard deviation)	73.6 (± 22.9)	()		

Notes:

[2] - Participant dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Negative PANSS score

End point title	Negative PANSS score

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	22.9 (± 8.9)	17.6 (± 5.7)	9 (± 0)	19.6 (± 5.2)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[3]		
Units: point				
arithmetic mean (standard deviation)	21.4 (± 6.9)	()		

Notes:

[3] - Participant dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Calgary Depression Scale

End point title	Calgary Depression Scale

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	1.8 (± 2.1)	2.1 (± 3.5)	5 (± 0)	5 (± 4.5)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[4]		
Units: point				
arithmetic mean (standard deviation)	2.2 (± 2.5)	()		

Notes:

[4] - Participant dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Severity Scale

End point title	Clinical Global Severity Scale

End point description:

End point type	Secondary

End point timeframe:

collected at 4, 8 and 12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	1	10
Units: point				
arithmetic mean (standard deviation)	3.2 (± 1.3)	3.2 (± 0.8)	1 (± 0)	3.3 (± 0.8)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	1	12	10
Units: point				
arithmetic mean (standard deviation)	3.3 (± 1.4)	4 (± 0)	3.4 (± 1.2)	3.2 (± 0.8)

End point values	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + No Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	10	12	1
Units: point				
arithmetic mean (standard deviation)	1 (± 0)	3.3 (± 0.8)	3.3 (± 1.4)	4 (± 0)

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	3.4 (± 1)	2.8 (± 0.8)	1 (± 0)	3.1 (± 1.1)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[5]		
Units: point				
arithmetic mean (standard deviation)	3.1 (± 1.3)	()		

Notes:

[5] - Participant dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Barnes Akathisia Scale from baseline

End point title	Change in Barnes Akathisia Scale from baseline

End point description:

End point type	Secondary

End point timeframe:

Measured at 4, 8, 12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	1	10
Units: point				
arithmetic mean (standard deviation)	-1 (± 1.9)	-1.3 (± 1.4)	0 (± 0)	-0.6 (± 0.8)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	1	12	10
Units: point				
arithmetic mean (standard deviation)	-0.5 (± 0.8)	-1 (± 0)	-1.3 (± 2.1)	-1.1 (± 1.4)

End point values	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + No Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	10	12	1
Units: point				
arithmetic mean (standard deviation)	0 (± 0)	-0.6 (± 2)	-0.8 (± 1.1)	-1 (± 0)

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	-1 (± 1.8)	-1.2 (± 1.1)	0 (± 0)	-0.3 (± 1.7)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[6]		
Units: point				
arithmetic mean (standard deviation)	-0.9 (± 1.4)	()		

Notes:

[6] - Participants dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Global clinical Assessment of Akathisia from baseline

End point title	Change in Global clinical Assessment of Akathisia from baseline

End point description:

End point type	Secondary

End point timeframe:

Measured at 4, 8 and 12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	1	10
Units: point				
arithmetic mean (standard deviation)	-0.6 (± 1.3)	-0.5 (± 0.8)	0 (± 0)	-0.2 (± 0.4)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	1	12	10
Units: point				
arithmetic mean (standard deviation)	-0.3 (± 0.6)	0 (± 0)	-0.8 (± 1.3)	-0.5 (± 0.8)

End point values	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + No Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	10	12	1
Units: point				
arithmetic mean (standard deviation)	0 (± 0)	-0.3 (± 0.8)	-0.6 (± 0.8)	0 (± 0)

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: point				
arithmetic mean (standard deviation)	-0.7 (± 1.3)	-0.4 (± 0.9)	0 (± 0)	-0.1 (± 0.7)

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[7]		
Units: point				
arithmetic mean (standard deviation)	-0.5 (± 0.8)	()		

Notes:

[7] - Participant dropped out at 12 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Mirtazapine

End point title	Adherence to Mirtazapine

End point description:

End point type	Secondary

End point timeframe:

at 4, 8, 12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	1	10
Units: subject				
Missing	1	0	0	0
Discontinued	1	1	0	0
<= 50%	0	0	0	0
51-70%	1	0	0	0
70-90%	1	0	0	0
>=91%	0	9	1	10

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	1	13	10
Units: subject				
Missing	0	0	1	0
Discontinued	1	0	2	1
<= 50%	0	0	0	0
51-70%	0	0	0	0
70-90%	0	0	1	0
>=91%	11	1	9	9

End point values	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + No Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	10	12	1
Units: subject				
Missing	0	0	0	0
Discontinued	0	3	3	1
<= 50%	0	0	0	0
51-70%	0	0	0	0
70-90%	0	0	1	0
>=91%	1	7	8	0

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine + No Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	1	10
Units: subject				
Missing	0	0	0	0
Discontinued	4	0	0	3
<= 50%	0	0	0	0
51-70%	0	0	0	0
70-90%	1	1	0	1
>=91%	8	8	1	6

End point values	Mirtazapine Placebo + Folic Acid Placebo	Mirtazapine Placebo + No Folic Acid		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	0[8]		
Units: subject				
Missing	0			
Discontinued	2			
<= 50%	0			
51-70%	0			
70-90%	1			
>=91%	8			

Notes:

[8] - Participant dropped out

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to Folate Acid

End point title	Adherence to Folate Acid

End point description:

End point type	Secondary

End point timeframe:

at 4, 8, 12 weeks

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	10	12
Units: Subject				
Missing	1	1	0	0
Discontinued	1	0	0	0
<=50%	1	0	0	0
51-70%	0	0	0	0
71-90%	1	9	0	0
>=91%	9	0	10	12

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid placebo	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	10	12
Units: Subject				
Missing	1	0	0	0
Discontinued	2	1	3	2
<=50%	0	0	0	0
51-70%	0	0	0	0

71-90%	1	0	0	1
>=91%	9	9	7	9

End point values	Mirtazapine + Folic Acid	Mirtazapine + Folic Acid Placebo	Mirtazapine Placebo + Folic Acid	Mirtazapine Placebo + Folic Acid Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	9	10	11
Units: Subject				
Missing	0	0	1	0
Discontinued	3	1	3	1
<=50%	1	1	0	0
51-70%	0	0	0	0
71-90%	1	1	0	1
>=91%	8	7	6	9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

+Investigators were required to report all suspected SAEs to the Chief Investigator within one working day of discovery. The event was assessed by the CI or delegate within one working day and SAE were immediately reporting to the DMC

Adverse event reporting additional description:

Investigators recorded SAEs and reportable AEs (those outwith the SmPC and/or leading to withdrawal) on trial forms. AEs were classified in terms of severity, causality and expectedness by both the investigator and the (CI or delegate). SAEs were reported to the DMC. Procedures were in place for reporting of SARs and SUSARs but none occurred.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Mirtazapine + Folic Acid
Reporting group description: -	
Reporting group title	Mirtazapine Placebo + No Folic Acid
Reporting group description: -	
Reporting group title	Mirtazapine Placebo + Folic Acid
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events only SAE.

Serious adverse events	Mirtazapine + Folic Acid	Mirtazapine Placebo + No Folic Acid	Mirtazapine Placebo + Folic Acid
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 1 (100.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			0
Psychiatric disorders			
Psychotic state	Additional description: Admission to hospital		
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 12 (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
Self-inflicted laceration	Additional description: Admission to hospital		
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 12 (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
Psychotic behaviour	Additional description: Admission to hospital		

subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 12 (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	Additional description: Admission to hospital		
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Mirtazapine + Folic Acid	Mirtazapine Placebo + No Folic Acid	Mirtazapine Placebo + Folic Acid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 12 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2011	Rating scales added at screening - Mini-International Neuropsychiatric Interview and AUDIT Alcohol Scale. Exclusion of patients with current mood episode. Change to minimisation variables and algorithm.
05 December 2011	Increase in minimum age for inclusion from 16 to 18 and option for researchers to provide trial medication in small quantities if there are concerns that the participant might take an overdose.
08 May 2012	Extension of recruitment period for the trial to 31/07/2013 with last patient out around the end of November 2013 (exact date depending on length of run-in phase of last participant).
13 March 2013	Change of manufacturer of folic acid placebo and of packager for both placebo and active tablets

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 September 2013	Recruitment was stopped in July 2013 due to withdrawal of funding. Participants already in the trial were given the option to terminate early or to complete the trial as per protocol. The final participant to complete the trial did so on 5th September 2013.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early termination of the trial only 53 participants entered the randomised phase and, of those, MMM did not complete the trial due to the forced termination.

Notes: