EU Clinical Trials Register

Clinical trial results:
OxLith: Exploration of the short-term physical and psychological effects of lithium in mood instability.

Summary

EudraCT number	2014-002699-98
Trial protocol	GB
Global end of trial date	15 January 2018

Results information

Result version number	v1 (current)
This version publication date	16 March 2022
First version publication date	16 March 2022
Summary attachment (see zip file)	OxLith full results and analysis (ST104-A_Statistical_Analysis_Report_OXLITH.pdf)

Trial information

Trial identification

Sponsor protocol code	CB001-OL

Additional study identifiers

ISRCTN number	ISRCTN91624955
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Warneford Hospital, Oxford, United Kingdom, OX3 7JX
Public contact	Professor John Geddes, University of Oxford , +44 (0)1865618202, john.geddes@psych.ox.ac.uk
Scientific contact	Professor John Geddes, University of Oxford , +44 (0)1865618202, 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	09 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is the evaluation of the effects of lithium on mood variability measured using weekly self-reports of manic and depressive symptoms.

Weekly self-rating is used routinely by many patients as part of ongoing self-management of mood by people with bipolar disorder and daily ratings have been used successfully in a number of research studies.

An understanding of the effects of lithium on mood will both inform its use and provide valuable information that will facilitate discovery of more effective and safer treatments.

Protection of trial subjects:

1. Inclusion of placebo arm. Risks associated with being allocated placebo were minimised by the excluding patients who required active treatment.
2. Lithium toxicity: The trial protocol included frequent checks of lithium levels and participants were fully informed of the potential adverse effects and the circumstances in which they should access immediate medical attention.
3. All staff completing questionnaires that contained potentially sensitive questions with participants were fully trained and instructed to stop if a participant became distressed and, if necessary, seek clinical advice.

Background therapy:

None

Evidence for comparator:

In the absence of an alternative standard therapy for this patient population, a placebo comparator was used for the trial.

Actual start date of recruitment	01 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 35
Worldwide total number of subjects	35
EEA total number of subjects	0

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)	35
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 15th August 2015 at the Oxford Health NHS Foundation Trust, Oxford UK. The last participant was recruited on 15th January 2018.

Pre-assignment

Screening details:

41 participants entered the pre-randomisation run-in phase. Patients meeting eligibility criteria were set-up for online reporting of mood on measures used to assess the primary outcome.

Participants were people with both bipolar disorder and current mood instability for whom there was uncertainty about the benefits of lithium treatment.

Pre-assignment period milestones

Number of subjects started	35
Number of subjects completed	35

Period 1

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

Blinding implementation details:

Minimisation was achieved using an online program which assigned medication according to allocation. Reporting actual/sham lithium levels to investigators was effected by an unblind staff member not otherwise involved in OxLith. Blood samples for participants on lithium were sent the laboratory. For participants on placebo an approved algorithm based on adherence and current IMP dose was used to select a sham level. The actual/sham level was then reported to the investigator who remained blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lithium

Arm description:

Treatment with Priadel - lithium carbonate.

Arm type	Experimental
Investigational medicinal product name	Priadel
Investigational medicinal product code	CAS number 554-13-2
Other name	Lithium carbonate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Priadel taken once daily at night. IMP was initiated at 400mg/day and titrated following blood tests at days 4 and 8 post-randomisation to a target serum level of 0.7mmol/L (range 0.4-1.0mmol/L). Additional lithium tests were carried out if required to achieve a stable, tolerable dose.

Titration schedule in the absence or clinical reasons to the contrary (e.g. :

Lithium level ≤ 0.3mmol/L   - dose increased to 800mg/day
Lithium level > 0.3mmol/L and < 0.6mmol/L   - dose increased to 600 or 800mg/day (clinical judgement)
Lithium level 0.6-1.0mmol/L   - continue current dose
Lithium level ≥ 0.3mmol/L   - dose decreased to by 200 or 400mg/day

(clinical judgement).

Arm title	Placebo

Arm description:

Treatment with placebo tablet matched to 400mg tablets of Priadel

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

Dosage and administration details:

As for active Priadel with titration and final dose based on sham lithium level.

Number of subjects in period 1	Lithium	Placebo
Started	19	16
Completed	19	14
Not completed	0	2
Protocol deviation	-	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Lithium
Reporting group description:	
Treatment with Priadel - lithium carbonate.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo tablet matched to 400mg tablets of Priadel	

Reporting group values	Lithium	Placebo	Total
Number of subjects	19	16	35
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)	19	16	35
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	28.9	35.2	
standard deviation	± 9.8	± 13.8	-
Gender categorical			
Units: Subjects			
Female	11	9	20
Male	8	7	15
Ethnic Group			
Units: Subjects			
White British	13	9	22
White other	1	1	2
Mixed	1	1	2
Asian	0	1	1
Black American	1	0	1
Other	3	4	7
Bipolar Diagnosis			
Units: Subjects			
BD I	3	4	7
BD II	16	11	27
BD	0	1	1
QIDS			
Quick inventory of depressive symptomology			
Units: Score			

arithmetic mean	10.6	11.6	
standard deviation	± 6.6	± 5.4	-

Altman

Altman self rating scale for mania

Units: score			
arithmetic mean	2.3	3.6	
standard deviation	± 3.7	± 3.9	-

PANAS +

Positive and negative affect scale, positive subscale

Units: Score			
arithmetic mean	6.8	7.1	
standard deviation	± 4.7	± 5.2	-

PANAS -

Positive and negative affect scale, negative subscale

Units: Score			
arithmetic mean	5.0	5.5	
standard deviation	± 4.5	± 5.9	-

CGI Mania

Clinical Global Impression, Mania

Units: Score			
median	1	1	
inter-quartile range (Q1-Q3)	1 to 2	1 to 2	-

CGI Depression

Clinical Global Impression, Depression

Units: Score			
median	2	3	
inter-quartile range (Q1-Q3)	1 to 4	2 to 3	-

CGI Bipolar

Clinical Global Impression, Bipolar

Units: Score			
median	2	2	
inter-quartile range (Q1-Q3)	2 to 4	2 to 3	-

IL6

Interleukin 6 - blood test

Units: pg/mL			
arithmetic mean	1.4	1.4	
standard deviation	± 0.6	± 0.6	-

NGAL

Neutrophil gelatinase-associated lipocalin - blood test

Units: ng/ml			
arithmetic mean	0.13	0.13	
standard deviation	± 0.03	± 0.03	-

T4

Thyroxine - blood test

Units: pmol/L			
arithmetic mean	12.9	13.1	
standard deviation	± 1.5	± 0.8	-

T3

Triiodothyronine - blood test

Units: pmol/L			
arithmetic mean	4.6	4.3	
standard deviation	± 0.6	± 0.4	-

TSH			
Thyroid stimulating hormone - blood test			
Units: mU/L			
arithmetic mean	1.3	1.3	
standard deviation	± 0.6	± 0.7	-
Calcium			
Calcium - blood test			
Units: mmol/L			
arithmetic mean	2.4	2.4	
standard deviation	± 0.1	± 0.1	-
PTH			
Parathyroid hormone - blood test			
Units: pmol/L			
arithmetic mean	5.3	5.4	
standard deviation	± 1.5	± 2.9	-
VItamin D			
Vitamin D - blood test			
Units: nmol/L			
arithmetic mean	45.9	53.7	
standard deviation	± 18.6	± 35.7	-
Creatinine			
Creatinine - blood test			
Units: umol/L			
arithmetic mean	68.1	67.3	
standard deviation	± 14.1	± 13.1	-
Cystatin C			
Cystatin C - blood test			
Units: mg/L			
arithmetic mean	0.90	0.87	
standard deviation	± 0.13	± 0.12	-
CRP			
C-reactive protein - blood test			
Units: mg/L			
arithmetic mean	1.9	2.5	
standard deviation	± 3.1	± 3.4	-

End points

End points reporting groups

Reporting group title	Lithium
Reporting group description:	
Treatment with Priadel - lithium carbonate.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo tablet matched to 400mg tablets of Priadel	

Primary: Change in QIDS score from baseline to 6 weeks

End point title	Change in QIDS score from baseline to 6 weeks
End point description:	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	13		
Units: Score				
arithmetic mean (standard deviation)	-1.94 (± 7.01)	-1.92 (± 5.81)		

Statistical analyses

Statistical analysis title	QIDS, change from baseline to 6 weeks
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8357
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	3.66

Primary: Change in ALTMAN score from baseline to 6 weeks

End point title	Change in ALTMAN score from baseline to 6 weeks
End point description:	

End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	13		
Units: Score				
arithmetic mean (standard deviation)	0.94 (± 3.57)	-0.46 (± 3.28)		

Statistical analyses

Statistical analysis title	ALTMAN, change from baseline to 6 weeks
Statistical analysis description:	

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.

Comparison groups	Placebo v Lithium
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9294
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	2.32

Primary: Change in PANAS + score from baseline to 6 weeks

End point title	Change in PANAS + score from baseline to 6 weeks
End point description:	
Change in PANAS positive affect ratings between baseline and 6 weeks	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Score				
arithmetic mean (standard deviation)	-2.44 (± 4.83)	0.50 (± 3.66)		

Statistical analyses

Statistical analysis title	PANAS +, change from baseline to 6 weeks
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0129
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.77
upper limit	-0.8

Primary: Change in PANAS - score from baseline to 6 weeks

End point title	Change in PANAS - score from baseline to 6 weeks
End point description:	
Change in PANAS negative affect ratings between baseline and 6 weeks	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: score				
arithmetic mean (standard deviation)	-1.19 (± 5.90)	-1.75 (± 4.61)		

Statistical analyses

Statistical analysis title	PANAS -, change from baseline to 6 weeks
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4482
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	4.16

Primary: Change in CGI Mania from baseline to 6 weeks

End point title	Change in CGI Mania from baseline to 6 weeks
End point description:	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 4)	4 (4 to 4)		

Statistical analyses

Statistical analysis title	CGI Mania, change from baseline to 6 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4453
Method	Wilcoxon (Mann-Whitney)

Primary: Change in CGI Depression from baseline to 6 weeks

End point title	Change in CGI Depression from baseline to 6 weeks
End point description:	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	3.5 (2 to 4)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	CGI Depression, change from baseline to 6 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Placebo v Lithium

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9047
Method	Wilcoxon (Mann-Whitney)

Primary: Change in CGI Bipolar from baseline to 6 weeks

End point title	Change in CGI Bipolar from baseline to 6 weeks
End point description:	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	3 (2 to 4)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	CGI Bipolar, change from baseline to 6 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in QIDS score from baseline to 8 days

End point title	Change in QIDS score from baseline to 8 days
End point description:	
End point type	Secondary
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	-0.95 (± 4.29)	0.40 (± 4.82)		

Statistical analyses

Statistical analysis title	Change in QIDS score from baseline to 8 days
Statistical analysis description:	

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3869
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	1.74

Secondary: Change in QIDS score from baseline to 4 weeks

End point title	Change in QIDS score from baseline to 4 weeks
End point description:	

End point type	Secondary
End point timeframe:	

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Score				
arithmetic mean (standard deviation)	-3.16 (± 5.59)	-0.21 (± 5.18)		

Statistical analyses

Statistical analysis title	QIDS, change from baseline to 4 weeks

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0578
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.26
upper limit	0.1

Secondary: Change in ALTMAN score from baseline to 8 days

End point title	Change in ALTMAN score from baseline to 8 days

End point description:

End point type	Secondary

End point timeframe:

8 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	0.53 (± 3.50)	-1.40 (± 5.37)		

Statistical analyses

Statistical analysis title	ALTMAN, change from baseline to 8 days
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3977
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	3.24
Variability estimate	Standard deviation

Secondary: Change in ALTMAN score from baseline to 4 weeks

End point title	Change in ALTMAN score from baseline to 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Score				
arithmetic mean (standard deviation)	1.05 (± 5.56)	-0.64 (± 2.68)		

Statistical analyses

Statistical analysis title	Change in ALTMAN score, baseline to 4 weeks
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4903
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	3.12

Secondary: Change in PANAS + score from baseline to 8 days

End point title	Change in PANAS + score from baseline to 8 days
End point description:	
Change in PANAS positive affect ratings between baseline and 8 days	
End point type	Secondary
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	-0.21 (± 5.24)	-2.67 (± 6.65)		

Statistical analyses

Statistical analysis title	Change in PANAS + score, baseline to 8 days
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2526
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	4.37

Secondary: Change in PANAS + score from baseline to 4 weeks

End point title	Change in PANAS + score from baseline to 4 weeks

End point description:

Change in PANAS positive affect ratings between baseline and 4 weeks

End point type	Secondary

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: Score				
arithmetic mean (standard deviation)	-1.24 (± 5.71)	-1.00 (± 5.01)		

Statistical analyses

Statistical analysis title	Change in PANAS + score, baseline to 4 weeks

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3171
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.34
upper limit	1.41

Secondary: Change in PANAS - score from baseline to 8 days

End point title	Change in PANAS - score from baseline to 8 days
End point description:	
Change in PANAS negative affect ratings between baseline and 8 days	
End point type	Secondary
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	-0.89 (± 4.81)	1.53 (± 5.33)		

Statistical analyses

Statistical analysis title	PANAS -, change from baseline to 8 days
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2965
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.34
upper limit	1.32

Secondary: Change in PANAS - score from baseline to 4 weeks

End point title	Change in PANAS - score from baseline to 4 weeks
End point description:	
Change in PANAS negative affect ratings between baseline and 4 weeks	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: Score				
arithmetic mean (standard deviation)	-2.41 (± 5.15)	0.07 (± 5.50)		

Statistical analyses

Statistical analysis title	PANAS -, change from baseline to 4 weeks
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3918
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	1.64

Secondary: Change in CGI Mania from baseline to 4 weeks

End point title	Change in CGI Mania from baseline to 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 4)	4 (4 to 4)		

Statistical analyses

Statistical analysis title	CGI Mania, change from baseline to 4 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in CGI Depression from baseline to 4 weeks

End point title	Change in CGI Depression from baseline to 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (3 to 4)	3.5 (3 to 4)		

Statistical analyses

Statistical analysis title	CGI Depression, change from baseline to 4 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Placebo v Lithium

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4233
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in CGI Bipolar from baseline to 4 weeks

End point title	Change in CGI Bipolar from baseline to 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 5)	3.5 (3 to 4)		

Statistical analyses

Statistical analysis title	CGI Bipolar, change from baseline to 4 weeks
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1739
Method	Wilcoxon (Mann-Whitney)

Secondary: PANAS + score at 8 days

End point title	PANAS + score at 8 days
End point description:	
PANAS positive affect ratings score at 8 days	
End point type	Secondary
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	5.5 (4.1 to 6.9)	5.3 (3.8 to 6.9)		

Statistical analyses

Statistical analysis title	PANAS + score, 8 days

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8734
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	2.3

Secondary: PANAS + score at 4 weeks

End point title	PANAS + score at 4 weeks

End point description:

PANAS positive affect rating score at 4 weeks

End point type	Secondary

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	5.0 (3.6 to 6.4)	6.9 (5.4 to 8.5)		

Statistical analyses

Statistical analysis title	PANAS + score, 4 weeks

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Placebo v Lithium
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0734
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.04
upper limit	0.18

Secondary: PANAS + score, 6 weeks

End point title	PANAS + score, 6 weeks

End point description:

PANAS positive affect rating score, 6 weeks

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	4.7 (3.2 to 6.1)	8.1 (6.4 to 9.7)		

Statistical analyses

Statistical analysis title	PANAS + score, 6 weeks

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.63
upper limit	-1.17

Secondary: PANAS - score, 8 days

End point title	PANAS - score, 8 days

End point description:

PANAS negative affect rating score, 8 days

End point type	Secondary

End point timeframe:

8 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	3.3 (1.8 to 4.8)	5.4 (3.7 to 7.0)		

Statistical analyses

Statistical analysis title	PANAS - score, 8 days

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0795
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.34
upper limit	0.24

Secondary: PANAS - score at 4 weeks

End point title	PANAS - score at 4 weeks

End point description:

PANAS negative affect rating score, 4 weeks

End point type	Secondary

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	3.6 (2.1 to 5.1)	4.3 (2.6 to 5.9)		

Statistical analyses

Statistical analysis title	PANAS - score, 4 weeks

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post

randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5487
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	1.58

Secondary: PANAS - score at 6 weeks

End point title	PANAS - score at 6 weeks
End point description:	
PANAS negative affect rating score, 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (confidence interval 95%)	3.7 (2.2 to 5.3)	3.5 (1.7 to 5.2)		

Statistical analyses

Statistical analysis title	PANAS - score, 6 weeks
Statistical analysis description:	

Linear mixed effects model with fixed effects for baseline total score, gender, age, continuous time, randomised group (Lithium or placebo), pre or post randomisation period, and the interaction between time and randomised group, between time and pre or post randomisation period and between pre or post randomisation period and randomised group, and the three way interaction between pre or post randomisation period, time and randomised group, and with a random effect for participant.

Comparison groups	Lithium v Placebo

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8363
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	2.62

Secondary: Change in PANAS+ SD, baseline to 6 weeks

End point title	Change in PANAS+ SD, baseline to 6 weeks

End point description:

Change from baseline to 6 weeks in the standard deviation of the PANAS positive affect scale.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: N/A				
arithmetic mean (standard deviation)	-0.73 (± 1.67)	-0.67 (± 1.87)		

Statistical analyses

Statistical analysis title	PANAS + SD, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7689
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.9

Secondary: Change in PANAS- SD, baseline to 6 weeks

End point title	Change in PANAS- SD, baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the standard deviation of the PANAS negative affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: N/A				
arithmetic mean (standard deviation)	-0.56 (± 1.68)	-1.31 (± 1.55)		

Statistical analyses

Statistical analysis title	PANAS - SD, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2609
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.74

Secondary: Change in PANAS+ rmssd,baseline to 6 weeks

End point title	Change in PANAS+ rmssd,baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the root mean square of successive differences (rmssd) of the PANAS positive affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: N/A				
arithmetic mean (standard deviation)	-0.53 (± 2.08)	-0.94 (± 2.06)		

Statistical analyses

Statistical analysis title	PANAS + rmssd, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7824
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	1.56

Secondary: Change in PANAS- rmssd,baseline to 6 weeks

End point title	Change in PANAS- rmssd,baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the root mean square of successive differences (rmssd) of the PANAS negative affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: N/A				
arithmetic mean (standard deviation)	-0.75 (± 2.51)	-1.59 (± 1.81)		

Statistical analyses

Statistical analysis title	PANAS - rmssd, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3685
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	1.96

Secondary: Change in PANAS+ entropy,baseline to 6 weeks

End point title	Change in PANAS+ entropy,baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the entropy of the PANAS positive affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: N/A				
arithmetic mean (standard deviation)	-0.33 (± 0.69)	0.05 (± 0.65)		

Statistical analyses

Statistical analysis title	PANAS + entropy, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0619
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.03

Secondary: Change in PANAS- entropy,baseline to 6 weeks

End point title	Change in PANAS- entropy,baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the entropy of the PANAS negative affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	10		
Units: N/A				
arithmetic mean (standard deviation)	-0.22 (± 0.92)	-0.22 (± 0.83)		

Statistical analyses

Statistical analysis title	PANAS - entropy, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.37

Secondary: Change in PANAS+ TKEO, baseline to 6 weeks

End point title	Change in PANAS+ TKEO, baseline to 6 weeks
End point description:	
Change from baseline to 6 weeks in the Teager Kaiser Energy Operator (TKEO) of the PANAS positive affect scale	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: N/A				
arithmetic mean (standard deviation)	-4.60 (± 12.5)	-4.95 (± 11.4)		

Statistical analyses

Statistical analysis title	Change in PANAS+ TKEO, baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-value obtained using bootstrapping with 10000 simulations.	
Comparison groups	Lithium v Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7162
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.18
upper limit	3.17

Secondary: Change in PANAS- TKEO, baseline to 6 weeks

End point title	Change in PANAS- TKEO, baseline to 6 weeks

End point description:

Change from baseline to 6 weeks in the Teager Kaiser Energy Operator (TKEO) of the PANAS negative affect scale

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: N/A				
arithmetic mean (standard deviation)	-4.3 (± 14.8)	-4.8 (± 7.3)		

Statistical analyses

Statistical analysis title	PANAS - TKEO, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo).
Confidence intervals and p-value obtained using bootstrapping with 10000 simulations.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5791
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	1.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	5.54

Secondary: Change in SCI, baseline to 6 weeks

End point title	Change in SCI, baseline to 6 weeks
End point description:	
Change in sleep pattern (SCI) from baseline to 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: N/A				
arithmetic mean (standard deviation)	-0.07 (± 5.21)	2.70 (± 7.59)		

Statistical analyses

Statistical analysis title	SCI, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9264
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	5.73

Secondary: Change in IL6, baseline to 6 weeks

End point title	Change in IL6, baseline to 6 weeks
End point description:	
Change in interleukin 6 from baseline to 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	14		
Units: pg/mL				
arithmetic mean (standard deviation)	0.34 (± 1.18)	0.01 (± 0.38)		

Statistical analyses

Statistical analysis title	IL6, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3351
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.84

Secondary: Change in NGAL, baseline to 6 weeks

End point title	Change in NGAL, baseline to 6 weeks
End point description:	
Change in neutrophil gelatinase-associated lipocalin (NGAL) from baseline to 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: ng/ml				
arithmetic mean (standard deviation)	0.02 (± 0.02)	0.00 (± 0.03)		

Statistical analyses

Statistical analysis title	NGAL, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0334
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.05

Secondary: Change in T4 , baseline to 6 weeks

End point title	Change in T4 , baseline to 6 weeks
End point description:	
Change in Thyroxine (T4) from baseline to 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: pmol/L				
arithmetic mean (standard deviation)	-0.81 (± 1.38)	-0.41 (± 0.76)		

Statistical analyses

Statistical analysis title	T4 thyroxine, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5405
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.7

Secondary: Change in T3, baseline to 6 weeks

End point title	Change in T3, baseline to 6 weeks

End point description:

Change in Triiodothyronine (T3) from baseline to 6 weeks

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	11		
Units: pmol/L				
arithmetic mean (standard deviation)	-0.14 (± 0.78)	0.10 (± 0.49)		

Statistical analyses

Statistical analysis title	Triiodothyronine, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.34

Secondary: Change in TSH, baseline to 6 weeks

End point title	Change in TSH, baseline to 6 weeks

End point description:

Change in thyroid stimulating hormone (TSH) from baseline to 6 weeks.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: mU/L				
arithmetic mean (standard deviation)	1.03 (± 1.04)	0.13 (± 0.56)		

Statistical analyses

Statistical analysis title	TSH, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0499
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.26

Secondary: Change in calcium, baseline to 6 weeks

End point title	Change in calcium, baseline to 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.01 (± 0.08)	0.00 (± 0.09)		

Statistical analyses

Statistical analysis title	Calcium, change from baseline to 6 weeks
Statistical analysis description:	

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.809
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.05

Secondary: Change in PTH, baseline to 6 weeks

End point title	Change in PTH, baseline to 6 weeks

End point description:

Change in parathyroid hormone (PTH) from baseline to 6 weeks

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: pmol/L				
arithmetic mean (standard deviation)	-0.21 (± 1.71)	-0.57 (± 1.46)		

Statistical analyses

Statistical analysis title	PTH, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3326
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.49

Secondary: Change in vitamin D, baseline to 6 weeks

End point title	Change in vitamin D, baseline to 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: nmol/L				
arithmetic mean (standard deviation)	1.67 (± 22.83)	-0.15 (± 18.74)		

Statistical analyses

Statistical analysis title	Vitamin D, change from baseline to 6 weeks
Statistical analysis description:	

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Placebo v Lithium
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2513
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	19.9

Secondary: Change in creatinine, baseline to 6 weeks

End point title	Change in creatinine, baseline to 6 weeks
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: umol/L				
arithmetic mean (standard deviation)	6.24 (± 4.78)	2.38 (± 6.41)		

Statistical analyses

Statistical analysis title	Creatinine, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0501
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	9.2

Secondary: Change in cystatin, baseline to 6 weeks

End point title	Change in cystatin, baseline to 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: mg/L				
arithmetic mean (standard deviation)	0.05 (± 0.11)	0.00 (± 0.05)		

Statistical analyses

Statistical analysis title	Cystatin C, change from baseline to 6 weeks
Statistical analysis description:	
Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.	
Comparison groups	Placebo v Lithium
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1226
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.13

Secondary: Change in CRP, baseline to 6 weeks

End point title	Change in CRP, baseline to 6 weeks
End point description:	
Change in C-reactive protein (CRP) from baseline to 6 weeks	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: mg/L				
arithmetic mean (standard deviation)	4.01 (± 10.5)	0.28 (± 5.02)		

Statistical analyses

Statistical analysis title	CRP, change from baseline to 6 weeks

Statistical analysis description:

Linear regression model with covariates for baseline measurement, gender, age, and randomised group (Lithium or placebo). Confidence intervals and p-values were obtained by bootstrapping with 10000 reps due to skewness in the data.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7857
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	8.2

Other pre-specified: Medication compliance, 4 days

End point title	Medication compliance, 4 days

End point description:

Compliance to study medication regime, reported at 4 days

End point type	Other pre-specified

End point timeframe:

4 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: People				
More than 65%	19	15		
Between 50 and 65%	0	1		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Medication compliance, 8 days

End point title	Medication compliance, 8 days

End point description:

Compliance to study medication regime, reported at 8 days

End point type	Other pre-specified

End point timeframe:

8 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: People				
More than 65%	19	15		
Between 50 and 65%	0	0		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Medication compliance, 4 weeks

End point title	Medication compliance, 4 weeks

End point description:

Compliance to study medication regime, reported at 4 weeks

End point type	Other pre-specified

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: People				
More than 65%	19	14		
Between 50 and 65%	0	0		
Missing	0	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Medication compliance, 6 weeks

End point title	Medication compliance, 6 weeks

End point description:	
Compliance to study medication regime, reported at 6 weeks	
End point type	Other pre-specified
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: People				
More than 65%	18	14		
Between 50 and 65%	0	0		
Missing	1	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in QIDS, baseline to 8 days, ITT

End point title	Change in QIDS, baseline to 8 days, ITT
End point description:	
Change in QIDS-SR16 (Quick Inventory of Depressive Symptomatology) score from baseline to 8 days, using the intention to treat population.	
End point type	Other pre-specified
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	-0.9 (± 4.3)	0.4 (± 4.8)		

Statistical analyses

Statistical analysis title	QIDS, change from baseline to 8 days, ITT
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.	
Comparison groups	Placebo v Lithium

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3841
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	1.7

Other pre-specified: Change in QIDS, baseline to 4 weeks, ITT

End point title	Change in QIDS, baseline to 4 weeks, ITT

End point description:

Change in QIDS-SR16 (Quick Inventory of Depressive Symptomatology) score from baseline to 4 weeks, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	-3.2 (± 5.6)	-0.07 (± 5.0)		

Statistical analyses

Statistical analysis title	QIDS, change from baseline to 4 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0473
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	-0.04

Other pre-specified: Change in QIDS, baseline to 6 weeks, ITT

End point title	Change in QIDS, baseline to 6 weeks, ITT
End point description:	

Change in QIDS-SR16 (Quick Inventory of Depressive Symptomatology) score from baseline to 6 weeks, using the intention to treat population.

End point type	Other pre-specified
End point timeframe:	

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Score				
arithmetic mean (standard deviation)	-1.7 (± 6.9)	-1.9 (± 5.6)		

Statistical analyses

Statistical analysis title	QIDS, change from baseline to 6 weeks, ITT
Statistical analysis description:	

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7577
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	3.6

Other pre-specified: Change in ALTMAN, baseline to 8 days, ITT

End point title	Change in ALTMAN, baseline to 8 days, ITT
End point description:	
Change in ALTMAN mania score from baseline to 8 days, using the intention to treat population.	
End point type	Other pre-specified
End point timeframe:	
8 days	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: score				
arithmetic mean (standard deviation)	0.5 (± 3.5)	-1.4 (± 5.4)		

Statistical analyses

Statistical analysis title	ALTMAN, change from baseline to 8 days, ITT
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4389
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.2

Other pre-specified: Change in ALTMAN, baseline to 4 weeks, ITT

End point title	Change in ALTMAN, baseline to 4 weeks, ITT
End point description:	
Change in ALTMAN mania score from baseline to 4 weeks, using the intention to treat population.	
End point type	Other pre-specified

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: Score				
arithmetic mean (standard deviation)	1.1 (± 5.6)	-0.9 (± 2.8)		

Statistical analyses

Statistical analysis title	ALTMAN, change from baseline to 4 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4091
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	3.2

Other pre-specified: Change in ALTMAN, baseline to 6 weeks, ITT	
End point title	Change in ALTMAN, baseline to 6 weeks, ITT

End point description:

Change in ALTMAN mania score from baseline to 6 weeks, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Score				
arithmetic mean (standard deviation)	0.3 (± 4.6)	-0.8 (± 3.4)		

Statistical analyses

Statistical analysis title	ALTMAN, change from baseline to 6 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8594
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	2.1

Other pre-specified: Change in PANAS + , baseline to 8 days, ITT

End point title	Change in PANAS + , baseline to 8 days, ITT

End point description:

Change in PANAS positive affect ratings between baseline and 8 days, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

8 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: score				
arithmetic mean (standard deviation)	-0.2 (± 5.2)	-2.7 (± 6.7)		

Statistical analyses

Statistical analysis title	PANAS +, change from baseline to 8 days, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	4.4

Other pre-specified: Change in PANAS + , baseline to 4 weeks, ITT

End point title	Change in PANAS + , baseline to 4 weeks, ITT

End point description:

Change in PANAS positive affect ratings between baseline and 4 weeks, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Score				
arithmetic mean (standard deviation)	-1.2 (± 5.7)	-1.0 (± 4.8)		

Statistical analyses

Statistical analysis title	PANAS + , change from baseline to 4 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4542
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	1.8

Other pre-specified: Change in PANAS + , baseline to 6 weeks, ITT

End point title	Change in PANAS + , baseline to 6 weeks, ITT

End point description:

Change in PANAS positive affect ratings between baseline and 6 weeks, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Score				
arithmetic mean (standard deviation)	-2.4 (± 4.8)	0.5 (± 3.7)		

Statistical analyses

Statistical analysis title	PANAS + , change from baseline to 6 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0177
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-0.6

Other pre-specified: Change in PANAS - , baseline to 8 days, ITT

End point title	Change in PANAS - , baseline to 8 days, ITT

End point description:

Change in PANAS negative affect ratings between baseline and 8 days, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

8 days

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: score				
arithmetic mean (standard deviation)	-0.9 (± 4.8)	1.5 (± 5.3)		

Statistical analyses

Statistical analysis title	PANAS - , change from baseline to 8 days, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2891
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	1.3

Other pre-specified: Change in PANAS - , baseline to 4 weeks, ITT

End point title	Change in PANAS - , baseline to 4 weeks, ITT

End point description:

Change in PANAS negative affect ratings between baseline and 4 weeks, using the intention to treat population.

End point type	Other pre-specified

End point timeframe:

4 weeks

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Score				
arithmetic mean (standard deviation)	-2.4 (± 5.1)	0.4 (± 5.4)		

Statistical analyses

Statistical analysis title	PANAS - , change from baseline to 4 weeks, ITT

Statistical analysis description:

Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.

Comparison groups	Lithium v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2965
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	1.3

Other pre-specified: Change in PANAS - , baseline to 6 weeks, ITT

End point title	Change in PANAS - , baseline to 6 weeks, ITT
End point description:	
Change in PANAS negative affect ratings between baseline and 6 weeks, using the intention to treat population.	
End point type	Other pre-specified
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Score				
arithmetic mean (standard deviation)	-1.2 (± 5.9)	-1.8 (± 4.6)		

Statistical analyses

Statistical analysis title	PANAS - , change from baseline to 6 weeks, ITT
Statistical analysis description:	
Linear mixed effects model with fixed effects for baseline total score, gender, age, assessment point (8 days, 4 weeks or 6 weeks), randomised group (Lithium or placebo) and interaction between assessment point and randomised group, and a random effect for participant. Analysis carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4931
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	4

Other pre-specified: Change in CGI Mania from baseline to 4 weeks, ITT

End point title	Change in CGI Mania from baseline to 4 weeks, ITT
End point description:	
Change in CGI mania scale between baseline and 4 weeks, using the intention to treat population	

End point type	Other pre-specified
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 4)	4 (4 to 4)		

Statistical analyses

Statistical analysis title	CGI Mania, change from baseline to 4 weeks, ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change in CGI Mania from baseline to 6 weeks, ITT

End point title	Change in CGI Mania from baseline to 6 weeks, ITT
End point description:	
Change in CGI mania scale between baseline and 6 weeks, using the intention to treat population	
End point type	Other pre-specified
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 4)	4 (4 to 4)		

Statistical analyses

Statistical analysis title	CGI Mania, change from baseline to 6 weeks, ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4453
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change in CGI Depression from baseline to 4 weeks, ITT

End point title	Change in CGI Depression from baseline to 4 weeks, ITT
End point description:	
Change in CGI depression scale between baseline and 4 weeks, using the intention to treat population	
End point type	Other pre-specified
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (3 to 4)	3.5 (3 to 4)		

Statistical analyses

Statistical analysis title	CGI Depression,change from baseline to 4 weeks,ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Placebo v Lithium
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4233
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change in CGI Depression from baseline to 6 weeks, ITT

End point title	Change in CGI Depression from baseline to 6 weeks, ITT
End point description:	
Change in CGI depression scale between baseline and 6 weeks, using the intention to treat population	

End point type	Other pre-specified
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	3.5 (2 to 4)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	CGI Depression,change from baseline to 6 weeks,ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9047
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change in CGI Bipolar from baseline to 4 weeks, ITT

End point title	Change in CGI Bipolar from baseline to 4 weeks, ITT
End point description:	
Change in CGI bipolar scale between baseline and 4 weeks, using the intention to treat population	
End point type	Other pre-specified
End point timeframe:	
4 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	4 (4 to 5)	3.5 (3 to 4)		

Statistical analyses

Statistical analysis title	CGI Bipolar, change from baseline to 4 weeks, ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1739
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Change in CGI Bipolar from baseline to 6 weeks, ITT

End point title	Change in CGI Bipolar from baseline to 6 weeks, ITT
End point description:	
Change in CGI bipolar scale between baseline and 6 weeks, using the intention to treat population	
End point type	Other pre-specified
End point timeframe:	
6 weeks	

End point values	Lithium	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: Score				
median (inter-quartile range (Q1-Q3))	3 (2 to 4)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	CGI Bipolar, change from baseline to 6 weeks, ITT
Statistical analysis description:	
Wilcoxon signed rank test, carried out on the ITT population.	
Comparison groups	Lithium v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Expedited reporting of commonly occurring SAEs (psychiatry admission for mood symptoms and/or suicidal behaviour) was not required. Reporting within 24 hours of the Investigator becoming aware of the event was required for all other SAEs/SUSARs.

Adverse event reporting additional description:

Reporting of non-serious adverse events was only required if they were judged to be reactions to lithium and were not consistent with the Reference Safety Information used for the trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Frequency threshold for reporting non-serious adverse events: 1 %

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: Previously described

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2015	OxLith SA02: New assessments introduced to measure: 1) Heart rate variability [using ePatches]. 2) Clinician rating of mood [Clinical Global Impression scales]. 3) Sleep patterns (Sleep Condition Indicator). Plus minor changes to procedures to facilitate the conduct of the trial.
01 June 2015	OxLith SA01-nd: Approval for a booklet to be given to participants providing information about visits and tasks.
28 June 2016	OxLith SA03: Introduction of an Information Leaflet to be placed in Oxford Health NHS Foundation Trust clinic areas.
13 July 2016	OxLith NSA04: Non-substantial amendment notifying REC of change of laboratory performing assays for lithium and calcium levels.
10 August 2016	OxLith SA05: Withdrawal of unused out-of-hours phone contact number for trial participants.
07 September 2016	OxLith SA07: Change of Principal Investigator for Oxford Health NHS Foundation Trust.
03 November 2016	OxLith SA06: Approval for trial information to be made available online.
22 December 2016	OxLith SA08: Update of Summary of Product Characteristics for Priadel which form the Research Safety Information provided to Trial Investigators.
23 February 2017	OxLith SA10: Changes to procedures: 1. Change of procedure for making payments to participants. 2. Recommendation to have scans on separate days. 3. Revision to time required to complete scans.
28 February 2017	OxLith SA09: Non-substantial notification to REC of extension to trial period from 04/01/2017 to 01/04/2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 February 2017	Recruitment was stopped because the supply of one IMP ran out. None of the 4 participants in the randomised phase when the problem occurred were left without treatment and only one had to be withdrawn from trial treatment prematurely to return to routine clinical care.	20 March 2017

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26936776