Clinical trial results:
Clinical evaluation of switching to Lithiofor® (Lithium Sulphate Slow – Release, Li-SR tablets) from Carbolithium® (Lithium Carbonate Immediate-Release, Li-IR, capsules) in Bipolar patients, poorly tolerant to lithium immediate-release treatment

Summary

EudraCT number	2016-001714-14
Trial protocol	IT
Global end of trial date	20 September 2019

Results information

Result version number	v1 (current)
This version publication date	05 October 2020
First version publication date	05 October 2020

Trial information

Trial identification

Sponsor protocol code	136PO15274

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03210480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AZIENDE CHIMICHE RIUNITE ANGELII FRANCESCO ACRAF S.p.A.
Sponsor organisation address	Via Amelia 70, Rome, Italy, 00181
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Scientific contact	CTAunit, AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO ACRAF S.p.A., 39 0691045335, ctaunit@angelini.it

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	20 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2019
Global end of trial reached?	Yes
Global end of trial date	20 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is the evaluation of the change in the lithium-induced tremor when switching from lithium IR formulation (Carbolithium®) to a new lithium Slow-Release (SR)/Prolonged Release (PR) formulation (Lithiofor®), after 1 week.

Protection of trial subjects:

The present study has been conducted in accordance with the study protocol, GCPs, Declaration of Helsinki (including up-to-date versions) and the applicable regulatory requirements.
Patients had written informed consent, after having been informed about benefits and potential risks of the clinical trial, as well as details of the insurance taken out to cover the subjects partecipating in the trial. No other specific measures were provided. In case of ineffective treatment the Investigator administered alternative drugs and the patients discontinued study.

Background therapy:

Not applicable

Evidence for comparator:

Lithium has been a cornerstone of therapy for bipolar disorder for several decades and is effective in the management of both manic and depressive episodes.
The effectiveness of lithium monotherapy in acute mania has been demonstrated in randomised active- and placebo-controlled trials and for this reason it is a first-line recommendation in the majority of the current clinical practice guidelines. Moreover, lithium salts have demonstrated efficacy in the prevention of mania, depression and suicidal behaviour and remain among the most commonly prescribed prophylactic medications for the maintenance phase of Bipolar Depression.

Actual start date of recruitment	01 December 2016
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	Italy: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

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

Subject disposition

Recruitment

Recruitment details:

Recruitment of 138 patients was planned. 85 were screened and 73 patients were randomised to allocated intervention (37 in Lithium PR and 36 in Lithium IR) from 28 March 2017 (FPFV) to 20 September 2019 (LPLV).

Pre-assignment

Screening details:

85 patients were screened and evaluated for relevant medical and psychiatric history, current medical conditions, age, sex, race, weight and height, clinical chemistry, hematology and urinalysis screens, screening of substance abuse and a pregnancy test in female subjects. 12 patients resulted screening failure. 73 patients were randomised.

Pre-assignment period milestones

Number of subjects started	85
Number of subjects completed	70

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Discontinued medication: 3
Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	Screening failure: 8

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. A blinded assessor performed the primary and secondary outcome evaluations, except for other safety evaluations, in order to limit bias due to the open-label conditions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test: Lithium PR

Arm description:

Lithium Sulphate Prolonged-Release 660 mg tablet (Lithiofor®) – Lithium PR

Arm type	Experimental
Investigational medicinal product name	Lithium Sulphate Prolonged-Release 660 mg tablet
Investigational medicinal product code	136
Other name	Lithiofor®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients had to take orally one tablet once or twice daily (one tablet in the morning and one tablet in the evening) or two tablets in a single dose (two tablets in the evening).

Arm title	Reference: Lithium IR

Arm description:

Lithium Carbonate Immediate-Release 150 mg and 300 mg capsules (Carbolithium®) – Lithium IR

Arm type	Active comparator

Investigational medicinal product name	Lithium Carbonate Immediate-Release 150 mg and 300 mg
Investigational medicinal product code	136
Other name	Carbolithium®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients had to take orally 300-1800 mg daily divided into 2-6 doses daily.

Number of subjects in period 1[1]	Test: Lithium PR	Reference: Lithium IR
Started	35	35
Completed	27	32
Not completed	8	3
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	-
Protocol deviation	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 85 patients were screened and evaluated. 73 patients were randomised.

Baseline characteristics

Reporting groups	
Reporting group title	Test: Lithium PR
Reporting group description:	
Lithium Sulphate Prolonged-Release 660 mg tablet (Lithiofor®) – Lithium PR	
Reporting group title	Reference: Lithium IR
Reporting group description:	
Lithium Carbonate Immediate-Release 150 mg and 300 mg capsules (Carbolithium®) – Lithium IR	

Reporting group values	Test: Lithium PR	Reference: Lithium IR	Total
Number of subjects	35	35	70
Age categorical			
Patients aged 18-65 - m-ITT			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
From 18 to 65 years	35	35	70
Age continuous			
Subjects			
Units: years			
arithmetic mean	45.20	45.54	
standard deviation	± 11.71	± 14.66	-
Gender categorical			
Gender - mITT			
Units: Subjects			
female	20	23	43
male	15	12	27

Subject analysis sets	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population included all randomized subjects who took at least one dose of the study treatments and consisted of 72 patients (1 patient did not take any study medication).	

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified ITT population consisted of all randomized patients who took at least one dose of study	

medication and had an evaluation of the primary endpoint (tremor) both at baseline and at 1 week of treatment. Following the Data Review Meeting, three patients (4003, 2009 and 7001) were excluded from the m-ITT that therefore it consisted of 70 patients.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of all patients in m-ITT with no major protocol deviations and a treatment compliance ≥80% from baseline to 1-week treatment period.Following the Data Review Meeting, 20 additional patients were excluded from the PP population leaving 50 PP patients.

Reporting group values	Safety population	m-ITT population	PP population
Number of subjects	72	70	50
Age categorical			
Patients aged 18-65 - m-ITT			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
From 18 to 65 years	72	70	50
Age continuous			
Subjects			
Units: years			
arithmetic mean	45.37	45.37	47.24
standard deviation	± 13.17	± 13.17	± 13.44
Gender categorical			
Gender - mITT			
Units: Subjects			
female	43	43	31
male	27	27	19

End points

End points reporting groups

Reporting group title	Test: Lithium PR

Reporting group description:

Lithium Sulphate Prolonged-Release 660 mg tablet (Lithiofor®) – Lithium PR

Reporting group title	Reference: Lithium IR

Reporting group description:

Lithium Carbonate Immediate-Release 150 mg and 300 mg capsules (Carbolithium®) – Lithium IR

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population included all randomized subjects who took at least one dose of the study treatments and consisted of 72 patients (1 patient did not take any study medication).

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT population consisted of all randomized patients who took at least one dose of study medication and had an evaluation of the primary endpoint (tremor) both at baseline and at 1 week of treatment. Following the Data Review Meeting, three patients (4003, 2009 and 7001) were excluded from the m-ITT that therefore it consisted of 70 patients.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of all patients in m-ITT with no major protocol deviations and a treatment compliance ≥80% from baseline to 1-week treatment period.Following the Data Review Meeting, 20 additional patients were excluded from the PP population leaving 50 PP patients.

Primary: Proportion of patients with Improvement in tremor at 1 week

End point title	Proportion of patients with Improvement in tremor at 1 week[1]

End point description:

The primary endpoint was the evaluation of the proportion of patients with an improvement in tremor assessed by a single item (2.5 tremor, see section 9.5.1.1) of the UKU side-effect rating scale after 1-week treatment period compared to baseline. Improvement was defined as a difference ≥1 between scoring system at baseline and scoring system after 1 week of treatment. m-ITT.
Statistical Analysis Fisher's exact test p-value (two-tail)

End point type	Primary

End point timeframe:

After 1 week of treatment vs baseline.

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: The primary endpoint was analyzed using a two tailed Fisher’s exact test with an alpha level of 0.05.

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
number (confidence interval 95%)	62.9 (46.85 to 78.86)	20 (6.75 to 33.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with Improvement in tremor at 4 weeks

End point title	Proportion of patients with Improvement in tremor at 4 weeks

End point description:

The evaluation of the proportion of patients with an improvement in tremor assessed using a single item of the UKU side-effect rating scale (item 2.5 tremor) at 4-weeks treatment period compared to baseline. m-ITT

End point type	Secondary

End point timeframe:

After 4 weeks of treatment vs baseline.

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
number (confidence interval 95%)	85.7 (72.75 to 98.68)	48.6 (32.01 to 65.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with Improvement in tremor at 12 weeks

End point title	Proportion of patients with Improvement in tremor at 12 weeks

End point description:

The evaluation of the proportion of patients with an improvement in tremor assessed using a single item of the UKU side-effect rating scale (item 2.5 tremor) at 12-weeks treatment period compared to baseline. m-ITT

End point type	Secondary

End point timeframe:

After 12 weeks of treatment vs baseline.

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
number (confidence interval 95%)	92.6 (82.71 to 100)	64.5 (47.67 to 81.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with an improvement in polyuria/polydipsia after 1 week

End point title	Proportion of patients with an improvement in polyuria/polydipsia after 1 week

End point description:

Proportion of patients with an improvement in polyuria/polydipsia; assessed by single item of the UKU side-effect rating scale (item 3.8 polyuria/polydipsia) after 1-week treatment periods compared to baseline; m-ITT

End point type	Secondary

End point timeframe:

After 1-week treatment periods compared to baseline;

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percent				
number (confidence interval 95%)	2.9 (0.00 to 8.38)	17.1 (4.66 to 29.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with an improvement in polyuria/polydipsia after 4 weeks

End point title	Proportion of patients with an improvement in polyuria/polydipsia after 4 weeks

End point description:

Proportion of patients with an improvement in polyuria/polydipsia; assessed by single item of the UKU side-effect rating scale (item 3.8 polyuria/polydipsia) after 4-weeks treatment periods compared to baseline; m-ITT

End point type	Secondary

End point timeframe:

After 4-weeks treatment periods compared to baseline;

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
number (confidence interval 95%)	21.4 (6.23 to 36.6)	17.1 (4.66 to 29.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with an improvement in polyuria/polydipsia after 12 weeks

End point title	Proportion of patients with an improvement in polyuria/polydipsia after 12 weeks

End point description:

Proportion of patients with an improvement in polyuria/polydipsia; assessed by single item of the UKU side-effect rating scale (item 3.8 polyuria/polydipsia) after 12-weeks treatment periods compared to baseline; m-ITT

End point type	Secondary

End point timeframe:

After 12-weeks treatment periods compared to baseline;

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
number (confidence interval 95%)	22.2 (6.54 to 37.90)	22.6 (7.86 to 37.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (MADRS scale) from baseline after 1-week

End point title	Changes in manic and depressive symptoms (MADRS scale) from baseline after 1-week

End point description:

Changes in manic and depressive symptoms were assessed from baseline after 1-week of treatment according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 1-week of treatment

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	9.19 (± 131.12)	18.6 (± 131.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (MADRS scale) from baseline after 4-weeks

End point title	Changes in manic and depressive symptoms (MADRS scale) from baseline after 4-weeks

End point description:

Changes in manic and depressive symptoms from baseline after 4-weeks of treatment. The manic and depressive symptoms assessment will be performed according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 4-weeks of treatment

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	-0.30 (± 95.44)	50 (± 175.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (MADRS scale) from baseline after 12-weeks

End point title	Changes in manic and depressive symptoms (MADRS scale) from baseline after 12-weeks

End point description:

Changes in manic and depressive symptoms from baseline after 12-weeks of treatment. The manic and depressive symptoms assessment will be performed according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 12-weeks of treatment

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	13.94 (± 96.24)	46.55 (± 201.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (YMRS scale) after 1-week

End point title	Changes in manic and depressive symptoms (YMRS scale) after 1-week

End point description:

Changes in manic and depressive symptoms were assessed from baseline after 1-week of treatment according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 1-week of treatment

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	-12.75 (± 66.74)	-19.21 (± 49.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (YMRS scale) after 4-weeks

End point title	Changes in manic and depressive symptoms (YMRS scale) after 4-weeks

End point description:

Changes in manic and depressive symptoms were assessed from baseline after 4-weeks of treatment according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 4-weeks of treatment

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	-43.14 (± 74.37)	15.87 (± 153.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in manic and depressive symptoms (YMRS scale) after 12 -weeks

End point title	Changes in manic and depressive symptoms (YMRS scale) after 12 -weeks

End point description:

Changes in manic and depressive symptoms were assessed from baseline after 12 -weeks of treatment according to the rating scale MADRS and YMRS scales.

End point type	Secondary

End point timeframe:

After 12 -weeks

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	-15.20 (± 83.81)	-42.06 (± 91.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in patient’s satisfaction from baseline at 1 week (TSQM)	
End point title	Changes in patient’s satisfaction from baseline at 1 week (TSQM)

End point description:

Patient’s satisfaction to the assigned treatment from baseline to 1 week of treatment was assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) Version II.

End point type	Secondary

End point timeframe:

After 1 week

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	22.18 (± 93.66)	-2.78 (± 27.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in patient’s satisfaction from baseline at 12 weeks (TSQM)	
End point title	Changes in patient’s satisfaction from baseline at 12 weeks (TSQM)

End point description:

Patient’s satisfaction to the assigned treatment from baseline to 12 weeks of treatment was assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) Version II.

End point type	Secondary

End point timeframe:

After 12 weeks

End point values	Test: Lithium PR	Reference: Lithium IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent				
arithmetic mean (standard deviation)	8.80 (± 83.70)	1.68 (± 30.69)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for reporting adverse events is from informed Consent signature up to the last visit scheduled in the study (12 weeks after Visit 1)

Adverse event reporting additional description:

The adverse events seen in the study were as expected for this population and this class of drugs. They were mostly mild and transient, did not seem to be dose-related and gave no indication of target organ toxicity or unexpected findings.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Test: Lithium PR

Reporting group description:

Lithium sulphate prolonged-release 660 mg tablet (Lithiofor). Patients took orally one tablet once or twice daily (one tablet in the morning and one tablet in the evening) or two tablets in a single dose (two tablets in the evening). 1 patient never took study medication.

Reporting group title	Reference: Lithium IR

Reporting group description:

Lithium carbonate immediate-release 150 mg and 300 mg capsules (Carbolithium®). Patients took orally 300-1800 mg daily divided into 2-6 doses.

Serious adverse events	Test: Lithium PR	Reference: Lithium IR	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	1 / 36 (2.78%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour	Additional description: Patient relatives informed directly the Investigators that the patient had committed suicide.		
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Test: Lithium PR	Reference: Lithium IR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 36 (52.78%)	16 / 36 (44.44%)	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoe			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 36 (5.56%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Psychiatric symptom			

subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	1 / 36 (2.78%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Elevated mood			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Bipolar disorder			
subjects affected / exposed	2 / 36 (5.56%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Panic attack			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Investigations			
Thyroid function test			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	2 / 36 (5.56%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Foot fracture			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Overdose			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Atrioventricular block			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Tremor			
subjects affected / exposed	4 / 36 (11.11%)	3 / 36 (8.33%)	
occurrences (all)	4	3	
Headache			
subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 36 (2.78%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	4 / 36 (11.11%)	5 / 36 (13.89%)	
occurrences (all)	5	7	
Leukocyturia			

subjects affected / exposed	1 / 36 (2.78%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 36 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 36 (5.56%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Prostatitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Herpes ophthalmic			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Polydipsia			
subjects affected / exposed	3 / 36 (8.33%)	4 / 36 (11.11%)	
occurrences (all)	4	6	
Dyslipidaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2017	Amendment no. 1 of 15-May 2017, (protocol version 3.0 dated 15/05/2017) was issued after the completion of the Italian commercialization procedure, in order to include the reference to the prolonged-release formulation marketed by Angelini S.p.A., with the commercial brand name Resilient™.
20 February 2018	Amendment no. 2 of 6 February 2018 issued to include two additional sites (Azienda Sanitaria dell'Alto Adige Servizio Psichiatrico del Comprensorio Sanitario di Bolzano and Ospedale San Giovanni di Dio di Orbetello Unità Funzionale Salute Mentale). Azienda Sanitaria dell'Alto Adige Servizio Psichiatrico del Comprensorio Sanitario di Bolzano later asked to be excluded from participation and did not randomize any patient.
17 August 2018	Amendment no. 4 of 19 April 2018 (protocol version 4.0 dated 19.04.2018), to introduce: • Changes in the Sponsor's personnel, due to internal reorganization, • Updated safety information and updated SPC of Carbolithium®, • Modification of the informed consent form following the entry into force of the Regulation 2016/679 EU (GDPR).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to the objective difficulties in patient recruitment (after the availability of Lithium PR -Resilient ™ on the Italian market), the Sponsor decided to terminate the study early in June 2019, including 85 patients out of 138 expected.

Notes: