Clinical trial results:
A pilot, open-label, rater-blinded, randomized, parallel-group, multi-center study to evaluate the safety, tolerability and preliminary efficacy of three add-on fixed doses of Evenamide in patients with treatment-resistant schizophrenia (TRS) not responding adequately to their stable, therapeutically active dose of a single antipsychotic medication

Summary

EudraCT number	2020-000437-41
Trial protocol	IT
Global end of trial date	22 December 2022

Results information

Result version number	v1 (current)
This version publication date	11 April 2024
First version publication date	11 April 2024
Summary attachment (see zip file)	Clinical Study Report (NW3509-014-II-2019-CSR.pdf)

Trial information

Trial identification

Sponsor protocol code	NW-3509/014/II/2019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Newron Pharmaceuticals SpA
Sponsor organisation address	Via Antonio Meucci 3, Bresso, Italy, 20091
Public contact	CRO, Pharmaceutical Development and Services, +39 0557224179, regulatoryaffairs@newron.com
Scientific contact	CRO, Pharmaceutical Development and Services, +39 0557224179, regulatoryaffairs@newron.com
Sponsor organisation name	Newron Pharmaceuticals SpA
Sponsor organisation address	Via Antonio Meucci 3, Bresso, Italy, 20091
Public contact	Pharmaceutical Development and Services, CRO, 0557224179, edimartino@pharmades.it, Ravi Anand, regulatoryaffairs@newron.com
Scientific contact	Pharmaceutical Development and Services, CRO, 0557224179, edimartino@pharmades.it, Ravi Anand, regulatoryaffairs@newron.com

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	17 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2022
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5, 15 and 30 mg bid) in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic doses of their current antipsychotic medication.

Protection of trial subjects:

A physician was responsible for the clinical aspects of the study and was available at all times during the study. All subjects were monitored from the screening for Safety. The evaluation of safety parameters comprised analysis of AEs, laboratory variables, vital signs, ECG, neurological and physical examination, Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) and Calgary Depression Scale for Schizophrenia (CDSS).

Background therapy:

Patients were receiving a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine)

Evidence for comparator: -

Actual start date of recruitment	16 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	India: 141
Country: Number of subjects enrolled	Sri Lanka: 16
Worldwide total number of subjects	161
EEA total number of subjects	4

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)	160
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients meeting inclusion/exclusion criteria were randomized to receive treatment (evenamide 7.5 mg or 15 mg or 30 mg bid) for 6-week.

Pre-assignment

Screening details:

Patients underwent screening assessments during a 3 to 21-day period. Patients meeting the inclusion/exclusion criteria at baseline (Day 0 pre-dose) were randomized to treatment.

Period 1

Period 1 title	6-week, open-label, randomized (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

This was an Open-label, rater-blinded study: Investigator and study staff, except for the blinded rater assessing safety and efficacy rating scales, were aware of the treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Evenamide 7.5 mg bid

Arm description:

The patients received evenamide 7.5 mg bid.

Arm type	Experimental
Investigational medicinal product name	Evenamide
Investigational medicinal product code	NW-3509
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Evenamide 7,5 mg bid, oral

Arm title	Evenamide 15 mg bid

Arm description:

The patients received evenamide 15 mg bid.

Arm type	Experimental
Investigational medicinal product name	Evenamide
Investigational medicinal product code	NW-3509
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Evenamide 15 mg bid, oral

Arm title	Evenamide 30 mg bid

Arm description:

The patients received evenamide 30 mg bid.

Arm type	Experimental

Investigational medicinal product name	Evenamide
Investigational medicinal product code	NW-3509
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Evenamide 30 mg bid, oral

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is an open-label, rater-blinded study; therefore, the Investigator and study staff, except for the blinded rater assessing safety and efficacy, were aware of the patient's treatment assignment.

Number of subjects in period 1	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid
Started	50	60	51
Completed	49	56	48
Not completed	1	4	3
Consent withdrawn by subject	-	4	3
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Evenamide 7.5 mg bid
Reporting group description:	
The patients received evenamide 7.5 mg bid.	
Reporting group title	Evenamide 15 mg bid
Reporting group description:	
The patients received evenamide 15 mg bid.	
Reporting group title	Evenamide 30 mg bid
Reporting group description:	
The patients received evenamide 30 mg bid.	

Reporting group values	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid
Number of subjects	50	60	51
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)	49	60	51
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.7	37.2	38.3
standard deviation	± 10.4	± 9.7	± 9.1
Gender categorical Units: Subjects			
Female	18	18	14
Male	32	42	37
PANSS total score			
Positive and Negative Syndrome Scale (PANSS)			
Units: Score 30-210			
arithmetic mean	80.1	79.2	79.4
standard deviation	± 5.2	± 5.2	± 4.8
CGI-S			
Clinical Global Impression – Severity of Illness (CGI-S) score			
Units: Score 1-7			
arithmetic mean	4.6	4.5	4.4
standard deviation	± 0.7	± 0.6	± 0.5

Reporting group values	Total		
Number of subjects	161		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	160		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	50		
Male	111		
PANSS total score			
Positive and Negative Syndrome Scale (PANSS)			
Units: Score 30-210			
arithmetic mean			
standard deviation	-		
CGI-S			
Clinical Global Impression – Severity of Illness (CGI-S) score			
Units: Score 1-7			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Evenamide 7.5 mg bid
Reporting group description:	
The patients received evenamide 7.5 mg bid.	
Reporting group title	Evenamide 15 mg bid
Reporting group description:	
The patients received evenamide 15 mg bid.	
Reporting group title	Evenamide 30 mg bid
Reporting group description:	
The patients received evenamide 30 mg bid.	

Primary: Safety and tolerability

End point title	Safety and tolerability[1]
End point description:	
Number of patients who experienced at least one Treatment Emergent Adverse Event (TEAE).	
End point type	Primary
End point timeframe:	
From Randomization to Week 6 (Day 43) plus 7-day safety FU	

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: For the safety end point descriptive statistics (e.g frequency, change from baseline, etc.) presented by treatment group and aggregate has been used. No inferential analysis was performed.

End point values	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50[2]	60[3]	50[4]	
Units: N				
number (not applicable)	13	10	18	

Notes:

[2] - Safety population

[3] - Safety population

[4] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PANSS Total Score (day 43)

End point title	Change from Baseline in PANSS Total Score (day 43)
End point description:	
To evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5, 15 and 30 mg bid) in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic doses of their current antipsychotic medication.	
End point type	Secondary

End point timeframe:

6-Week Treatment Period

End point values	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[5]	56[6]	48[7]	
Units: PANSS Total Score				
arithmetic mean (standard deviation)	-9.0 (± 7.4)	-10.6 (± 7.5)	-8.6 (± 6.4)	

Notes:

[5] - mITT population

[6] - mITT population

[7] - mITT population

Statistical analyses

Statistical analysis title	Paired t-test - mITT population

Statistical analysis description:

The mean change from Baseline at Day 43 in PANSS Total Score using within group comparisons was analyzed by using a paired t-test for the mITT Population (a mITT population comprises all patients who received at least one dose of the study medication and had both a baseline and at least one post-baseline PANSS efficacy assessment).

Comparison groups	Evenamide 7.5 mg bid v Evenamide 15 mg bid v Evenamide 30 mg bid
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.05 [9]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[8] - No comparison between treatment groups (7.5, 15 and 30 mg bid): only within group comparisons was analised

[9] - A significant (p<0.001) mean change from baseline IN PANSS total score of -9.0, -10.6 and -8.6 was observed in evenamide 7.5 mg, 15 mg and 30 mg bid treated groups respectively.

Secondary: Change from Baseline in Clinical Global Impression – Severity of Illness (CGI-S) score

End point title	Change from Baseline in Clinical Global Impression – Severity of Illness (CGI-S) score

End point description:

Change from Baseline in Clinical Global Impression – Severity of Illness (CGI-S) score

End point type	Secondary

End point timeframe:

From Randomization to Week 6 (Day 43).

End point values	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[10]	56[11]	48[12]	
Units: Score 1-7				
arithmetic mean (standard deviation)	-0.6 (± 0.8)	-0.8 (± 0.7)	-0.7 (± 0.6)	

Notes:

[10] - mITT population

[11] - mITT population

[12] - mITT population

Statistical analyses

Statistical analysis title	Paired t-test - mITT population

Statistical analysis description:

The mean change from Baseline at Day 43 in CGI-S using within group comparisons was analyzed by using a paired t-test for the mITT Population.

Comparison groups	Evenamide 7.5 mg bid v Evenamide 15 mg bid v Evenamide 30 mg bid
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [13]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[13] - The results of the paired t-test performed at post-dose visits to analyze CGI-S change from baseline within each dose group showed a significant (p<0.001) reduction in the mean change from baseline of -0.6, -0.8 and -0.7 at Day 43 in evenamide 7.5 mg

Adverse events

Adverse events information

Timeframe for reporting adverse events:

for Treatment emergent adverse events (TEAEs) the time frame was from randomization to the end of the safety follow-up period (1 week after last dose of study medication). 30 days after last dose for SAEs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Evenamide 7.5 mg bid

Reporting group description:

Subjects affected by non-serious adverse events: 10. This is the number of adverse events with a threshold > 3%
Subjects who had at least one adverse event non-serious are totally 13.

Reporting group title	Evenamide 15 mg bid

Reporting group description:

Subjects affected by non-serious adverse events: 1. This is the number of adverse events with a threshold > 3%
Subjects who had at least one adverse event non-serious are totally 10.

Reporting group title	Evenamide 30 mg bid

Reporting group description:

Subjects affected by non-serious adverse events: 9. This is the number of adverse events with a threshold > 3%
Subjects who had at least one adverse event non-serious are totally 18.

Serious adverse events	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 60 (0.00%)	7 / 50 (14.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Medication error	Additional description: Medication errors, asymptomatic and not associated with adverse events, were reported in 7/160 (4.4%) in the safety population (reported as per protocol as SAE). None of the subjects in any treatment groups reported a treatment-related SAE.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 60 (0.00%)	7 / 50 (14.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Evenamide 7.5 mg bid	Evenamide 15 mg bid	Evenamide 30 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 50 (20.00%)	1 / 60 (1.67%)	9 / 50 (18.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 60 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 60 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	2 / 50 (4.00%)	0 / 60 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 50 (0.00%)	0 / 60 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 60 (1.67%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 60 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 60 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 50 (4.00%)	0 / 60 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2019	AMENDMENT 1 India. Reporting overdose: Section 13.1.6 of the protocol, Reporting of Overdose, has been modified to indicate that the procedures to be followed are based on Sponsor safety reporting standards. The new language conforms to the reporting requirements specified in previous clinical study protocols for evenamide. This modification of the protocol was a procedural change and had no impact on the safety of patients enrolled in the study
02 February 2020	AMENDMENT 2 Increase in the number of participating sites (up to 25); sites in Sri Lanka and Italy being added to the study. Changes based on feedback from investigators for the use of concomitant psychotropic medication: e.g. maximum dose of quetiapine increased up to 150 mg hs as soporific, no restrictions on the maximum dose of lorazepam, or equivalent short half-life BDZ, for patients not receiving a benzodiazepine upon entry into the trial, administration of 0.5 mg lorazepam (or equivalent dose of another benzodiazepine) is allowed as rescue medication during the study on a prn basis, with a maximum daily dose of 2 mg. The protocol has been modified to allow daily doses greater than 2 mg (or equivalent) to be administered, if clinically necessary.
05 July 2020	AMENDMENT 3 Update of information related to the study, and correct some errors and inconsistencies in the protocol, change/addition of the local CROs (Malaysia and Italy) and change of Planned Trial Period in light of the global COVID 19 pandemic.
18 September 2020	AMENDMENT 4 Protocol modifications in response to the following requests made by the Agenzia Italiana del Farmaco (AIFA) to allow opening of investigational centers in Italy: criteria have been added regarding discontinuation of a subject from treatment, in addition to the reasons for discontinuing the subject from the study. Procedures have been described for collecting data from subjects who discontinue treatment but remain in the study and return for scheduled visits.
04 February 2021	AMENDMENT 5 Based on an Investigators request, indicating that the requirement for the diagnosis of schizophrenia within the past 10 years was too restrictive then excluding many patients who would otherwise be eligible for the trial. The Amendment modified the inclusion criteria related to the duration of the diagnosis of schizophrenia and the classification of the patient as "treatment-resistant." Patients were eligible for the study if the diagnosis of schizophrenia was made within the past 15 years. Additionally, patients must have been identified as being treatment-resistant within the past 10 years. Additional modifications have been made to correct minor errors and omissions and clarification of the timing of the following assessments Vital signs, ECGs, Ratings of PANSS, CGI-S and CGI-C, Sample collection for laboratory tests, have been made.
17 June 2021	AMENDMENT 6 The dosing and the randomization to the three treatment groups, were modified based on the interim safety assessment of the data from the first 50 patients randomized in Study 014, as well as the available results from Study 008 (NW-3509/008/II/2019). This safety data were reviewed by the Independent Safety Monitoring Board, which determined that it was safe to proceed with the 30 mg bid dose. This decision, lead to the discontinuation of the evenamide 7.5 mg bid dose group from the study, and the modification of the randomization to a 1:3 ratio for the 15 mg bid and 30 mg bid dose groups, respectively.

16 March 2022	AMENDMENT 7 Addition of an interim analysis of the data for all efficacy measures from the first 100 patients who complete their participation in the study. This analysis was performed as the Independent Safety Monitoring Board has requested evidence of benefit following their review of the safety data from these 100 patients, to determine whether a benefit-risk assessment justifies the long-term treatment of patients with evenamide. None of these changes impacted the patient population to be enrolled, or the planned safety and efficacy assessments to be performed in the trial.
03 May 2022	AMENDMENT 8 The study sample size was increased from a minimum of 150 to approximately 180 patients. This change was made to ensure that at least 50 patients are randomized to each of the three treatment groups (evenamide 7.5 mg, 15 mg and 30 mg, bid). Malaysia was removed as a participating country in the study. Appropriate changes have been made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37349110