Clinical trial results:
A phase II/III, prospective, multi-center, randomized, 4-week, double-blind, placebo-controlled study, designed to determine the safety, tolerability, EEG effects and efficacy of oral doses of 30 mg bid of evenamide (NW-3509) in patients with chronic schizophrenia who are symptomatic on their current second-generation antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone) medication.

Summary

EudraCT number	2020-006062-36
Trial protocol	IT HU LV ES CZ RO DE EE PL
Global end of trial date	06 November 2024

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Clinical Study Report (CSR_008A_Final Version 1.0, dated 06th July 2024_Clean (5).pdf)

Trial information

Trial identification

Sponsor protocol code	NW-3509/008A/II/2020

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	Ravi Anand, Newron Pharmaceuticals S.p.A., 41 793741364, ravi@anand.ch
Scientific contact	Ravi Anand, Newron Pharmaceuticals SpA, 41 793741364, ravi@anand.ch
Sponsor organisation name	Newron Pharmaceuticals SpA
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Scientific contact	Rodolfo Giuliani, Newron Pharmaceuticals SpA, +39 3358100233, 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	06 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the safety and tolerability (including EEG and ECG effects) of an oral dose of evenamide of 30 mg bid [60 mg/day]), achieved after a 1-week titration starting with 15 mg bid, compared to placebo, in patients with schizophrenia who are being treated with stable doses of antipsychotic medication (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone)
-To evaluate the efficacy of evenamide at a dose of 30 mg bid, achieved after a 1-week titration starting with 15 mg bid, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) total score.

Protection of trial subjects:

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 with chronic schizophrenia who are symptomatic on their current second-generation antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone) medication.

Evidence for comparator: -

Actual start date of recruitment	08 September 2021
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	Argentina: 54
Country: Number of subjects enrolled	Czechia: 63
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	Hungary: 8

Country: Number of subjects enrolled	India: 112
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	291
EEA total number of subjects	116

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)	280
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients meeting inclusion/exclusion criteria were randomized to receive treatment (evenamide 30 mg bid, achieved after a 1-week titration starting with 15 mg bid) or placebo for 4-week.

Pre-assignment

Screening details:

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	4-week, double-blind, placebo-controlled (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Evenamide 30 mg bid

Arm description:

Evenamide

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

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

twice a day

Number of subjects in period 1	Evenamide 30 mg bid	Placebo
Started	132	159
Completed	126	154
Not completed	6	5
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	4
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Evenamide 30 mg bid
Reporting group description: Evenamide	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Evenamide 30 mg bid	Placebo	Total
Number of subjects	132	159	291
Age categorical			
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)	126	154	280
From 65-84 years	6	5	11
85 years and over	0	0	0
Age continuous			
Age continuous			
Units: years			
median	40.0	40.6	
standard deviation	± 12.47	± 11.78	-
Gender categorical			
Units: Subjects			
Female	36	48	84
Male	96	111	207

End points

End points reporting groups

Reporting group title	Evenamide 30 mg bid
Reporting group description: Evenamide	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Safety and tolerability

End point title	Safety and tolerability
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 4 (Day 29) plus 30-day safety FU	

End point values	Evenamide 30 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[1]	159[2]		
Units: Number patient	34	44		

Notes:

[1] - Patients who received at least on dose of evenamide 30 mg bid

[2] - Patients who took placebo

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in PANSS Total Score (day 29) MMRM ITT pop

End point title	Change from Baseline in PANSS Total Score (day 29) MMRM ITT pop
End point description: To evaluate the efficacy of evenamide at a dose of 30 mg bid, achieved after a 1-week titration starting with 15 mg bid, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) total score.	
End point type	Primary
End point timeframe: From Randomization to Week 4 (Day 29) plus 30-day safety FU	

End point values	Evenamide 30 mg bid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	159		
Units: Change total score PANSS				
arithmetic mean (standard deviation)	-10.1 (± 7.81)	-7.1 (± 7.47)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

-From the time of signing of informed consent 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	24.0

Reporting groups

Reporting group title	Evenamide 30 mg bid
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Evenamide 30 mg bid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 132 (1.52%)	1 / 159 (0.63%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
General disorders and administration site conditions			
Accidental death	Additional description: Accidental death/suspected suicide		
subjects affected / exposed	0 / 132 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 132 (0.76%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Evenamide 30 mg bid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 132 (9.85%)	11 / 159 (6.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 132 (2.27%)	4 / 159 (2.52%)	
occurrences (all)	3	5	
Somnolence			
subjects affected / exposed	2 / 132 (1.52%)	5 / 159 (3.14%)	
occurrences (all)	2	5	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 132 (2.27%)	1 / 159 (0.63%)	
occurrences (all)	3	1	
Diarrhoea			
subjects affected / exposed	2 / 132 (1.52%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 132 (2.27%)	1 / 159 (0.63%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2021	The primary purpose of this amendment to the protocol for Study NW-3509/008A/II/2020 (Study 008A) is to increase the sample size of the study so that it will be adequate to assess the efficacy of evenamide as adjunctive treatment in patients with schizophrenia on a stable dose of an atypical antipsychotic. With this change, the study has become a Phase II/III study (Amendment 2.0 dated 4 May 2021)
22 February 2022	Patients receiving clozapine had their randomization stratified within each center to achieve an approximately equal number of clozapine-treated patients in both evenamide and placebo groups (Amendment 2.4, dated 22 February 2022).
19 September 2022	A blood sample to confirm each patient's compliance with their background antipsychotic medication was obtained and the results of blood plasma levels were to be available before randomization (Amendment 3.0, dated 19 September 2022).
11 November 2022	The primary purpose of this amendment to the protocol for Study NW-3509/008A/II/2020 (Study 008A) is to eliminate the requirement for performing electroencephalograms (EEGs) and the Seizure Checklist, which specifically assesses seizure-like symptoms in the trial (Amendment 4.0 dated 11 November 2022)

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/39708914