Clinical trial results:
A Randomized, Double-blind, Parallel-group Study to Investigate the Efficacy, Safety, and Tolerability of Cariprazine in Patients with Predominant Negative Symptoms of Schizophrenia

Summary

EudraCT number	2012-005485-36
Trial protocol	HU CZ ES PL BG
Global end of trial date	17 November 2014

Results information

Result version number	v1 (current)
This version publication date	24 October 2021
First version publication date	24 October 2021

Trial information

Trial identification

Sponsor protocol code	RGH-188-005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gedeon Richter Plc
Sponsor organisation address	Gyömrői út 19-21, Budapest, Hungary, H-1103
Public contact	Dr. Balázs Lázár, Gedeon Richter Plc, +36 1 432 6437, RA.ctaRichter@richter.hu
Scientific contact	Medical Information Scientific Service, Gedeon Richter Plc, +36 1 505 7032, medinfo@richter.hu

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	29 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2014
Global end of trial reached?	Yes
Global end of trial date	17 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety and tolerability of cariprazine for the treatment of patients with schizophrenia having predominant negative symptoms.

Protection of trial subjects:

This clinical study was designed to comply with the International Conference on Harmonisation (ICH) Guidances on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113,17 December 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Studies for Pharmaceuticals (ICH-M3 [R2]; 62 FR 62922, 25 November 1997), and Good Clinical Practice (GCP) (ICH-E6; 62 FR 25692, 9 May 1997).

Before the study began, the study centers required approval from an IEC. Compliance with these requirements also indicated conformity with the ethical principles that have their origins in the Declaration of Helsinki. The clinical study protocol, informed consent form (ICF), and all other appropriate study-related documents were reviewed and approved by local independent ethics committees (IECs) constituted in accordance with national regulations as applicable. The ICF was written in compliance with ICH guidelines and other national regulations as appropriate. The informed consent of the patients participating in the study were obtained in line with the ICH GCP guidelines at screening before participating in any study-related procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2013
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	Poland: 30
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Czechia: 48
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Croatia: 15
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 108
Country: Number of subjects enrolled	Serbia: 46
Country: Number of subjects enrolled	Ukraine: 118

Worldwide total number of subjects	460
EEA total number of subjects	188

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)	458
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 533 patients were screened for eligibility; 461 patients were randomized to receive double-blind treatment; 460 subjects received at least 1 dose of double-blind treatment..

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cariprazine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cariprazine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral formulation, once daily with doses of 3.0 mg/day, 4.5 mg/day, 6.0 mg/day.

Day 0 to 6: 1.5 mg/day, Day 7 to 13: 3.0 mg/day, Day 14 to 182: 4.5 mg/day with the option to decrease to 3.0 mg/day from Day 21, in case of poor tolerability, or to increase to 6.0 mg/day from Day 21, in case of impending psychotic deterioration. Decreasing or increasing the dose of the double-blind study medication from the target dose was allowed only once for each modification.

Arm title	Risperidone

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral formulation, once daily with doses of 3.0 mg/day, 4.0 mg/day, 6.0 mg/day.

Day 0 to 6: 2.0 mg/day, Day 7 to 13: 3.0 mg/day, Day 14 to 182: 4.0 mg/day with the option to decrease to 3.0 mg/day from Day 21, in case of poor tolerability, or to increased to 6.0 mg/day from Day 21, in case of impending psychotic deterioration. Decreasing or increasing the dose of the double-blind study medication from the target dose was allowed only once for each modification.

Number of subjects in period 1	Cariprazine	Risperidone
Started	230	230
Completed	178	178
Not completed	52	52
Consent withdrawn by subject	15	15
Adverse event, non-fatal	22	25
Other	5	7
Non compliance	3	2
Lost to follow-up	2	1
Protocol deviation	3	-
Lack of efficacy	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Cariprazine
Reporting group description: -	
Reporting group title	Risperidone
Reporting group description: -	

Reporting group values	Cariprazine	Risperidone	Total
Number of subjects	230	230	460
Age categorical Units: Subjects			
Adults (18-64 years)	228	230	458
65 years	2	0	2
Age continuous Units: years			
arithmetic mean	40.2	40.7	
standard deviation	± 10.5	± 11.2	-
Gender categorical Units: Subjects			
Female	106	90	196
Male	124	140	264

Subject analysis sets	
Subject analysis set title	Cariprazine - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

PANSS= Positive and Negative Syndrome Scale
The ITT population consisted of all patients in the safety population who had at least 1 post baseline assessment on the PANSS factor scores for negative symptoms.

Subject analysis set title	Risperidone - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

PANSS= Positive and Negative Syndrome Scale
The ITT population consisted of all patients in the safety population who had at least 1 post baseline assessment on the PANSS factor scores for negative symptoms.

Reporting group values	Cariprazine - ITT	Risperidone - ITT	
Number of subjects	227	229	
Age categorical Units: Subjects			
Adults (18-64 years)	225	229	
65 years	2	0	
Age continuous Units: years			
arithmetic mean	40.1	40.8	
standard deviation	± 10.4	± 11.1	

Gender categorical Units: Subjects			
Female	105	90	
Male	122	139	

End points

End points reporting groups

Reporting group title	Cariprazine
Reporting group description: -	
Reporting group title	Risperidone
Reporting group description: -	
Subject analysis set title	Cariprazine - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
PANSS= Positive and Negative Syndrome Scale The ITT population consisted of all patients in the safety population who had at least 1 post baseline assessment on the PANSS factor scores for negative symptoms.	
Subject analysis set title	Risperidone - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
PANSS= Positive and Negative Syndrome Scale The ITT population consisted of all patients in the safety population who had at least 1 post baseline assessment on the PANSS factor scores for negative symptoms.	

Primary: Change from baseline to endpoint (Week 26 or early termination) in the PANSS factor score for negative symptoms

End point title	Change from baseline to endpoint (Week 26 or early termination) in the PANSS factor score for negative symptoms
End point description:	
Change from Baseline = CFB; PANSS=Positive and Negative Symptom Scale; MMRM=mixed-effects model for repeated measures; The primary efficacy parameter was the CFB to endpoint (Week 26/ET) in the PANSS factor score for negative symptoms. The PANSS factor score for negative symptoms ranged from 7 to 49, a lower score was favorable. The primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as the fixed effects and the baseline value and baseline value–by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores.	
End point type	Primary
End point timeframe:	
from Baseline to Week 26 (Endpoint)	

End point values	Cariprazine - ITT	Risperidone - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	229		
Units: Mean change from baseline				
least squares mean (standard error)				
Week 1	-1.08 (± 0.095)	-0.91 (± 0.118)		
Week 2	-2.41 (± 0.145)	-2.19 (± 0.159)		
Week 3	-3.67 (± 0.195)	-3.34 (± 0.209)		
Week 4	-4.65 (± 0.234)	-4.11 (± 0.222)		

Week 6	-5.38 (± 0.246)	-4.99 (± 0.247)		
Week 10	-6.48 (± 0.266)	-5.89 (± 0.268)		
Week 14	-7.50 (± 0.295)	-6.38 (± 0.301)		
Week 18	-8.17 (± 0.303)	-6.75 (± 0.307)		
Week 22	-8.59 (± 0.310)	-7.15 (± 0.328)		
Week 26	-8.90 (± 0.324)	-7.44 (± 0.347)		

Statistical analyses

Statistical analysis title	Mean Difference at week 26
Comparison groups	Cariprazine - ITT v Risperidone - ITT
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.002 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.5

Notes:

[1] - Change from Baseline = CFB; LS=Least Square
Using this model, there was a statistically significant difference (P = 0.002) in favor of cariprazine over risperidone at Week 26. The LS mean CFB at Week 26 were -8.9 and -7.4 for cariprazine and risperidone, respectively.
[2] - Cariprazine was statistically significant compared with risperidone, P < 0.01.

Secondary: Change from baseline to endpoint (Week 26) in the Personal and Social Performance scores

End point title	Change from baseline to endpoint (Week 26) in the Personal and Social Performance scores

End point description:

Change from Baseline = CFB; PSP= Personal and Social Performance scale; MMRM=mixed-effects model for repeated measures; LS=Least Squares

The CFB in PSP total score was analyzed using an MMRM similar to the one used for the principal analysis of the primary efficacy parameter. The PSP score ranged from 1 to 100, a higher score was favorable.The analysis was only to be formally assessed in case the result of the primary efficacy parameter was determined to be statistically significant.

End point type	Secondary

End point timeframe:

from Baseline to Endpoint (Week 26 or Early Termination)

End point values	Cariprazine - ITT	Risperidone - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227	229		
Units: Mean change from baseline				
least squares mean (standard deviation)				
Week 6	6.3 (± 0.5)	4.9 (± 0.5)		
Week 10	8.6 (± 0.5)	6.4 (± 0.6)		
Week 14	10.5 (± 0.6)	8.0 (± 0.7)		
Week 18	11.8 (± 0.6)	8.5 (± 0.7)		
Week 22	13.2 (± 0.7)	8.9 (± 0.7)		
Week 26	14.3 (± 0.6)	9.7 (± 0.8)		

Statistical analyses

Statistical analysis title	Mean Difference at week 26
Comparison groups	Cariprazine - ITT v Risperidone - ITT
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	6.6

Notes:

[3] - Change from Baseline = CFB; PSP= Personal and Social Performance scale; LS=Least Square Using this model, there was a statistically significant difference (P < 0.001) in CFB in the PSP score in favor of cariprazine over risperidone at Week 26. The LS mean CFB in the PSP scores at Week 26 were 14.3 and 9.7 for cariprazine and risperidone, respectively. The pairwise difference was 4.6 (95% CI: 2.7, 6.6). The CFB in the PSP total score always favored

[4] - Cariprazine was statistically significant compared with risperidone, P < 0.001.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the Double-Blind Period	
Adverse event reporting additional description:	
Adverse event summaries contain reported adverse events during the double-blind treatment period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Cariprazine Safety population - DB treatment period
Reporting group description:	
DB= double blind All patients in the randomized population who took at least 1 dose of Cariprazine. For this safety population, adverse event summaries contain reported adverse events during the double-blind treatment period.	
Reporting group title	Risperidone Safety population - DB treatment period
Reporting group description:	
DB= double blind All patients in the randomized population who took at least 1 dose of Cariprazine. For this safety population, adverse event summaries contain reported adverse events during the double-blind treatment period.	

Serious adverse events	Cariprazine Safety population - DB treatment period	Risperidone Safety population - DB treatment period	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 230 (3.04%)	7 / 230 (3.04%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to the mediastinum			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carcinoid tumour pulmonary			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	4 / 230 (1.74%)	4 / 230 (1.74%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persecutory delusion			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (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: 3 %

Non-serious adverse events	Cariprazine Safety population - DB treatment period	Risperidone Safety population - DB treatment period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 230 (36.09%)	92 / 230 (40.00%)	
Nervous system disorders			
Akathisia			
subjects affected / exposed	19 / 230 (8.26%)	12 / 230 (5.22%)	
occurrences (all)	20	12	
Cogwheel rigidity			
subjects affected / exposed	4 / 230 (1.74%)	8 / 230 (3.48%)	
occurrences (all)	4	8	
Dizziness			
subjects affected / exposed	4 / 230 (1.74%)	11 / 230 (4.78%)	
occurrences (all)	4	13	
Headache			
subjects affected / exposed	13 / 230 (5.65%)	24 / 230 (10.43%)	
occurrences (all)	20	30	
Somnolence			
subjects affected / exposed	9 / 230 (3.91%)	13 / 230 (5.65%)	
occurrences (all)	10	13	
General disorders and administration			

site conditions Fatigue subjects affected / exposed occurrences (all)	5 / 230 (2.17%) 5	10 / 230 (4.35%) 10	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	9 / 230 (3.91%) 9	6 / 230 (2.61%) 8	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Schizophrenia subjects affected / exposed occurrences (all)	13 / 230 (5.65%) 14 21 / 230 (9.13%) 22 15 / 230 (6.52%) 16	11 / 230 (4.78%) 11 23 / 230 (10.00%) 27 10 / 230 (4.35%) 11	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 230 (1.30%) 3	7 / 230 (3.04%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2013	Changes included, but were not limited to clarifications on inclusion/exclusion criteria; harmonization on blinding/unblinding procedures; prechilled vacutainers and flash-freezing were removed from the protocol; summarize details of the laboratory methods for urine microscopy testing; addition of IOP measurement to the summary list of assessments; summarize details of opthalmic examination.
04 June 2013	Changes included, but were not limited to the following: increase number of study centers; changes in the responsabilities for review EAF and issue of the MMAF; the schedule of procedures was edited; chilling of blood samples in an ice bath was removed; Text was added to clarify the fluctuating nature and disease course of schizophrenia; a reference was updated for the most current SmPC for Risperidone.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported