Clinical trial results:
Effects of F17464 in acute exacerbation of schizophrenia.
A randomised, double-blind, placebo-controlled, parallel-group, fixed-dose, multicentre study

Summary

EudraCT number	2013-005451-32
Trial protocol	HU LV RO
Global end of trial date	22 December 2015

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	F17464GE201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02151656
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PIERRE FABRE MEDICAMENT
Sponsor organisation address	45 Place Abel Gance, Boulogne, France, 92100
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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	23 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2015
Global end of trial reached?	Yes
Global end of trial date	22 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the potential efficacy of 40 mg/day of oral F17464 in comparison to placebo over 6 weeks in patients with acute exacerbation of schizophrenia

Protection of trial subjects:

This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki (1964 and its subsequent amendments). This study was conducted in agreement with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and with applicable national regulations in biomedical research (except in one Romanian centre: see "Recruitment details" caption). The first study protocol version in use (Protocol Version 4, Amendment 3, 02 July 2014), all its amendments, and the patient information sheets, were reviewed by the appropriate independent ethics committees (IECs), including local IECs.
This study was placebo-controlled (see rationale in "Evidence for comparator" caption). The placebo group received the same medical care as the F17464 group, according to that which would have been provided if they had not participated in this study. If patients showed any early signs of safety concerns or aggravation of symptoms during the study, they were eligible to receive alternative active therapy at any time.

Background therapy:

There was no systematic concomitant administration of any other product than investigational products. Concomitant administration of the following treatments was used as rescue medication for symptom exacerbation and was permitted for severe anxiety, agitation or insomnia:
- Lorazepam up to 8 mg/day (oral route), or 4 mg/day (intramuscular [IM] administration); and/or
- Oxazepam up to 60 mg/day

Evidence for comparator:

This study was placebo-controlled as there is still a medical need for alternative treatments for acute episodes in schizophrenia with a better efficacy and safety profile. Therefore, it was necessary to demonstrate the efficacy of F17464. The use of a placebo control was critical to the study to allow discrimination between patient outcomes caused by F17464 and outcomes caused by other factors (e.g. the observer or patient expectations, the natural progression of the disease, the conditions of study participation).

Actual start date of recruitment	20 August 2014
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	Romania: 58
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 13

Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Russian Federation: 45
Worldwide total number of subjects	134
EEA total number of subjects	89

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)	134
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

41 centres located in 5 countries (France, Hungary, Romania, Latvia, Russian Federation) were initiated and 30 recruited patients. 158 patients were screened, 134 were randomised and analysed. An additional 13 screened patients (10 randomised) from the Romanian centre 5404 were excluded from the final database due to GCP violation.

Pre-assignment

Screening details:

Age 18-64 yrs
Primary diagnosis of schizophrenia for ≥1 yr; acute exacerbation with prominent active phase symptoms as described by DSM-IV-TR using MINI 6.0
PANSS total score ≥70 and <120 and no reduction ≥20% over pre-assignment period
CGI-S ≥4
≥2 positive sympt. /delusions, hallucin. behav., concept. disorganisation or suspiciousness rated ≥4

Pre-assignment period milestones

Number of subjects started	158[1]
Number of subjects completed	134

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 21
Reason: Number of subjects	Consent withdrawn by subject: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 158 patients were screened; 24 were not randomised (21 did not meet all eligibility criteria and 3 withdrew their consent).

Period 1

Period 1 title	6-week treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blinding was ensured by identical:
- colour, size and aspect of F17464 and placebo capsules,
- packaging, labelling and administration of study treatments.
A specific process was applied to maintain the blind in data transfer to the IDMC interim analyst, the only person who had access to a partial randomisation list (71 first randomised patients) during the study. Individual prolactin and F17464 plasma levels were kept blinded to the Sponsor and investigators during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients randomised at Visit 2 to placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral administration: 4 capsules/day (2 capsules b.i.d.)

Arm title	F17464

Arm description:

Patients randomised at Visit 2 to F17464

Arm type	Experimental
Investigational medicinal product name	F17464
Investigational medicinal product code	F17464
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

40 mg (4 capsules) /day (2 capsules b.i.d)

Number of subjects in period 1	Placebo	F17464
Started	67	67
Completed	37	44
Not completed	30	23
Consent withdrawn by subject	7	9
Physician decision	-	1
Adverse event, non-fatal	7	11
Lack of efficacy	16	2

Period 2

Period 2 title	1-week Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

During this 7-day Follow-up period, patients were not to take any study treatment; thus, no blinding was needed.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo Follow-up

Arm description:

Patients in placebo arm during Period 1 (study treatment period) having entered Period 2 (7-day Follow-up period without study treatment).
Note: even if patients had not completed Period 1, they could enter Period 2; as this possibility is not accepted by the EudraCT system, the numbers of patients having started and completed Period 2 indicated in this form ("milestones" caption) correspond to the subgroup of patients having completed Period 1 on placebo and having started and completed Period 2. The actual number of patients previously receiving placebo in Period 1 and having started Period 2 is 59; of them, 58 completed Period 2 (1 patient did not complete Period 2 for "other" reason ["could not come to site"]).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	F17464 Follow-up

Arm description:

Patients in F17464 arm during Period 1 (study treatment period) having entered Period 2 (7-day Follow-up period without study treatment).
Note: even if patients had not completed Period 1, they could enter Period 2; as this possibility is not accepted by the EudraCT system, the numbers of patients having started and completed Period 2 indicated in this form ("milestones" caption) correspond to the subgroup of patients having completed Period 1 (on F17464) and having started and completed Period 2. The actual number of patients previously receiving F17464 in Period 1 and having started Period 2 is 56; all of them completed Period 2.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[2]	Placebo Follow-up	F17464 Follow-up
Started	36	44
Completed	35	44
Not completed	1	0
Patient could not come to site	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 1 patient in the Placebo group completed the Treatment period (Period 1) but did not enter the Follow-up period (Period 2) as a new treatment with antipsychotic was initiated.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients randomised at Visit 2 to placebo	
Reporting group title	F17464
Reporting group description:	
Patients randomised at Visit 2 to F17464	

Reporting group values	Placebo	F17464	Total
Number of subjects	67	67	134
Age categorical Units: Subjects			
Adults (18-64 years)	67	67	134
Age continuous Units: years			
arithmetic mean	36.48	38.09	
standard deviation	± 11.61	± 11.32	-
Gender categorical Units: Subjects			
Female	28	27	55
Male	39	40	79
PANSS total score			
PANSS is a 30-item score measuring specific symptoms, each item ranging from 1 (absent) to 7 (extreme). The total score is built by adding up the single items and the same applies to sub–scale calculations, i.e. positive symptoms (7 items), negative symptoms (7 items) and a general psychopathology scale (16 items). The total score ranges from 30 to 210.			
Units: points			
arithmetic mean	90	87.9	
standard deviation	± 9.2	± 9	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients randomised at Visit 2 to placebo	
Reporting group title	F17464
Reporting group description:	
Patients randomised at Visit 2 to F17464	
Reporting group title	Placebo Follow-up
Reporting group description:	
Patients in placebo arm during Period 1 (study treatment period) having entered Period 2 (7-day Follow-up period without study treatment). Note: even if patients had not completed Period 1, they could enter Period 2; as this possibility is not accepted by the EudraCT system, the numbers of patients having started and completed Period 2 indicated in this form ("milestones" caption) correspond to the subgroup of patients having completed Period 1 on placebo and having started and completed Period 2. The actual number of patients previously receiving placebo in Period 1 and having started Period 2 is 59; of them, 58 completed Period 2 (1 patient did not complete Period 2 for "other" reason ["could not come to site"]).	
Reporting group title	F17464 Follow-up
Reporting group description:	
Patients in F17464 arm during Period 1 (study treatment period) having entered Period 2 (7-day Follow-up period without study treatment). Note: even if patients had not completed Period 1, they could enter Period 2; as this possibility is not accepted by the EudraCT system, the numbers of patients having started and completed Period 2 indicated in this form ("milestones" caption) correspond to the subgroup of patients having completed Period 1 (on F17464) and having started and completed Period 2. The actual number of patients previously receiving F17464 in Period 1 and having started Period 2 is 56; all of them completed Period 2.	

Primary: Change in PANSS from baseline to end of treatment (Day 43-LOCF)

End point title	Change in PANSS from baseline to end of treatment (Day 43-LOCF)
End point description:	
End point type	Primary
End point timeframe:	
Day 43 (V9)	

End point values	Placebo	F17464		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	67		
Units: points	67	67		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

PANSS total score change from baseline to D43 was analysed using an ANCOVA model after LOCF imputation of missing values, with treatment group as fixed factor on the full analysis set. Both PANSS total score at baseline and country factor were incorporated in the model as covariates.
France (with only 1 randomised patient) was grouped with Romania that included the greatest number of patients. Treatment effect was estimated by the difference between adjusted means; a 95% CI was also provided.

Comparison groups	Placebo v F17464
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0141 [2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.08
upper limit	-1.27
Variability estimate	Standard deviation
Dispersion value	2.5

Notes:

[1] - Hypotheses tested:
H01: F17464 is not > to placebo versus H11: F17464 is > to placebo;
H02: no difference between groups versus H12: F17464 is different from placebo.
H01 was tested first. If H01 was not rejected, H02 was not to be tested. Such sequential strategy does not require adjustment for multiplicity of tests. Therefore, the test of H01 is one-sided whereas the test of H02 is two-sided. This procedure permits a statistical conclusion about the superiority of F17464 over placebo.
[2] - 0.0141 is the p value for the two-sided test (H02); 0.007 is the p value for the 1-sided test (H01)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Whole study duration from signature of consent (V1) to End of Study Visit (expected to be V10/D50 after 1 week of post-treatment follow-up or V9/D43 the End of Treatment Visit if the patient did not enter the follow-up)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	F17464

Reporting group description: -

Serious adverse events	Placebo	F17464	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 67 (22.39%)	10 / 67 (14.93%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Drug ineffective	Additional description: Reported terms: lack of efficacy; lack of response SAE if led to extension of per-protocol hospitalisation period		
subjects affected / exposed	11 / 67 (16.42%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	10 / 11	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia	Additional description: Reported term: worsening of schizophrenia SAE if led to extension of per-protocol hospitalisation period		
subjects affected / exposed	4 / 67 (5.97%)	8 / 67 (11.94%)	
occurrences causally related to treatment / all	2 / 4	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	F17464	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 67 (50.75%)	44 / 67 (65.67%)	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	2 / 67 (2.99%)	5 / 67 (7.46%)	
occurrences (all)	3	6	
Blood bilirubin increased			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	
Hepatic enzyme increased			
subjects affected / exposed	0 / 67 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 67 (4.48%)	4 / 67 (5.97%)	
occurrences (all)	3	7	
Akathisia			
subjects affected / exposed	0 / 67 (0.00%)	3 / 67 (4.48%)	
occurrences (all)	0	4	
Dizziness			
subjects affected / exposed	0 / 67 (0.00%)	3 / 67 (4.48%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Drug ineffective			
subjects affected / exposed	4 / 67 (5.97%)	0 / 67 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	2 / 67 (2.99%)	3 / 67 (4.48%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	2 / 67 (2.99%)	2 / 67 (2.99%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 67 (0.00%)	3 / 67 (4.48%)	
occurrences (all)	0	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 67 (8.96%)	13 / 67 (19.40%)	
occurrences (all)	18	20	
Agitation			
subjects affected / exposed	4 / 67 (5.97%)	7 / 67 (10.45%)	
occurrences (all)	22	10	
Anxiety			
subjects affected / exposed	8 / 67 (11.94%)	5 / 67 (7.46%)	
occurrences (all)	11	6	
Schizophrenia			
subjects affected / exposed	2 / 67 (2.99%)	4 / 67 (5.97%)	
occurrences (all)	4	5	
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 67 (2.99%)	0 / 67 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2015	Change in an eligibility criterion related to schizophrenia history (criterion #5) assessed at Visit 1: - Under the first protocol in use (Protocol Version 4), this eligibility criterion was "Schizophrenia history for a minimum of 1 year and maximum 5 years, well documented diagnosis with the first hospitalisation for acute exacerbation of schizophrenia." - This inclusion criterion was amended in Protocol Version 5 to the following: "Well-documented diagnosis of schizophrenia for a minimum of 1 year before the screening visit (V1)" Rationale: the characteristics of the pre-screened population showed that a significant proportion of the patients had a duration of schizophrenia >5 years and were not enrolled in the study; the population included might therefore be only partly representative of the target population. Consequently, the upper limit of 5 years was deleted.
21 October 2015	Genotype determination of D2, 5HT1A, 5HT2A and 5HT2C receptors was added to that of D3 receptor with the objective of better documenting the response to F17464 activity (substantial part of the amendment). An independent external expert for blinded PANSS review (Professor Rabinowitz) was included in order to reinforce the validity of the primary efficacy criterion.

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/16330718

http://www.ncbi.nlm.nih.gov/pubmed/17650054

http://www.ncbi.nlm.nih.gov/pubmed/25413553

http://www.ncbi.nlm.nih.gov/pubmed/24813414