



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 |
| Public contact | Agnès MONTAGNE, Institut de Recherche Pierre Fabre, +33 534 50 63 50, agnes.montagne@pierre-fabre.com |
| Scientific contact | Agnès MONTAGNE, Institut de Recherche Pierre Fabre, +33 534 50 63 50, agnes.montagne@pierre-fabre.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 | 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 $\geq 20\%$ 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 occurrences (all) | 2 / 67 (2.99%) 2 | 3 / 67 (4.48%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 67 (2.99%) 2 | 2 / 67 (2.99%) 3 | |
| Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 67 (0.00%) 0 | 3 / 67 (4.48%) 3 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 18 | 13 / 67 (19.40%) 20 | |
| Agitation subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 22 | 7 / 67 (10.45%) 10 | |
| Anxiety subjects affected / exposed occurrences (all) | 8 / 67 (11.94%) 11 | 5 / 67 (7.46%) 6 | |
| Schizophrenia subjects affected / exposed occurrences (all) | 2 / 67 (2.99%) 4 | 4 / 67 (5.97%) 5 | |
| Infections and infestations Rhinitis subjects affected / exposed occurrences (all) | 2 / 67 (2.99%) 2 | 0 / 67 (0.00%) 0 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 67 (1.49%) 1 | 2 / 67 (2.99%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 February 2015 | <p>Change in an eligibility criterion related to schizophrenia history (criterion #5) assessed at Visit 1:</p> <ul style="list-style-type: none">- 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)" <p>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.</p> |
| 21 October 2015 | <p>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.</p> |

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>