# EU Clinical Trials Register

## Clinical trial results:
## Efficacy and safety of Passiflora Compose in patients newly diagnosed with adjustment disorder with anxiety, as first-line treatment, compared to Alprazolam

## Efficacité et tolérance de Passiflora composé dans l'anxiété réactionnelle récente, en première intention, en comparaison de l' Alprazolam

### Summary

| | |
|---|---|
| EudraCT number | 2017-002263-17 |
| Trial protocol | FR |
| Global end of trial date | 30 August 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 March 2023 |
| First version publication date | 31 March 2023 |
| Summary attachment (see zip file) | 2017-002263-17 Synopsis PASSIANCE (2017-002263-17_EudraCT Synospis - PASSIANCE.pdf) |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BRN-C-2017-01 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | U2017-0022-6317 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Laboratoires BOIRON |
| Sponsor organisation address | 2 Avenue de l'Ouest Lyonnais, Messimy, France, 69510 |
| Public contact | R&D Affaires scientifiques & médicales - BOIRON, Isabelle Chanel, +33 472164315, isabelle.chanel@boiron.fr |
| Scientific contact | R&D Affaires scientifiques & médicales - BOIRON, Isabelle Chanel, +33 472164315, isabelle.chanel@boiron.fr |

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 | 27 June 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study is to demonstrate the non-inferiority of PC in comparison to Alprazolam in anxiety disorders after 4 weeks of treatment (efficacy objective).

Protection of trial subjects:

The Sponsor submitted the study protocol and all information necessary for a detailed review of the clinical study to the competent authorities. The study was started after written approval by the competent authority was available (ANSM: Ref. 170451A-31 and CPP Sud Méditerranée I - Ref. 17 55). This study was performed in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, in its revision of Somerset West 1996, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.
Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject. It was the responsibility of the investigator to obtain signed informed consent from the patient prior to the patient's inclusion in the study. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 January 2018 |
| 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 | France: 104 |
| Worldwide total number of subjects | 104 |
| EEA total number of subjects | 104 |

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) | 95 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

Study performed with general practitioners from January 2018 to May 2019.
Randomization to one of the 2 treatment groups (PC or APZ) was performed with a 1:1 ratio using a block randomization method and stratification by site.

## Pre-assignment

Screening details:

None study-related procedure was started before ICF was signed and dated by both the patient and the investigator - Checked the eligibility criteria list and perform the exams.
104 subjects were enrolled and randomized, 104 subjects were included in the safety population.
84 subjects were included in PP population.

## 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 | Investigator, Monitor, Data analyst, Carer, Assessor, Subject |

Blinding implementation details:

Study medication was presented as visually indistinguishable doses.
Each treatment box contained 90 IMP units which was sufficient medication for 1 patient (28 days – 3 doses daily 1:1:1), IMP and counterpart Placebo.

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Arm PC |

Arm description:

Experimental Passiflora Composé (PC) along with Placebo of APZ

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Passiflora Composé |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules |
| Routes of administration | Oral use |

Dosage and administration details:

Passiflora Composé ® was provided as globuli. Passiflora Composé ® contained Passiflora incarnata 3DH ; Coffea cruda 5CH ; Ignatia amara 4CH ; Nyckterinia capensis 4CH ; Tellurium metallicum 5CH ; Phosphoricum acidum 7CH ; Palladium metallicum 5CH and Magnesium metallicum 5CH. The granuli excipients were saccharose and lactose.
Patients were instructed to take 5 globuli, 3 times a day during 4 weeks.

| Investigational medicinal product name | Placebo - Alprazolam |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo of Alprazolam was provided as tablets. It contained no active component. The tablet excipients consisted of microcrystalline cellulose, lactose monohydrate, magnesium stearate and anhydrous colloidal silica. It was not possible to differentiate it from Alprazolam by its appearance and taste.
Patients were instructed to take 1 tablet, 3 times a day during 4 weeks.

| **Arm title** | Arm APZ |
|---|---|

Arm description:

Experimental Comparator - Alprazolam (APZ) along with Placebo of PC

| Arm type | Active comparator |
|---|---|
| Investigational medicinal product name | Alprazolam |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Alprazolam was provided as tablets. It contained 0.25 mg of active component (APZ) per tablet. The tablet excipients consisted of microcrystalline cellulose, lactose monohydrate, magnesium stearate and anhydrous colloidal silica. Patients were instructed to take 1 tablet, 3 times a day during 4 weeks.

| Investigational medicinal product name | Placebo - Passiflora Composé |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Granules |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo of Passiflora Composé was provided as globuli. It contained no active component. The granuli excipients were Saccharose and lactose. It was not possible to differentiate it from Passiflora Composé® by its appearance and taste.
Patients were instructed to take 5 globuli, 3 times a day during 4 weeks.

| Number of subjects in period 1 | Arm PC | Arm APZ |
|---|---|---|
| Started | 52 | 52 |
| Completed | 45 | 49 |
| Not completed | 7 | 3 |
|    Adverse event, serious fatal | - | 1 |
|    Consent withdrawn by subject | 2 | 1 |
|    Physician decision | 1 | - |
|    Adverse event, non-fatal | 1 | - |
|    Lost to follow-up | 1 | 1 |
|    Protocol deviation | 2 | - |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | Arm PC |
| Reporting group description: | |
| Experimental Passiflora Composé (PC) along with Placebo of APZ | |
| Reporting group title | Arm APZ |
| Reporting group description: | |
| Experimental Comparator - Alprazolam (APZ) along with Placebo of PC | |

| Reporting group values | Arm PC | Arm APZ | Total |
|---|---|---|---|
| Number of subjects | 52 | 52 | 104 |
| 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.1 | 45.0 | |
| standard deviation | ± 12.1 | ± 13.1 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 34 | 38 | 72 |
| Male | 18 | 14 | 32 |

### Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Arm PC - Primary Endpoint |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per protocol (PP) population: defined as all patients randomized and treated without any deviation to protocol preventing primary endpoint analysis. | |
| Subject analysis set title | Arm PC – Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety population: defined as all patients randomized who received at least one study treatment dose. | |
| Subject analysis set title | Arm APZ - Primary Endpoint |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per protocol (PP) population: defined as all patients randomized and treated without any deviation to protocol preventing primary endpoint analysis. | |

| Subject analysis set title | Arm APZ – Safety Population |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Safety population: defined as all patients randomized who received at least one study treatment dose.

| **Reporting group values** | Arm PC - Primary Endpoint | Arm PC – Safety population | Arm APZ - Primary Endpoint |
|---|---|---|---|
| Number of subjects | 41 | 52 | 45 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | 45.0 | |
| standard deviation | ± | ± 13.1 | ± |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 15 | 38 | 11 |
| Male | 26 | 14 | 34 |

| **Reporting group values** | Arm APZ – Safety Population | | |
|---|---|---|---|
| Number of subjects | 52 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.1 | | |
| standard deviation | ± 12.1 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 34 | | |
| Male | 18 | | |

## End points

### End points reporting groups

| Reporting group title | Arm PC |
|---|---|
| Reporting group description: | |
| Experimental Passiflora Composé (PC) along with Placebo of APZ | |
| Reporting group title | Arm APZ |
| Reporting group description: | |
| Experimental Comparator - Alprazolam (APZ) along with Placebo of PC | |
| Subject analysis set title | Arm PC - Primary Endpoint |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per protocol (PP) population: defined as all patients randomized and treated without any deviation to protocol preventing primary endpoint analysis. | |
| Subject analysis set title | Arm PC – Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety population: defined as all patients randomized who received at least one study treatment dose. | |
| Subject analysis set title | Arm APZ - Primary Endpoint |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per protocol (PP) population: defined as all patients randomized and treated without any deviation to protocol preventing primary endpoint analysis. | |
| Subject analysis set title | Arm APZ – Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety population: defined as all patients randomized who received at least one study treatment dose. | |

### Primary: Efficacy Primary Endpoint

| End point title | Efficacy Primary Endpoint |
|---|---|
| End point description: | |
| The evolution of the total HAM-A score is measured by the variation of the score between V0 and V2 on the HAM-A scale which comprises 14 questions rated by a 5-point Likert scale from 0 to 4 points, a high score indicates more severe anxiety. The total HAM-A score is calculated by the sum of the answers to the 14 questions (or items) of the HAM-A scale and it can vary from 0 to 56. | |
| End point type | Primary |
| End point timeframe: | |
| 4 weeks | |

| End point values | Arm PC - Primary Endpoint | Arm APZ - Primary Endpoint | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 41[1] | 45[2] | | |
| Units: Score Value Change | 13 | 14 | | |

Notes:

[1] - Score Value Change
Arithmetic mean : -12,9
Standard deviation: 8,9

[2] - Score Value Change
Arithmetic mean : -13,9
Standard deviation: 7,9

## Statistical analyses

| Statistical analysis title | Arm APZ vs Arm PC |
|---|---|
| Comparison groups | Arm PC - Primary Endpoint v Arm APZ - Primary Endpoint |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 2.8 |
| Method | ANCOVA |

## Adverse events

### Adverse events information

| Timeframe for reporting adverse events: | |
|---|---|
| From first dose (i.e., Day 1) of study drug to last dose date of study drug (i.e., Day 28) | |
| Assessment type | Systematic |

### Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 20.0 |

### Reporting groups

| Reporting group title | Arm PC |
|---|---|
| Reporting group description: | |
| Arm PC – Safety population | |
| Reporting group title | Arm APZ |
| Reporting group description: | |
| Arm APZ – Safety Population | |

| Serious adverse events | Arm PC | Arm APZ | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Carbon monoxide poisoning | Additional description: PT10007238 | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Arm PC | Arm APZ | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 14 / 52 (26.92%) | |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 2 | |
| Somnolence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| **Headache** | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 2 / 52 (3.85%) | |
| occurrences (all) | 2 | 3 | |
| **General disorders and administration site conditions** | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 2 | |
| **Asthenia** | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 1 | |
| **Ear and labyrinth disorders** | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 2 | |
| **Gastrointestinal disorders** | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 2 / 52 (3.85%) | |
| occurrences (all) | 1 | 2 | |
| **Abdominal pain upper** | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 0 | 2 | |
| **Dry mouth** | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| **Constipation** | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 1 | |
| **Diarrhoea** | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 1 | |
| **Gastrooesophageal reflux disease** | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 0 | 1 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |

| | | |
|---|---|---|
| **Asthma** | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) |
| occurrences (all) | 0 | 1 |
| **Allergic respiratory disease** | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 0 |
| **Cough** | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 0 |
| **Skin and subcutaneous tissue disorders** | | |
| **Hyperhidrosis** | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 52 (1.92%) |
| occurrences (all) | 1 | 1 |
| **Pruritus** | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 52 (3.85%) |
| occurrences (all) | 0 | 2 |
| **Psychiatric disorders** | | |
| **Insomnia** | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 0 |
| **Musculoskeletal and connective tissue disorders** | | |
| **Musculoskeletal pain** | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 1 | 0 |
| **Infections and infestations** | | |
| **Bronchitis** | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) |
| occurrences (all) | 0 | 1 |
| **Laryngitis** | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) |
| occurrences (all) | 0 | 1 |
| **Influenza** | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 52 (1.92%) |
| occurrences (all) | 0 | 1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 10 January 2018 | MS1 - Amendment 1 (Ethic Committee's approval); included changes in investigative team's composition: addition of new investigators. |
| 12 June 2018 | MS2- Amendment 2 (Ethic Committee's approval and Competent Authority's notification): Due to low recruitment rate, the sponsor submitted a protocol update allowing an extended inclusion period. Amendment 2. |
| 12 September 2018 | MS3- Amendment 3 (Ethic Committee's approval); included changes in investigative team's composition: addition of new investigators. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  Yes

| Date | Interruption | Restart date |
|---|---|---|
| 28 May 2019 | During the course of this study, the recruitment target was not met within the initial time frame. The sponsor decided to extend the recruitment period (see above Amendment 2). Despite this extension of the recruitment period, 104 patients were included instead of the 282 initially planned. The recruitment period was not extended again. | - |

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| The main objective was to demonstrate the non-inferiority of PC in comparison to Alprazolam in anxiety disorders. The trial terminated before reaching the targeted analysis population. That constitutes limitations to the results. |

Notes: