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: