Clinical trial results:
A multi-centre, randomized, parallel-group, single blind Phase II trial to evaluate the pharmacokinetics and PKPD relationship of trazodone after single and repeated oral doses in children from 2 to 17 years of age, suffering from insomnia, with autism, intellectual disability or attention deficit hyperactivity disorder (ADHD)

Summary

EudraCT number	2018-001166-42
Trial protocol	ES IT
Global end of trial date	08 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	Study Report Synopsis (ANGI-02109_CSR_Final_20211008_synopsis redacted.pdf)

Trial information

Trial identification

Sponsor protocol code	152PO17433

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aziende Chimiche Riunite Angelini Francesco ACRAF S.p.A (Angelini S.p.A)
Sponsor organisation address	Viale Amelia, 70, Rome, Italy, 00181
Public contact	Valeria Tellone-Study Manager, Aziende Chimiche Riunite Angelini Francesco ACRAF S.p.A (Angelini S.p.A), 0039 0691045306, valeria.tellone@angelinipharma.com
Scientific contact	Valeria Tellone-Study Manager, Aziende Chimiche Riunite Angelini Francesco ACRAF S.p.A (Angelini S.p.A), 0039 0691045306, valeria.tellone@angelinipharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002142-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2021
Global end of trial reached?	Yes
Global end of trial date	08 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the PK of trazodone after single and repeated doses in patients aged from 2 to ≤ 17 years. Last subject last visit was 23/12/2019.

Protection of trial subjects:

A favourable opinion of the relevant IECs was obtained before the start of the study. For each patient, a written ICF (signed by the parent(s)) and a written assent form signed and dated by the patients, if applicable, was obtained. Children received adequate written/oral information on the study, in accordance with age and maturity level.

Background therapy:

Use of prior medications was reported for 3 patients (17%). Three patients (17%) used melatonin; of which 2 (11%) also used clonidine. Use of concomitant medications was reported for 9 patients (50%). The most frequently reported concomitant medications were in the group of psychoanaleptics (6 patients, 33%), such as lisdexamfetamine (3 patients, 17%) and methylphenidate hydrochloride (2 patients, 11%); all other concomitant medications were reported for 1 patient only.

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 February 2019
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	Spain: 5
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	12
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After consent from the parent(s) had been obtained and assent from the patients had been documented, the patients were screened for eligibility at the screening visit.

Pre-assignment

Screening details:

At the start of the screening period, an actigraphy device was delivered to the patient and used for at least 1 week to ensure that the patient had become familiarised with device use before the start of the treatment phase. Sleep latency and total sleeping time were recorded by actigraphy starting from 3 consecutive days before Visit 1.

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was conducted in a single-blind fashion, i.e., the investigator and other centre staff performing safety and clinical evaluations did not know which patients were receiving which dose of trazodone. To ensure this condition, the trazodone solution for administration was prepared out of sight (e.g., in a separate room) of the investigator and other centre staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM 1 - 0.25 mg/Kg/day

Arm description:

Patients were treated with 0.25 mg/kg/day from Days 1 to Day 10.

Arm type	Experimental
Investigational medicinal product name	Trazodone Hydrochloride
Investigational medicinal product code	039
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Patients from 2 to 5 years (inclusive) received trazodone oral drops 1.5%, and patients from 6 to 17 years (inclusive) received trazodone oral drops 3%.
Patients received trazodone once daily in the evening, approximately 30 minutes before the usual bedtime, for a total of 10 days. The intake was to occur in a fed state; a list of recommended snacks to maintain the fed state was included in the study manual.
Trazodone oral drops were diluted in approximately 20 mL of sugar water (half a teaspoon of sugar, corresponding to approximately 2 g, dissolved in 20 mL water) or red orange juice by the parent(s) immediately before administration. The diluted solution was to be administered within 30 minutes of preparation.
Immediately after IMP intake, patients were requested to swallow an additional 100 mL (from 2 through 6 years) or 200 mL (from 7 through 17 years) of water or red orange juice to ensure complete intake of any IMP remaining in the oral cavity.

Arm title	ARM 2 - 0.4 mg/Kg/day

Arm description:

Patients were treated with 0.4 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.4 mg/kg/day on Days 4 through 10)

Arm type	Experimental

Investigational medicinal product name	Trazodone Hydrochloride
Investigational medicinal product code	039
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Patients from 2 to 5 years (inclusive) received trazodone oral drops 1.5%, and patients from 6 to 17 years (inclusive) received trazodone oral drops 3%.
Patients received trazodone once daily in the evening, approximately 30 minutes before the usual bedtime, for a total of 10 days. The intake was to occur in a fed state; a list of recommended snacks to maintain the fed state was included in the study manual.
Trazodone oral drops were diluted in approximately 20 mL of sugar water (half a teaspoon of sugar, corresponding to approximately 2 g, dissolved in 20 mL water) or red orange juice by the parent(s) immediately before administration. The diluted solution was to be administered within 30 minutes of preparation.
Immediately after IMP intake, patients were requested to swallow an additional 100 mL (from 2 through 6 years) or 200 mL (from 7 through 17 years) of water or red orange juice to ensure complete intake of any IMP remaining in the oral cavity.

Arm title	ARM3 - 0.5 mg/kg/day

Arm description:

Patients were treated with 0.5 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.5 mg/kg/day on Days 4 through 10)

Arm type	Experimental
Investigational medicinal product name	Trazodone Hydrochloride
Investigational medicinal product code	039
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Patients from 2 to 5 years (inclusive) received trazodone oral drops 1.5%, and patients from 6 to 17 years (inclusive) received trazodone oral drops 3%.
Patients received trazodone once daily in the evening, approximately 30 minutes before the usual bedtime, for a total of 10 days. The intake was to occur in a fed state; a list of recommended snacks to maintain the fed state was included in the study manual.
Trazodone oral drops were diluted in approximately 20 mL of sugar water (half a teaspoon of sugar, corresponding to approximately 2 g, dissolved in 20 mL water) or red orange juice by the parent(s) immediately before administration. The diluted solution was to be administered within 30 minutes of preparation.
Immediately after IMP intake, patients were requested to swallow an additional 100 mL (from 2 through 6 years) or 200 mL (from 7 through 17 years) of water or red orange juice to ensure complete intake of any IMP remaining in the oral cavity.

Number of subjects in period 1	ARM 1 - 0.25 mg/Kg/day	ARM 2 - 0.4 mg/Kg/day	ARM3 - 0.5 mg/kg/day
Started	3	6	10
Completed	3	5	10
Not completed	0	1	0
QT prolongation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	PERIOD 1 (overall period)

Reporting group description: -

Reporting group values	PERIOD 1 (overall period)	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	12	12	
Adolescents (12-17 years)	7	7	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	10.1		
standard deviation	± 3.69	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	17	17	

Subject analysis sets

Subject analysis set title	PK analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who had been randomly assigned to a treatment arm, taken at least 1 dose of the IMP, and at least 1 postdose blood sample that was available and evaluable

Reporting group values	PK analysis set		
Number of subjects	18		
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)	11		
Adolescents (12-17 years)	7		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	10.1		
standard deviation	± 3.69		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	ARM 1 - 0.25 mg/Kg/day
Reporting group description:	
Patients were treated with 0.25 mg/kg/day from Days 1 to Day 10.	
Reporting group title	ARM 2 - 0.4 mg/Kg/day
Reporting group description:	
Patients were treated with 0.4 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.4 mg/kg/day on Days 4 through 10)	
Reporting group title	ARM3 - 0.5 mg/kg/day
Reporting group description:	
Patients were treated with 0.5 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.5 mg/kg/day on Days 4 through 10)	
Subject analysis set title	PK analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who had been randomly assigned to a treatment arm, taken at least 1 dose of the IMP, and at least 1 postdose blood sample that was available and evaluable	

Primary: AUCss

End point title	AUCss[1]
End point description:	
The primary objective of this study was to assess the PK of trazodone after single and repeated doses in patients aged from 2 to ≤17 years by means of the prior estimation of oral clearance, intercompartmental clearance, apparent volume of distribution, and absorption rate constant.	
End point type	Primary
End point timeframe:	
At Steady state (10 days)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were applied

End point values	ARM 1 - 0.25 mg/Kg/day	ARM 2 - 0.4 mg/Kg/day	ARM3 - 0.5 mg/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	10	
Units: mg*h/l				
median (confidence interval 90%)	1399.8 (1150.9 to 1620.4)	3081.8 (2757.2 to 4444.2)	3184.9 (1471.9 to 6260.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax, ss

End point title	Cmax, ss
End point description:	
The primary objective of this study was to assess the PK of trazodone after single and repeated doses in	

patients aged from 2 to ≤17 years.

End point type	Primary

End point timeframe:

At Steadystate (10 days)

End point values	ARM 1 - 0.25 mg/Kg/day	ARM 2 - 0.4 mg/Kg/day	ARM3 - 0.5 mg/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	10	
Units: ng/ml				
median (confidence interval 90%)	192.1 (113.6 to 217.6)	309.4 (279.1 to 343.2)	333.7 (165.9 to 564.6)	

Statistical analyses

Statistical analysis title	Predicted PK parameter estimation
Comparison groups	ARM 1 - 0.25 mg/Kg/day v ARM 2 - 0.4 mg/Kg/day v ARM3 - 0.5 mg/kg/day
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	median
Point estimate	1399.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	1150.9
upper limit	1620.4

Primary: AUC

End point title	AUC[2]

End point description:

The primary objective of this study was to assess the PK of trazodone after single and repeated doses in patients aged from 2 to ≤17 years.

End point type	Primary

End point timeframe:

Single dose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were applied

End point values	ARM 1 - 0.25 mg/Kg/day	ARM 2 - 0.4 mg/Kg/day	ARM3 - 0.5 mg/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	10	
Units: mg*h/l				
median (confidence interval 90%)	1399.8 (1150.9 to 1620.4)	2947.9 (2683.1 to 4194.9)	3008.5 (1404.1 to 5649.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax

End point title	Cmax[3]

End point description:

The primary objective of this study was to assess the PK of trazodone after single and repeated doses in patients aged from 2 to ≤17 years.

End point type	Primary

End point timeframe:

Single dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were applied

End point values	ARM 1 - 0.25 mg/Kg/day	ARM 2 - 0.4 mg/Kg/day	ARM3 - 0.5 mg/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	10	
Units: ng/ml				
median (confidence interval 90%)	192.1 (113.6 to 217.6)	297.3 (271.2 to 332.0)	304.6 (157.2 to 525.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator carefully monitored the patients' symptoms and/or signs, either spontaneously reported or detected, throughout the whole study period from the signing and dating of the ICF up to the last scheduled visit.

Adverse event reporting additional description:

Treatment-Emergent Adverse Event (TEAE) are considered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	ARM 1

Reporting group description:

Arm 1: Patients treated with Trazodone Hydrochloride 0.25 mg/kg/day from Days 1 to Day 10

Reporting group title	ARM 2

Reporting group description:

Patients treated with Trazodone Hydrochloride 0.4 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.4 mg/kg/day on Days 4 through 10)

Reporting group title	ARM 3

Reporting group description:

Patients treated with Trazodone Hydrochloride 0.5 mg/kg/day (0.25 mg/kg/day on Days 1 through 3 and 0.5 mg/kg/day on Days 4 through 10)

Serious adverse events	ARM 1	ARM 2	ARM 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ARM 1	ARM 2	ARM 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	6	0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rush erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2018	Substantial - Spain. Linked to protocol 2.0 to harmonize study in the two countries
18 February 2019	Substantial - Italy. To harmonize IMPD document in the two countries, after request from AEMPS
07 November 2019	Substantial - Italy and Spain. New IMPD generated.
09 April 2020	Substantial - Italy and Spain. Halt of enrollment due to COVID-19
27 April 2020	Substantial - Italy and Spain. Linked to protocol 3.0: modification of interim analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	After a study-specific risk assessment, in which subject safety and data integrity were a priority, Angelini S.p.A. decided to temporarily stop the enrolment in the clinical trial 152PO17433, especially taking into consideration the fragile population to be included. There is to underline that no patients were on-going in the study at that time; last patient was screened 06/MAR/2020 and dropped-out 12/MAR/2020 as for relevant site's hospital board request to stop all unnecessary study visits.	-

Notes:

Limitations and caveats

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

This study was prematurely stopped due to difficulties in enrolling patients. In addition, interim analysis results revealed that an increase of the dose would have been needed to obtain the desired effect.

Notes: