Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Monotherapy in Patients with Major Depressive Disorder

Summary

EudraCT number	2018-000060-29
Trial protocol	HU SK PL
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	26 July 2020
First version publication date	26 July 2020

Trial information

Trial identification

Sponsor protocol code	RAP-MD-30

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03675776
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area Head, Allergan, 001 862-261-7000, IR-CTRegistration@Allergan.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	11 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the efficacy, safety, and tolerability of 225 milligrams (mg) and 450 milligrams (mg) of Rapastinel, compared to placebo in participants with major depressive disorder (MDD).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2018
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	Japan: 24
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Hungary: 15
Worldwide total number of subjects	50
EEA total number of subjects	23

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)	49

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 68 participants were screened for eligibility; 50 participants randomized to receive double-blind treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo (prefilled syringe, weekly IV administration).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous IV administration

Arm title	Rapastinel 225mg

Arm description:

Rapastinel (prefilled syringe, weekly intravenous IV administration).

Arm type	Experimental
Investigational medicinal product name	Rapastinel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rapastinel intravenous IV administration

Arm title	Rapastinel 450mg

Arm description:

Rapastinel (prefilled syringe, weekly intravenous IV administration).

Arm type	Experimental
Investigational medicinal product name	Rapastinel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
Rapastinel intravenous IV administration

Number of subjects in period 1	Placebo	Rapastinel 225mg	Rapastinel 450mg
Started	15	17	18
Completed	9	11	10
Not completed	6	6	8
Study Terminated by Sponsor	5	6	8
Lack of efficacy	1	-	-

Period 2

Period 2 title	Safety Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:
Placebo (prefilled syringe, weekly IV administration).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
Intravenous IV administration

Arm title	Rapastinel 225mg

Arm description:
Rapastinel (prefilled syringe, weekly intravenous IV administration).

Arm type	Experimental

Investigational medicinal product name	Rapastinel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rapastinel intravenous IV administration

Arm title	Rapastinel 450mg

Arm description:

Rapastinel (prefilled syringe, weekly intravenous IV administration).

Arm type	Experimental
Investigational medicinal product name	Rapastinel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rapastinel intravenous IV administration

Number of subjects in period 2[1]	Placebo	Rapastinel 225mg	Rapastinel 450mg
Started	6	8	7
Completed	6	8	7

Notes:

[1] - 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: Nine patients who entered the extension study (RAP-MD-33) did not enter the Safety Follow Up Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (prefilled syringe, weekly IV administration).	
Reporting group title	Rapastinel 225mg
Reporting group description:	
Rapastinel (prefilled syringe, weekly intravenous IV administration).	
Reporting group title	Rapastinel 450mg
Reporting group description:	
Rapastinel (prefilled syringe, weekly intravenous IV administration).	

Reporting group values	Placebo	Rapastinel 225mg	Rapastinel 450mg
Number of subjects	15	17	18
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	16	18
From 65-84 years	0	1	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	42.4	44.7	43.2
standard deviation	± 10.36	± 10.83	± 11.06
Gender Categorical Units: Subjects			
Female	7	13	7
Male	8	4	11
Race/Ethnicity, Customized Units: Subjects			
White	7	10	9
Black or African American	0	0	0
Asian	8	7	9
Hispanic	0	0	0
Montgomery-Asberg Depression Rating Scale (MADRS)			
The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Participants are rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change score indicates improvement.			
Units: Score on a Scale			
arithmetic mean	34.5	35.2	34.8

standard deviation	± 4.34	± 4.78	± 4.72

Reporting group values	Total		
Number of subjects	50		
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)	49		
From 65-84 years	1		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	27		
Male	23		
Race/Ethnicity, Customized Units: Subjects			
White	26		
Black or African American	0		
Asian	24		
Hispanic	0		
Montgomery-Asberg Depression Rating Scale (MADRS)			
The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Participants are rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change score indicates improvement.			
Units: Score on a Scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo (prefilled syringe, weekly IV administration).	
Reporting group title	Rapastinel 225mg
Reporting group description: Rapastinel (prefilled syringe, weekly intravenous IV administration).	
Reporting group title	Rapastinel 450mg
Reporting group description: Rapastinel (prefilled syringe, weekly intravenous IV administration).	
Reporting group title	Placebo
Reporting group description: Placebo (prefilled syringe, weekly IV administration).	
Reporting group title	Rapastinel 225mg
Reporting group description: Rapastinel (prefilled syringe, weekly intravenous IV administration).	
Reporting group title	Rapastinel 450mg
Reporting group description: Rapastinel (prefilled syringe, weekly intravenous IV administration).	

Primary: Change from Baseline on Montgomery-Asberg Depression Rating Scale (MADRS) total score at end of double-blind treatment (end of week 6).

End point title	Change from Baseline on Montgomery-Asberg Depression Rating Scale (MADRS) total score at end of double-blind treatment (end of week 6).[1]

End point description:

The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Participants are rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change score indicates improvement

End point type	Primary

End point timeframe:

Baseline to end of Week 6

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: No inferential statistical analyses were performed for the efficacy parameters.

End point values	Placebo	Rapastinel 225mg	Rapastinel 450mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	11	10	
Units: Score on a Scale				
arithmetic mean (standard deviation)	-11.3 (± 9.06)	-21.3 (± 10.31)	-12.9 (± 11.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MADRS total score at 1 Day after first dose of treatment

End point title	Change from Baseline in MADRS total score at 1 Day after first dose of treatment

End point description:

The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Participants are rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to 1 Day post-first dose

End point values	Placebo	Rapastinel 225mg	Rapastinel 450mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	17	18	
Units: Score on a scale				
arithmetic mean (standard deviation)	-6.7 (± 5.36)	-7.4 (± 9.10)	-6.4 (± 9.11)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The study consisted of a 6 week double-blind treatment period, followed by a 2-week safety follow-up period.	
Adverse event reporting additional description:	
Safety Population consisted of all randomized patients who received at least 1 dose of randomized investigational product (IP).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (prefilled syringe, weekly IV administration).	
Reporting group title	Rapastinel 225mg
Reporting group description:	
Rapastinel (prefilled syringe, weekly intravenous IV administration).	
Reporting group title	Rapastinel 450mg
Reporting group description:	
Rapastinel (prefilled syringe, weekly intravenous IV administration).	

Serious adverse events	Placebo	Rapastinel 225mg	Rapastinel 450mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	0 / 18 (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	Placebo	Rapastinel 225mg	Rapastinel 450mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	1 / 17 (5.88%)	6 / 18 (33.33%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			

subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Glucose urine present			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Feeling abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Drug Withdrawal Syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Musculoskeletal stiffness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to study termination, the target number of participants needed to achieve target power and statistically reliable results was not met.

Notes: