

**Clinical trial results:****A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel in the Prevention of Relapse in Patients with Major Depressive Disorder****Summary**

EudraCT number	2018-000064-28
Trial protocol	HU SE SK PL BG
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	27 July 2020
First version publication date	27 July 2020

Trial information**Trial identification**

Sponsor protocol code	RAP-MD-33
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03614156
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow, Marlow Buckinghamshire SL7 1YL, 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 450 milligrams (mg) or 225 mg of Rapastinel compared to placebo in the prevention of relapse 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	02 August 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	Hungary: 11
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	United States: 335
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Slovakia: 5
Worldwide total number of subjects	363
EEA total number of subjects	17

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)	330

From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients from RAP-MD-33 completed one of the rapastinel lead-in studies - RAP-MD-30, RAP-MD-31, or RAP-MD-32.

Pre-assignment

Screening details:

A total of 363 patients enrolled in the Open Label Treatment Period (OLTP). Of these, 209 completed the OLTP and 137 entered the Double Blind Treatment Period (DBTP) and were randomized.

Pre-assignment period milestones

Number of subjects started	363
Intermediate milestone: Number of subjects	Completed Open Label Treatment Period: 209
Number of subjects completed	137

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 7
Reason: Number of subjects	Lack of efficacy: 18
Reason: Number of subjects	Consent withdrawn by subject: 36
Reason: Number of subjects	Lost to follow-up: 10
Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Protocol-specified withdrawal met: 6
Reason: Number of subjects	Non-compliance with study drug: 1
Reason: Number of subjects	Study terminated by sponsor: 74
Reason: Number of subjects	Did not meet stability criteria: 72

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo weekly

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 in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous IV administration once per week.

Arm title	Rapastinel clinically driven schedule
Arm description: Rapastinel 450 mg or 225 mg (prefilled syringe, clinically driven schedule IV administration, variable interval, placebo on intervening weeks)	
Arm type	Experimental
Investigational medicinal product name	Rapastinel
Investigational medicinal product code	AGN-241659 (previously GLYX-13)
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use
Dosage and administration details: Rapastinel intravenous IV administration	
Arm title	Rapastinel weekly
Arm description: Rapastinel 450 mg or 225 mg (prefilled syringe, weekly intravenous IV administration)	
Arm type	Experimental
Investigational medicinal product name	Rapastinel
Investigational medicinal product code	AGN-241659 (previously GLYX-13)
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use
Dosage and administration details: Rapastinel intravenous IV administration	

Number of subjects in period 1^[1]	Placebo weekly	Rapastinel clinically driven schedule	Rapastinel weekly
Started	40	42	55
Entered Safety Follow Up Period	26	30	35
Completed	10	11	10
Not completed	30	31	45
Consent withdrawn by subject	4	1	1
Adverse event, non-fatal	2	-	1
Miscellaneous Reasons	1	-	-
Study terminated by sponsor	22	26	38
Lost to follow-up	-	3	4
Protocol deviation	1	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline period consists only of those 137 participants who were randomized out of the overall 363 enrolled participants.

Baseline characteristics

Reporting groups

Reporting group title	Placebo weekly
Reporting group description: Placebo (prefilled syringe, weekly IV administration)	
Reporting group title	Rapastinel clinically driven schedule
Reporting group description: Rapastinel 450 mg or 225 mg (prefilled syringe, clinically driven schedule IV administration, variable interval, placebo on intervening weeks)	
Reporting group title	Rapastinel weekly
Reporting group description: Rapastinel 450 mg or 225 mg (prefilled syringe, weekly intravenous IV administration)	

Reporting group values	Placebo weekly	Rapastinel clinically driven schedule	Rapastinel weekly
Number of subjects	40	42	55
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)	33	40	53
From 65-84 years	7	2	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	47.0	43.6	43.9
standard deviation	± 13.95	± 12.57	± 11.66
Sex: Female, Male Units: Participants			
Female	30	29	44
Male	10	13	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	3	2	2
Native Hawaiian or Other Pacific Islander	1	2	0
Black or African American	8	5	11
White	27	33	42
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	8	9

Not Hispanic or Latino	37	34	46
Unknown or Not Reported	0	0	0

Weight Units: kg			
arithmetic mean	84.84	85.88	88.53
standard deviation	± 17.856	± 19.207	± 19.240
Height Units: cm			
arithmetic mean	168.31	166.92	168.47
standard deviation	± 8.996	± 9.858	± 9.196
BMI Units: kg/m ²			
arithmetic mean	29.89	30.95	31.15
standard deviation	± 5.686	± 7.289	± 6.279

Reporting group values	Total		
Number of subjects	137		
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)	126		
From 65-84 years	11		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean	-		
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	103		
Male	34		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	7		
Native Hawaiian or Other Pacific Islander	3		
Black or African American	24		
White	102		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	20		

Not Hispanic or Latino	117		
Unknown or Not Reported	0		

Weight Units: kg arithmetic mean standard deviation	-		
Height Units: cm arithmetic mean standard deviation	-		
BMI Units: kg/m ² arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo weekly
Reporting group description: Placebo (prefilled syringe, weekly IV administration)	
Reporting group title	Rapastinel clinically driven schedule
Reporting group description: Rapastinel 450 mg or 225 mg (prefilled syringe, clinically driven schedule IV administration, variable interval, placebo on intervening weeks)	
Reporting group title	Rapastinel weekly
Reporting group description: Rapastinel 450 mg or 225 mg (prefilled syringe, weekly intravenous IV administration)	

Primary: Time to First Relapse During the 52 Weeks of the Double-Blind Treatment Period (DBTP)

End point title	Time to First Relapse During the 52 Weeks of the Double-Blind Treatment Period (DBTP) ^[1]
End point description: Time in days from randomization to relapse. The primary efficacy analysis will compare the time to relapse between placebo and rapastinel treatment groups using the log-rank test. Due to study termination, there are not enough events to allow for any statistically meaningful estimation of the Time to First Relapse. As a result, only the time to relapse at the 25th percentile is presented for each study arm, without confidence intervals.	
End point type	Primary
End point timeframe: 52 Weeks	

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: Due to study termination, there are not enough events to allow for any meaningful statistical analysis.

End point values	Placebo weekly	Rapastinel clinically driven schedule	Rapastinel weekly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	42	55	
Units: Days(Time of Relapse at 25th percentile)				
number (not applicable)	94	177	157	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The study consisted of an 8 to 16 week OLTP; followed by a randomized DBTP of up to 52 weeks; followed by a 2 week safety period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.2

Reporting groups

Reporting group title	Open-Label Treatment Period
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Reporting group description:

Rapastinel 225 milligrams (mg) or 450 mg intravenous (IV) once a week during OLTP.

Reporting group title	Placebo weekly
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Reporting group description:

Placebo (prefilled syringe, weekly IV administration)

Reporting group title	Rapastinel clinically driven schedule
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Reporting group description:

Rapastinel 450 mg or 225 mg (prefilled syringe, clinically driven schedule IV administration, variable interval, placebo on intervening weeks)

Reporting group title	Rapastinel weekly
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Reporting group description:

Rapastinel 450 mg or 225 mg (prefilled syringe, weekly intravenous IV administration)

Serious adverse events	Open-Label Treatment Period	Placebo weekly	Rapastinel clinically driven schedule
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 363 (1.10%)	1 / 40 (2.50%)	1 / 42 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Partial seizures			
subjects affected / exposed	1 / 363 (0.28%)	0 / 40 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 363 (0.00%)	1 / 40 (2.50%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	1 / 363 (0.28%)	0 / 40 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 363 (0.28%)	0 / 40 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 363 (0.28%)	0 / 40 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	0 / 363 (0.00%)	0 / 40 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rapastinel weekly		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Partial seizures			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcoholism			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Open-Label Treatment Period	Placebo weekly	Rapastinel clinically driven schedule
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 363 (12.12%)	17 / 40 (42.50%)	9 / 42 (21.43%)
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 363 (5.51%)	3 / 40 (7.50%)	1 / 42 (2.38%)
occurrences (all)	23	5	1
Dizziness			
subjects affected / exposed	1 / 363 (0.28%)	2 / 40 (5.00%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 363 (0.55%)	2 / 40 (5.00%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 363 (0.28%) 1	4 / 40 (10.00%) 4	0 / 42 (0.00%) 0
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	4 / 363 (1.10%) 4	2 / 40 (5.00%) 2	1 / 42 (2.38%) 1
Vomiting subjects affected / exposed occurrences (all)	2 / 363 (0.55%) 2	3 / 40 (7.50%) 3	0 / 42 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 363 (0.55%) 3	2 / 40 (5.00%) 2	1 / 42 (2.38%) 1
Gastritis subjects affected / exposed occurrences (all)	0 / 363 (0.00%) 0	2 / 40 (5.00%) 2	0 / 42 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	18 / 363 (4.96%) 19	1 / 40 (2.50%) 1	4 / 42 (9.52%) 4
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	15 / 363 (4.13%) 16	3 / 40 (7.50%) 3	1 / 42 (2.38%) 1
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	26 / 363 (7.16%) 31	0 / 40 (0.00%) 0	4 / 42 (9.52%) 4
Bronchitis subjects affected / exposed occurrences (all)	2 / 363 (0.55%) 2	2 / 40 (5.00%) 2	0 / 42 (0.00%) 0
Non-serious adverse events	Rapastinel weekly		
Total subjects affected by non-serious adverse events subjects affected / exposed	13 / 55 (23.64%)		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 4		
Dizziness subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2 1 / 55 (1.82%) 1 0 / 55 (0.00%) 0 0 / 55 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

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: