



## Clinical trial results:

### A PHASE 2 MULTICENTER, OPEN-LABEL, UNCONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF RA101495 IN SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

#### Summary

EudraCT number	2016-003522-16
Trial protocol	FI GB HU DK
Global end of trial date	28 March 2018

#### Results information

Result version number	v1 (current)
This version publication date	05 July 2019
First version publication date	05 July 2019

#### Trial information

##### Trial identification

Sponsor protocol code	RA101495-01.201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03078582
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Ra Pharmaceuticals, Inc.
Sponsor organisation address	87 Cambridge Park Drive, Cambridge, United States, MA 02140
Public contact	Ra Pharmaceuticals, Inc., Ra Pharmaceuticals, Inc., +1 6174014060, trials@rapharma.com
Scientific contact	Ra Pharmaceuticals, Inc., Ra Pharmaceuticals, Inc., +1 6174014060, trials@rapharma.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	14 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2018
Global end of trial reached?	Yes
Global end of trial date	28 March 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To assess the safety and tolerability of RA101495 in subjects with PNH
- To assess preliminary efficacy of RA101495 in subjects with PNH
- To assess PK and PD of RA101495 in subjects with PNH

Protection of trial subjects:

Patients were to give freely their written informed consent before entering the study.

Patients were provided with updated information and re-consented if substantial changes in the study occurred.

This study was performed in accordance with Good Clinical Practice standards.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 2017
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	United Kingdom: 5
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	New Zealand: 4
Worldwide total number of subjects	26
EEA total number of subjects	16

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)	18
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 29 subjects were screened for enrollment into the study. A total of 26 subjects were enrolled into the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort A

Arm description:

Eculizumab Naïve - included subjects who have not received eculizumab for treatment of PNH

Arm type	Experimental
Investigational medicinal product name	RA101495
Investigational medicinal product code	RA101495
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

RA101495 was provided as a solution for injection containing 40mg/mL of active ingredient in a daily prefilled syringe. Doses provided for the study included 0.1mg/kg and 0.3mg/kg.

<b>Arm title</b>	Cohort B
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Arm description:

Eculizumab Switch - included subjects who have received treatment with eculizumab for at least 6 months prior to Screening

Arm type	Experimental
Investigational medicinal product name	RA101495
Investigational medicinal product code	RA101495
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

RA101495 was provided as a solution for injection containing 40mg/mL of active ingredient in a daily prefilled syringe. Doses provided for the study included 0.1mg/kg and 0.3mg/kg.

<b>Number of subjects in period 1</b>	Cohort A	Cohort B
Started	10	16
Completed	10	8
Not completed	0	8
Adverse event, non-fatal	-	8

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort A
Reporting group description:	
Eculizumab Naïve - included subjects who have not received eculizumab for treatment of PNH	
Reporting group title	Cohort B
Reporting group description:	
Eculizumab Switch - included subjects who have received treatment with eculizumab for at least 6 months prior to Screening	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	10	16	26
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	11	18
From 65-84 years	3	5	8
Age continuous			
Units: years			
median	56.0	53.0	
full range (min-max)	32 to 81	22 to 72	-
Gender categorical			
Units: Subjects			
Female	6	7	13
Male	4	9	13
Race			
Units: Subjects			
White	10	14	24
Black or African American	0	2	2
Weight			
Units: kg			
median	78.10	80.15	
full range (min-max)	46.0 to 100.8	54.9 to 109.7	-
Height			
Units: cm			
median	165.00	169.00	
full range (min-max)	157.5 to 188.0	154.2 to 182.0	-

## End points

### End points reporting groups

Reporting group title	Cohort A
Reporting group description: Eculizumab Naïve - included subjects who have not received eculizumab for treatment of PNH	
Reporting group title	Cohort B
Reporting group description: Eculizumab Switch - included subjects who have received treatment with eculizumab for at least 6 months prior to Screening	

### Primary: Primary Efficacy Endpoint: Change in serum LDH levels

End point title	Primary Efficacy Endpoint: Change in serum LDH levels <sup>[1]</sup>
End point description: Primary Efficacy Endpoint: Change from baseline in serum LDH levels during the primary evaluation period, defined as the mean LDH values of Weeks 6, 8, 10, and 12 minus the baseline LDH value. Efficacy Evaluable Population analysis is presented. For Cohort A subjects' baseline LDH is the average of the study Day 1 and Screening Period values. In Cohort A a Wilcoxon signed rank test is applied to assess the change from Baseline in the Primary Evaluation Period (p=0.0020 in the Efficacy Evaluable Population).	
End point type	Primary
End point timeframe: Primary Evaluation Period value is the patient's mean value across the Week 6, 8, 10, and 12 visits.	

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: The planned statistical test on the Primary Efficacy Endpoint is a comparison between the Baseline value and the Primary Evaluation Period within Cohort A only. Since statistical tests are expected to compare different groups, this statistical test cannot be entered without evoking validation error message.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 <sup>[2]</sup>	8 <sup>[3]</sup>		
Units: U/L				
arithmetic mean (standard deviation)	-695.2 (± 589.2)	216.7 (± 209.2)		

Notes:

[2] - Efficacy Evaluable Population analysis is presented here.

[3] - Efficacy Evaluable Population analysis is presented here.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For all subjects, the AE reporting period started with the first administration of study drug on Day 1 and ended with the final study visit, after which no new AEs were to be reported.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Cohort A
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Reporting group description:

Eculizumab Naïve - included subjects who have not received eculizumab for treatment of PNH

Reporting group title	Cohort B
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Reporting group description:

Eculizumab Switch - included subjects who have received treatment with eculizumab for at least 6 months prior to Screening

Serious adverse events	Cohort A	Cohort B	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			



subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Cohort A	Cohort B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	15 / 16 (93.75%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Injection site bruising			
subjects affected / exposed	3 / 10 (30.00%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Crepitations			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vaccination site pain			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Reproductive system and breast disorders Vaginal discharge subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2  1 / 10 (10.00%) 1  1 / 10 (10.00%) 1  0 / 10 (0.00%) 0	0 / 16 (0.00%) 0  0 / 16 (0.00%) 0  0 / 16 (0.00%) 0  1 / 16 (6.25%) 1	
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)  Anxiety subjects affected / exposed occurrences (all)  Insomnia subjects affected / exposed occurrences (all)  Sleep disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0  1 / 10 (10.00%) 1  0 / 10 (0.00%) 0  1 / 10 (10.00%) 1	1 / 16 (6.25%) 1  0 / 16 (0.00%) 0  1 / 16 (6.25%) 1  0 / 16 (0.00%) 0	
Product issues Device failure subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	

Investigations			
Blood glucose fluctuation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Liver function test increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	7 / 16 (43.75%)	
occurrences (all)	1	7	
Dizziness			
subjects affected / exposed	2 / 10 (20.00%)	3 / 16 (18.75%)	
occurrences (all)	2	3	
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Presyncope			

subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Haemolysis			
subjects affected / exposed	0 / 10 (0.00%)	7 / 16 (43.75%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Proctalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vomiting			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Skin and subcutaneous tissue disorders Actinic keratosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Renal and urinary disorders Paroxysmal nocturnal haemoglobinuria subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 16 (12.50%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)  Flank pain subjects affected / exposed occurrences (all)  Musculoskeletal chest pain subjects affected / exposed occurrences (all)  Musculoskeletal pain subjects affected / exposed occurrences (all)  Myalgia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1  0 / 10 (0.00%) 0  0 / 10 (0.00%) 0  1 / 10 (10.00%) 1  0 / 10 (0.00%) 0  1 / 10 (10.00%) 1  0 / 10 (0.00%) 0	3 / 16 (18.75%) 3  2 / 16 (12.50%) 2  2 / 16 (12.50%) 2  0 / 16 (0.00%) 0  1 / 16 (6.25%) 1  0 / 16 (0.00%) 0  1 / 16 (6.25%) 1	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	1 / 16 (6.25%) 1	

Localised infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Rhinitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 16 (6.25%) 1	
Urosepsis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 16 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported