Clinical trial results:
A Phase 3, double-blind, randomized study of RVT-101 versus placebo when added to existing stable donepezil treatment in subjects with mild to moderate Alzheimer's Disease

Summary

EudraCT number	2015-002957-37
Trial protocol	DE GB CZ SK ES BG HR IT
Global end of trial date	31 August 2017

Results information

Result version number	v1 (current)
This version publication date	29 December 2018
First version publication date	29 December 2018

Trial information

Trial identification

Sponsor protocol code	RVT-101-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02585934
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Axovant Sciences Ltd.
Sponsor organisation address	2 Church Street, Hamilton, Bermuda,
Public contact	Project Management, Worldwide Clinical Trials, +44 207121 61 61,
Scientific contact	Project Management, Worldwide Clinical Trials, 646 8220512,

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	20 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy:
- on cognitive function as measured by the ADAS-Cog-11 after 24 weeks of treatment.
- on activities of daily living as measured by ADCS-ADL scale after 24 weeks of treatment

Protection of trial subjects:

Subjects were required to provide full written informed consent prior to the performance of any protocol-specified procedure; or if unable to provide informed consent due to cognitive status, subject has provided assent and a legally acceptable representative has provided full written informed consent on behalf of the subject. Collection of AEs and SAEs were collected at the time of informed consent and continued until the follow-up contact. SAEs that were spontaneously reported by the subject or subject representative or discovered by the investigator or designee after the follow-up visit and up to 30 days after the last dose of investigational product were collected and reported. Subjects were withdrawn from the study based on consultation between the principal investigator and Medical Monitor, with the ultimate decision by the principal investigator or subject. Study safety data was periodically reviewed by an independent data monitoring committee.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 December 2015
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	Taiwan: 17
Country: Number of subjects enrolled	United States: 349
Country: Number of subjects enrolled	Canada: 48
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Argentina: 123
Country: Number of subjects enrolled	Chile: 52
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 10
Country: Number of subjects enrolled	Serbia: 29
Country: Number of subjects enrolled	Singapore: 16
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Slovakia: 48
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	United Kingdom: 193

Country: Number of subjects enrolled	Croatia: 32
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Czech Republic: 58
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 75
Country: Number of subjects enrolled	Italy: 67
Worldwide total number of subjects	1315
EEA total number of subjects	635

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)	202
From 65 to 84 years	1088
85 years and over	25

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for eligibility during the Screening Period. An ICF was signed by each subject or by the caregiver with subject assent. Consent forms were also signed by the caregiver before any study-specific procedures were performed. Subjects were screened according to study inclusion/exclusion criteria.

Period 1

Period 1 title	Double-Blind (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

Blinding implementation details:

A 24-week Double-Blind Treatment Period when neither subjects nor their caregivers nor investigators knew which of the 2 treatments the subject was receiving. Subjects were not informed of transition from the Single-Blind Run-In Period to the Double-Blind Treatment Period. RVT-101 and placebo were provided as tablets that are indistinguishable in appearance, smell, and taste.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as tablets. Subjects were instructed to take 1 tablet orally each morning without regard to food for 24 weeks.

Arm title	RVT-101 35 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	RVT-101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RVT-101 was administered as pink film-coated round 35-mg tablets. Subjects were instructed to take 1 tablet orally each morning without regard to food for 24 weeks.

Number of subjects in period 1	Placebo	RVT-101 35 mg
Started	654	661
Safety Population	651	656
Intent-to-Treat Population	633	643
Per-Protocol Population	582	603
Completed	581	592
Not completed	73	69
Adverse event, serious fatal	2	3
Physician decision	2	3
Consent withdrawn by subject	21	7
Adverse event, non-fatal	20	18
Other	5	10
Death	-	2
Sponsor Termination	2	1
Caregiver withdrew consent	7	7
Lost to follow-up	2	2
Protocol deviation	11	14
Lack of efficacy	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	RVT-101 35 mg
Reporting group description: -	

Reporting group values	Placebo	RVT-101 35 mg	Total
Number of subjects	654	661	1315
Age categorical			
Intent-To-Treat (ITT) Population baseline characteristics have been entered for the Placebo (number of subjects=633) and RVT-101 (number of subjects=643) arms.			
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)	97	99	196
From 65-84 years	551	557	1108
85 years and over	6	5	11
Age continuous			
Intent-To-Treat (ITT) Population baseline characteristics have been entered for the Placebo (number of subjects=633) and RVT-101 (number of subjects=643) arms.			
Units: years			
arithmetic mean	72.5	72.7	
full range (min-max)	50 to 86	50 to 85	-
Gender categorical			
Units: Subjects			
Female	406	398	804
Male	248	263	511

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	RVT-101 35 mg
Reporting group description: -	
Subject analysis set title	RVT-101 Concentration Summary Statistics at Week 6
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis completed on subjects in the PK population. The PK population will include all subjects in the Safety Population who undergo plasma PK sampling and have at least one post-baseline evaluable PK concentration result.	
Subject analysis set title	RVT-101 Concentration Summary Statistics at Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis completed on subjects in the PK population. The PK population will include all subjects in the Safety Population who undergo plasma PK sampling and have at least one post-baseline evaluable PK concentration result.	
Subject analysis set title	RVT-101 Concentration Summary Statistics at Week 18
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis completed on subjects in the PK population. The PK population will include all subjects in the Safety Population who undergo plasma PK sampling and have at least one post-baseline evaluable PK concentration result.	
Subject analysis set title	RVT-101 Concentration Summary Statistics at Week 24
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis completed on subjects in the PK population. The PK population will include all subjects in the Safety Population who undergo plasma PK sampling and have at least one post-baseline evaluable PK concentration result.	

Primary: Alzheimer’s Disease Assessment Scale – Cognitive Subscale 11 Items (ADAS-Cog-11) Score Change From Baseline to Week 24

End point title	Alzheimer’s Disease Assessment Scale – Cognitive Subscale 11 Items (ADAS-Cog-11) Score Change From Baseline to Week 24
End point description:	
The 11-item ADAS-Cog assesses a range of cognitive abilities including memory, comprehension, orientation in time and place, and spontaneous speech. The ADAS-Cog-11 total score range is from 0 to 70, with a higher score indicating more severe cognitive impairment.	
End point type	Primary
End point timeframe:	
Baseline, 24 weeks	

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	584	577		
Units: NA	584	577		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg
Number of subjects included in analysis	1161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2249 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.22

Notes:

[1] - The threshold for statistical significance was p=0.05

Primary: Alzheimer’s Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) Score Change From Baseline to Week 24

End point title	Alzheimer’s Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) Score Change From Baseline to Week 24

End point description:

The ADCS-ADL scale measures functional impairment in terms of activities of daily living. The score ranges from 0 to 78. The lower the score, the greater the impairment; higher scores indicate better (more desirable) function

End point type	Primary

End point timeframe:

Baseline, 24 weeks

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	575	588		
Units: NA	575	588		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg

Number of subjects included in analysis	1163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.826 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.72

Notes:

[2] - Tthe threshold for statistical significance was p=0.05

Secondary: Clinical Global Impression of Change - Plus Caregiver Interview (CIBIC+) Score at Week 24

End point title	Clinical Global Impression of Change - Plus Caregiver Interview (CIBIC+) Score at Week 24

End point description:

The CIBIC+ assessment measures the global functioning of the subject. The CIBIC+ is scored as a seven-point categorical rating, ranging from a score of 1 (indicating "very much improved"), to a score of 4 (indicating "no change"), or to a score of 7 (indicating "very much worse.") Lower CIBIC+ scores indicate better (more desirable) function

End point type	Secondary

End point timeframe:

24 weeks

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	568	577		
Units: NA	568	577		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg
Number of subjects included in analysis	1145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0234 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	-0.02

Notes:

[3] - The threshold for statistical significance was p=0.05

Secondary: The Dependence Scale (DS) Score Change From Baseline to Week 24

End point title	The Dependence Scale (DS) Score Change From Baseline to Week 24

End point description:

The DS measures the amount of assistance patients with dementia require in performing daily activities. The scale consists of 13 items, representing a range of severity from mild to severe levels of dependency. The score range is from 0 to 15 with higher scores indicating greater dependency.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	568	580		
Units: NA	568	580		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg
Number of subjects included in analysis	1148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2096 [4]
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.32

Notes:

[4] - The threshold for statistical significance was p=0.05

Secondary: Neuropsychiatric Inventory (NPI) Score Change From Baseline to Week 24

End point title	Neuropsychiatric Inventory (NPI) Score Change From Baseline

	to Week 24

End point description:

End point type	Secondary

End point timeframe:

The NPI is a behavior rating scale composed of a 12-item structured interview of the caregiver that is scored from 0 to 144 (the higher the score, the greater the psychiatric disturbance). It assesses 12 behavioral disturbances occurring in dementia patie

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	570	583		
Units: NA	570	583		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg
Number of subjects included in analysis	1153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.8

Notes:

[5] - The threshold for statistical significance was p=0.05

Secondary: ADAS-Cog-13 Score Change From Baseline to Week 24

End point title	ADAS-Cog-13 Score Change From Baseline to Week 24

End point description:

13-item ADAS-Cog assesses a range of cognitive abilities including memory, comprehension, orientation in time and place, and spontaneous speech. Most items are evaluated by tests, but some are dependent on clinician ratings on a 5-point scale. The ADAS-Cog-13 is the ADAS-Cog-11 with 2 additional items: delayed word recall and total digit cancellation. Scores for the ADAS-Cog-13 range from 0 to 85 with higher scores indicating greater dysfunction.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks

End point values	Placebo	RVT-101 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	576	583		
Units: NA	576	583		

Statistical analyses

Statistical analysis title	Repeated Measures Analysis
Comparison groups	Placebo v RVT-101 35 mg
Number of subjects included in analysis	1159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2472 [6]
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.27

Notes:

[6] - The threshold for statistical significance was p=0.05

Secondary: Measurement of Concentrations of RVT-101 in Plasma

End point title	Measurement of Concentrations of RVT-101 in Plasma

End point description:

Measurement collected at timepoints Week 6, Week 12, Week 18, and Week 24

End point type	Secondary

End point timeframe:

Week 6, Week 12, Week 18, Week 24

End point values	RVT-101 Concentration Summary Statistics at Week 6	RVT-101 Concentration Summary Statistics at Week 12	RVT-101 Concentration Summary Statistics at Week 18	RVT-101 Concentration Summary Statistics at Week 24
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	563	579	454	562
Units: ng/mL				
geometric mean (confidence interval 95%)	201.11 (191.88 to 210.78)	170.95 (164.40 to 177.76)	198.69 (189.36 to 208.48)	193.36 (184.60 to 202.53)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Collection of AEs and SAEs will begin at the time a subject signs informed consent and continues until the follow-up contact.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	RVT-101

Reporting group description: -

Serious adverse events	Placebo	RVT-101	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 651 (6.76%)	40 / 656 (6.10%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 651 (0.46%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor peripheral circulation			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 651 (0.00%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatic symptom disorder			

subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 651 (0.46%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 651 (0.46%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma obstruction			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 651 (0.15%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mitral valve prolapse			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 651 (0.31%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	3 / 651 (0.46%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia			

subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 651 (0.00%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 651 (0.31%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 651 (0.15%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 651 (0.15%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal vascular ectasia			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 651 (0.15%)	0 / 656 (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			
Appendicitis			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	2 / 651 (0.31%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 651 (0.15%)	2 / 656 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 651 (0.15%)	1 / 656 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 651 (0.00%)	1 / 656 (0.15%)	
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: 2 %

Non-serious adverse events	Placebo	RVT-101	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 651 (25.50%)	191 / 656 (29.12%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	29 / 651 (4.45%)	37 / 656 (5.64%)	
occurrences (all)	29	37	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 651 (1.84%)	19 / 656 (2.90%)	
occurrences (all)	12	19	
Headache			

subjects affected / exposed	18 / 651 (2.76%)	17 / 656 (2.59%)	
occurrences (all)	18	17	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 651 (2.61%)	13 / 656 (1.98%)	
occurrences (all)	17	13	
Nausea			
subjects affected / exposed	13 / 651 (2.00%)	17 / 656 (2.59%)	
occurrences (all)	13	17	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	10 / 651 (1.54%)	14 / 656 (2.13%)	
occurrences (all)	10	14	
Cough			
subjects affected / exposed	7 / 651 (1.08%)	15 / 656 (2.29%)	
occurrences (all)	7	15	
Nasopharyngitis			
subjects affected / exposed	19 / 651 (2.92%)	23 / 656 (3.51%)	
occurrences (all)	19	23	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 651 (2.30%)	11 / 656 (1.68%)	
occurrences (all)	15	11	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	26 / 651 (3.99%)	25 / 656 (3.81%)	
occurrences (all)	26	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2015	Amendment #1 includes the changes to the original protocol RVT-101-3001, version 1.0 dated 24 August 2015: modifying the creatinine clearance exclusion criterion, clarifying the contact information for serious adverse events (SAEs), and removing the requirement for including subject initials in SAE reports.
13 April 2016	Protocol RVT-101-3001 version 3.0 includes the following changes to protocol version 2.0 dated 19 November 2015: subjects will now have the option to enter a 12-month Open-Label Extension study (study RVT-101-3002) after completion of the current lead-in study (RVT-101-3001); subjects will not be required to undergo the follow-up visit/Visit 9 of this study if they enter the open-label extension study; and administrative changes were made for clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported