



Clinical trial results:

A Phase II, Multicenter , Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of RO4602522 Added to Background Alzheimer's Disease Therapy in Patients with Moderate Alzheimer's Disease

Summary

EudraCT number	2012-000943-29
Trial protocol	SE DE GB CZ IT PL
Global end of trial date	03 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	BP28248
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01677754
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333,
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333,

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	03 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a 12-month treatment of RO4602522 versus placebo added to background therapy of donepezil or rivastigmine in patients with moderate severity Alzheimer's Disease (AD) (Mini Mental State Examination [MMSE] 13-20 inclusive), based on the mean change in Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale [ADAS-Cog-11) scores cognitive endpoint, from baseline over time.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy:

Study participation required a background therapy of treatment with acetylcholinesterase inhibitors (AChEIs) alone or in combination with memantine for at least 4 months, with the dose (of mono or dual therapy) stabilized for at least 3 months before screening. All formulations and dosages of the AChEIs donepezil, rivastigmine, and galantamine, as well as the combination of any AChEI with memantine were allowed, except treatment including donepezil 23 mg due to poor tolerability. Patients were to remain on the same dosing regimen of background treatment throughout the study.

Evidence for comparator: -

Actual start date of recruitment	24 October 2012
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	Poland: 53
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Czech Republic: 82
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	United States: 102
Worldwide total number of subjects	540
EEA total number of subjects	334

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)	98
From 65 to 84 years	404
85 years and over	38

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

45-day screening period. At least 495 participants with moderate severity AD (MMSE 13-20 inclusive at screening) were randomized, equal ratio (1:1:1) to one of following 3 treatments: placebo, RO4602522 1 mg, or RO4602522 5 mg, as add-on to background therapy of AChEI (donepezil, rivastigmine, or galantamine) alone or in combination with memantine.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RO4602522 1 mg

Arm description:

2 x 0.5 mg tablets taken daily orally for 12 months in addition to background therapy.

Arm type	Experimental
Investigational medicinal product name	RO4602522 1 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 0.5 mg tablet orally from each of two 0.5 mg tablet bottles at the same time every day throughout the study.

Arm title	RO4602522 5mg
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Arm description:

2 x 2.5 mg tablets taken daily orally for 12 months in addition to background therapy.

Arm type	Experimental
Investigational medicinal product name	RO4602522 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 2.5 mg tablet orally from each of two 2.5 mg tablet bottles at the same time every day throughout the study.

Arm title	Placebo
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Arm description:

Matching dose tablet (0.5 mg or 2.5 mg) taken from each of 2 bottles daily for 12 months, in addition to background therapy.

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

Dosage and administration details:

One matching dose tablet (0.5 mg or 2.5 mg) taken orally from each of two bottles at the same time every day throughout the study.

Number of subjects in period 1	RO4602522 1 mg	RO4602522 5mg	Placebo
Started	179	180	181
Completed	134	142	143
Not completed	45	38	38
Adverse event, non-fatal	15	16	12
Death	2	1	2
Investigator-specified reasons	11	2	3
Non-compliance with study medication	-	1	2
Lost to follow-up	4	2	-
Sponsor decision	1	-	1
Lack of efficacy	1	1	3
Withdrawal by subject	11	15	15

Baseline characteristics

Reporting groups

Reporting group title	RO4602522 1 mg
Reporting group description: 2 x 0.5 mg tablets taken daily orally for 12 months in addition to background therapy.	
Reporting group title	RO4602522 5mg
Reporting group description: 2 x 2.5 mg tablets taken daily orally for 12 months in addition to background therapy.	
Reporting group title	Placebo
Reporting group description: Matching dose tablet (0.5 mg or 2.5 mg) taken from each of 2 bottles daily for 12 months, in addition to background therapy.	

Reporting group values	RO4602522 1 mg	RO4602522 5mg	Placebo
Number of subjects	179	180	181
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)	37	35	26
From 65-84 years	132	131	141
85 years and over	10	14	14
Age continuous Units: years			
arithmetic mean	72.9	72.5	73.8
standard deviation	± 9	± 9.47	± 8.26
Gender categorical Units: Subjects			
Female	111	123	104
Male	68	57	77

Reporting group values	Total		
Number of subjects	540		
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)	98		
From 65-84 years	404		
85 years and over	38		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	338		
Male	202		

End points

End points reporting groups

Reporting group title	RO4602522 1 mg
Reporting group description: 2 x 0.5 mg tablets taken daily orally for 12 months in addition to background therapy.	
Reporting group title	RO4602522 5mg
Reporting group description: 2 x 2.5 mg tablets taken daily orally for 12 months in addition to background therapy.	
Reporting group title	Placebo
Reporting group description: Matching dose tablet (0.5 mg or 2.5 mg) taken from each of 2 bottles daily for 12 months, in addition to background therapy.	

Primary: Mean Change from Baseline in Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale (ADAS-Cog-11)

End point title	Mean Change from Baseline in Alzheimer's Disease Assessment Scale – Cognitive Behavior Subscale (ADAS-Cog-11)
End point description: Analysis of Intent to Treat (ITT) population	
End point type	Primary
End point timeframe: Baseline to 52 weeks	

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	142	142	
Units: Number				
arithmetic mean (standard deviation)	5.074 (± 7.7956)	5.979 (± 7.3505)	4.857 (± 7.6222)	

Statistical analyses

Statistical analysis title	RO4602522 1mg vs Placebo
Comparison groups	RO4602522 1 mg v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.855
Method	Mixed models analysis

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	1.59

Statistical analysis title	RO4602522 5mg vs Placebo
Comparison groups	RO4602522 5mg v Placebo
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.259
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	2.75

Secondary: Mean Alzheimer's Disease Cooperative Study Clinician Global Impression of Change (ADCS-CGIC) Score

End point title	Mean Alzheimer's Disease Cooperative Study Clinician Global Impression of Change (ADCS-CGIC) Score
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End point description:

Percentages are based on the number of patients in the intent to treat population with an assessment at each visit.

End point type	Secondary
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End point timeframe:

Baseline to week 52

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	147	147	
Units: Percentage				
number (not applicable)				
Marked Improvement	2.1	0.7	0	
Moderate Improvement	0.7	1.4	2	
Minimal Improvement	5.6	4.8	5.4	
No change	24.6	23.8	21.8	
Minimal worsening	32.4	36.7	34.7	
Moderate worsening	29.6	25.9	30.6	
Marked worsening	4.9	6.8	5.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline over Time in Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) Score

End point title	Mean Change from Baseline over Time in Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) Score
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End point description:

Analysis of the Intent to Treat (ITT) population

End point type	Secondary
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End point timeframe:

Baseline to week 52

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	145	145	
Units: Number				
arithmetic mean (standard deviation)	-6 (± 12.14)	-6.8 (± 11.75)	-8.2 (± 10.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline over Time in Behavioral Pathology in Alzheimer's Disease Frequency- Weighted Severity Scale (BEHAVE-AD-FW) Total Score

End point title	Mean Change from Baseline over Time in Behavioral Pathology in Alzheimer's Disease Frequency- Weighted Severity Scale (BEHAVE-AD-FW) Total Score
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End point description:

Analysis of the Intent to Treat (ITT) population

End point type	Secondary
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End point timeframe:

Baseline to 52 weeks

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143	148	146	
Units: Number				
arithmetic mean (standard deviation)	1.1 (± 8.09)	1.4 (± 10.1)	4.5 (± 11.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline over Time in Apathy Evaluation Scale (AES) Score

End point title	Mean Change from Baseline over Time in Apathy Evaluation Scale (AES) Score
End point description: Analysis of the Intent to Treat (ITT) population	
End point type	Secondary
End point timeframe: Baseline to 52 weeks	

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	148	145	
Units: Number				
arithmetic mean (standard deviation)	4.3 (± 8.92)	4.5 (± 9.77)	4.2 (± 9.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline over Time in Global Deterioration Scale (GDS) Score

End point title	Percentage Change from Baseline over Time in Global Deterioration Scale (GDS) Score
End point description: Baseline is defined as the most recent value recorded prior to first dose of study medication. Percentages are based on the number of patients with a score at each visit and at Baseline.	
End point type	Secondary
End point timeframe: Baseline to week 52	

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	141	145	145	
Units: Percentage				
number (not applicable)				
Decrease of 3	0	0.7	0	
Decrease of 2	1.4	0.7	1.4	
Decrease of 1	2.8	2.8	2.8	
No change	61.7	60	63.4	
Increase of 1	27	31	26.9	
Increase of 2	7.1	4.1	5.5	
Increase of 3	0	0.7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Worsening over Time in Behavioral Pathology in Alzheimer's Disease Frequency- Weighted Severity Scale (BEHAVE-AD-FW) Score

End point title	Percentage of Patients Worsening over Time in Behavioral Pathology in Alzheimer's Disease Frequency- Weighted Severity Scale (BEHAVE-AD-FW) Score
End point description:	
Analysis of Intent to Treat (ITT) population; BEHAVE-AD-FW worsening, defined as an increase of more than 20% in any domain, where the baseline score for the same domain was > 0 (across the 3 treatment groups, 2 patients did not have total score at baseline and 138 had a score of 0).	
End point type	Secondary
End point timeframe:	
Baseline to 52 weeks	

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	111	101	
Units: Percentage				
number (not applicable)	44.1	44.1	54.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Worsening over Time in Alzheimer's Disease Cooperative Study Clinician Global Impression of Change (ADCS-CGIC) Scores

End point title	Percentage of Patients Worsening over Time in Alzheimer's Disease Cooperative Study Clinician Global Impression of
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End point description:

Analysis of the Intent to Treat (ITT) population; Percentages were based on the number of patients in the intent-to-treat population with a rating at each visit. Worsened for ADCS-CGIC is defined as a rating of "Minimal Worsening," "Moderate Worsening," or "Marked Worsening."

End point type

Secondary

End point timeframe:

Baseline to 52 weeks

End point values	RO4602522 1 mg	RO4602522 5mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	147	147	
Units: Percentage				
number (not applicable)	66.9	69.4	70.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe was 52 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo Group
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Reporting group description: -

Reporting group title	R04602522 1 mg Group
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Reporting group description: -

Reporting group title	R04602522 5 mg
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Reporting group description: -

Serious adverse events	Placebo Group	R04602522 1 mg Group	R04602522 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 181 (12.71%)	18 / 179 (10.06%)	19 / 180 (10.56%)
number of deaths (all causes)	3	3	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Uterine cancer			

subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Haemorrhage			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Pyrexia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			

subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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			
Aggression			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Agitation			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression Suicidal			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Suicide attempt			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 181 (1.10%)	0 / 179 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	2 / 180 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 181 (0.55%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial Bones Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Femur Fracture			

subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Laceration			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Overdose			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			

Syncope			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance disorder			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Epilepsy			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Lacunar infarction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Eye disorders			
Vitritis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Gastric ulcer			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Gastritis			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Inguinal hernia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Cholangitis acute			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 181 (0.55%)	3 / 179 (1.68%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Escherichia urinary tract infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (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
Labyrinthitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	0 / 180 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 181 (0.00%)	0 / 179 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo Group	R04602522 1 mg Group	R04602522 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 181 (40.88%)	77 / 179 (43.02%)	75 / 180 (41.67%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 181 (6.08%)	11 / 179 (6.15%)	9 / 180 (5.00%)
occurrences (all)	15	13	11
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 181 (7.73%)	14 / 179 (7.82%)	12 / 180 (6.67%)
occurrences (all)	24	15	16
Eye disorders			
Cataract			
subjects affected / exposed	17 / 181 (9.39%)	11 / 179 (6.15%)	13 / 180 (7.22%)
occurrences (all)	19	12	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 181 (7.18%)	11 / 179 (6.15%)	16 / 180 (8.89%)
occurrences (all)	19	13	21
Vomiting			
subjects affected / exposed	10 / 181 (5.52%)	8 / 179 (4.47%)	9 / 180 (5.00%)
occurrences (all)	10	10	24
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 181 (4.42%)	10 / 179 (5.59%)	7 / 180 (3.89%)
occurrences (all)	8	11	7
Insomnia			
subjects affected / exposed	4 / 181 (2.21%)	7 / 179 (3.91%)	9 / 180 (5.00%)
occurrences (all)	4	7	9
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 181 (7.18%)	13 / 179 (7.26%)	12 / 180 (6.67%)
occurrences (all)	16	17	13
Nasopharyngitis			

subjects affected / exposed	10 / 181 (5.52%)	14 / 179 (7.82%)	12 / 180 (6.67%)
occurrences (all)	12	15	14
Upper respiratory tract infection			
subjects affected / exposed	6 / 181 (3.31%)	10 / 179 (5.59%)	4 / 180 (2.22%)
occurrences (all)	8	11	5
Influenza			
subjects affected / exposed	1 / 181 (0.55%)	3 / 179 (1.68%)	11 / 180 (6.11%)
occurrences (all)	1	3	11

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

None reported