Clinical trial results:
A Double-blind, Randomised, Comparative Pharmacokinetic, Pharmacodynamic, Efficacy and Safety Evaluation of RGB-03 and MabThera® Combined with Methotrexate in Rheumatoid Arthritis Patients

Summary

EudraCT number	2014-003255-54
Trial protocol	CZ
Global end of trial date	24 April 2018

Results information

Result version number	v1 (current)
This version publication date	25 July 2020
First version publication date	25 July 2020

Trial information

Trial identification

Sponsor protocol code	RGB-03-104

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gedeon Richter Plc
Sponsor organisation address	Gyömrői út 19-21, Budapest, Hungary, H-1103
Public contact	Gedeon Richter Plc, Gedeon Richter Plc, RA.ctaRichter@richter.hu
Scientific contact	Gedeon Richter Plc, Gedeon Richter Plc, jelineki@richter.hu

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	04 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2017
Global end of trial reached?	Yes
Global end of trial date	24 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the PK of RGB-03 and its reference product (MabThera) in a comparative manner in RA patients to establish biosimilarity.

Protection of trial subjects:

The investigators and all designees involved in the study conducted the study in adherence to the ethical principles based on the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice guidelines, and the applicable national and local laws and regulatory requirements. All safety parameters were being assessed during the whole study until last patient last visit. Safety was assessed by adverse events (AEs), serum laboratory tests, vital signs, physical examination, 12-lead electrocardiogram, body weight, body mass index and immunogenicity.

Background therapy:

Methotrexate and folic acid

Evidence for comparator:

RGB-03 is being developed as a biosimilar rituximab to MabThera. The study population reflects the approved indication for MabThera and the posology is based on the SmPC of MabThera.

Actual start date of recruitment	18 March 2015
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	Poland: 47
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Ukraine: 45
Worldwide total number of subjects	129
EEA total number of subjects	79

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)	110
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 60 study centres were initiated in Europe and Middle East. There were a total of 129 participants randomly assigned in this study: 66 in the RGB-03 arm and 63 in the MabThera arm.

Pre-assignment

Screening details:

During the up to 4-week Screening Period assessments were performed to evaluate patient's eligibility, and informed consent was obtained before any study-related assessment was performed. The patient's eligibility was evaluated based on the Screening results and randomisation occurred before the Baseline Visit.

Period 1

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

Blinding implementation details:

The patient, the Investigator, the study coordinator, the Sponsor, and the entire study processing team except the dedicated unblinded team member remained blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	RGB-03

Arm description:

RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Experimental
Investigational medicinal product name	RGB-03
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of RGB-03 was 1000 mg for i.v. administration.

Arm title	MabThera

Arm description:

MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of MabThera was 1000 mg for i.v. administration.

Number of subjects in period 1[1]	RGB-03	MabThera
Started	64	58
Completed	62	55
Not completed	2	3
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	1
Pregnancy	-	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: Not applicable.

Period 2

Period 2 title	1st Retreatment Course
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject, Assessor

Blinding implementation details:

The patient, the Investigator, the study coordinator, the Sponsor, and the entire study processing team except the dedicated unblinded team member remained blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	RGB-03

Arm description:

RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Experimental
Investigational medicinal product name	RGB-03
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of RGB-03 was 1000 mg for i.v. administration.

Arm title	MabThera

Arm description:

MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of MabThera was 1000 mg for i.v. administration.

Number of subjects in period 2	RGB-03	MabThera
Started	62	55
Completed	58	53
Not completed	4	2
Consent withdrawn by subject	3	1
Physician decision	1	-
Adverse event, non-fatal	-	1

Period 3

Period 3 title	Open-label (2nd and 3rd Retreatment Cour
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

From the 2nd Retreatment Course all patients received MabThera were switched to receive RGB-03 treatment, from this time point the study was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	RGB-03

Arm description:

RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Experimental
Investigational medicinal product name	RGB-03
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of RGB-03 was 1000 mg for i.v. administration.

Arm title	MabThera

Arm description:

Patients who were assigned to receive MabThera for the Treatment period and 1st Retreatment Course were switched from MabThera group and received RGB-03 for the 2nd and 3rd Retreatment Courses. RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).

Arm type	Experimental
Investigational medicinal product name	RGB-03
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose of RGB-03 was 1000 mg for i.v. administration.

Number of subjects in period 3[2]	RGB-03	MabThera
Started	58	52
Completed	57	47
Not completed	1	5
Physician decision	1	2
Consent withdrawn by subject	-	2
INCOMPLIANCE WITH REQUIREMENTS FOR RETREATMENT 3	-	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: -

Baseline characteristics

Reporting groups	
Reporting group title	RGB-03
Reporting group description:	
RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	MabThera
Reporting group description:	
MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	

Reporting group values	RGB-03	MabThera	Total
Number of subjects	64	58	122
Age categorical Units: Subjects			
Adults (18-64 years)	56	47	103
From 65-84 years	8	11	19
Gender categorical Units: Subjects			
Female	51	47	98
Male	13	11	24

End points

End points reporting groups

Reporting group title	RGB-03
Reporting group description:	
RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	MabThera
Reporting group description:	
MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	RGB-03
Reporting group description:	
RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	MabThera
Reporting group description:	
MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	RGB-03
Reporting group description:	
RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	MabThera
Reporting group description:	
Patients who were assigned to receive MabThera for the Treatment period and 1st Retreatment Course were switched from MabThera group and received RGB-03 for the 2nd and 3rd Retreatment Courses. RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	

Primary: AUC0-tlast

End point title	AUC0-tlast
End point description:	
AUC0-tlast: The area under the serum concentration versus time curve, from time 0 to last data point above the limit of quantitation during the Treatment Period, calculated by the linear trapezoidal method.	
End point type	Primary
End point timeframe:	
over the first 24 weeks	

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	54		
Units: h × µg/mL				
geometric mean (geometric coefficient of variation)	183519.5 (± 29.2)	176994.4 (± 35.2)		

Statistical analyses

Statistical analysis title	Primary Pharmacokinetics Endpoints - AUC0-tlast

Statistical analysis description:

Log-transformed AUC0-tlast values were compared by analysis of variance (ANOVA), with treatment allocation as the independent and individual ln(AUC0-tlast) as the dependent variable. Point estimates with 2-sided 90% confidence intervals for the ratios of geometric means of RGB-03 relative to MabThera® were constructed for AUC0-tlast. 90% CIs for the ratios were derived by exponentiation of the CIs obtained for the difference between treatment Least Square Means (LSMs) resulting from the ANOVA on

Comparison groups	RGB-03 v MabThera
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of geometric least square means
Point estimate	103.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.54
upper limit	114.94

Secondary: Cmax

End point title	Cmax

End point description:

Maximum measured serum concentration over the Treatment Period (taken directly from the raw data).

End point type	Secondary

End point timeframe:

over the first 24 weeks

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	54		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	380.1328 (± 19.6)	357.7597 (± 21.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-15d

End point title	AUC0-15d

End point description:

The area under the serum concentration versus time curve, from time 0 to Day 15 time point of the Treatment Period, calculated by the linear trapezoidal method.

End point type	Secondary

End point timeframe:

over the first 24 weeks

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	54		
Units: h × µg/mL				
geometric mean (geometric coefficient of variation)	44803.5 (± 24.2)	45148.7 (± 27.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-inf

End point title	AUC0-inf

End point description:

The area under the serum concentration versus time curve, from time 0 extrapolated to infinity.

End point type	Secondary

End point timeframe:

over the first 24 weeks

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	54		
Units: h × µg/mL				
geometric mean (geometric coefficient of variation)	191877.8 (± 26.7)	180405.4 (± 34.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under CD19+ B-cell Count Versus Time Curve

End point title	Area Under CD19+ B-cell Count Versus Time Curve

End point description:

It refers to the CD19+ B-cell count from time 0 (before drug administration) to the last measured count at Day 169.

End point type	Secondary

End point timeframe:
over the first 24 weeks

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	54		
Units: cells/µL/day				
geometric mean (standard deviation)	3684.33 (± 891.312)	3448.45 (± 623.276)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-ESR by Visit

End point title	Change from Baseline in DAS28-ESR by Visit

End point description:

The DAS28-ESR was calculated from tender joints, swollen joints, ESR, and Patient's Global Assessment of Disease Activity. Categorization of the DAS28-ESR scores: high disease activity - 5.1 < DAS28, moderate disease activity - 3.2 < DAS28 ≤ 5.1, low disease activity - DAS28 ≤ 3.2 and remission - DAS28 < 2.6.

End point type	Secondary

End point timeframe:
over the first 24 weeks

End point values	RGB-03	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	54		
Units: change from baseline				
geometric mean (standard deviation)	6.629 (± 0.8691)	6.530 (± 0.6885)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 48 weeks (Double-blind period)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20
Reporting groups	
Reporting group title	RGB-03
Reporting group description: RGB-03 (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	
Reporting group title	MabThera
Reporting group description: MabThera (1000mg) coadministered with MTX (10 to 25 mg weekly orally or parenterally) and folic acid (according to local standard of care).	

Serious adverse events	RGB-03	MabThera	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 64 (10.94%)	8 / 58 (13.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 64 (1.56%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic foot infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			

subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroborreliosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	RGB-03	MabThera	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 64 (70.31%)	45 / 58 (77.59%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 64 (7.81%)	2 / 58 (3.45%)	
occurrences (all)	6	3	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 64 (6.25%)	2 / 58 (3.45%)	
occurrences (all)	4	3	
Blood cholesterol increased			
subjects affected / exposed	3 / 64 (4.69%)	0 / 58 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	

Transaminases increased			
subjects affected / exposed	0 / 64 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	8 / 64 (12.50%)	6 / 58 (10.34%)	
occurrences (all)	11	12	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 64 (4.69%)	4 / 58 (6.90%)	
occurrences (all)	4	5	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 64 (6.25%)	2 / 58 (3.45%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 64 (6.25%)	1 / 58 (1.72%)	
occurrences (all)	4	1	
Hypochromic anaemia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 64 (3.13%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
Hepatobiliary disorders			

Hepatic steatosis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	2 / 64 (3.13%)	2 / 58 (3.45%)	
occurrences (all)	2	2	
Renal cyst			
subjects affected / exposed	2 / 64 (3.13%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	2 / 64 (3.13%)	2 / 58 (3.45%)	
occurrences (all)	2	2	
Arthralgia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 64 (4.69%)	9 / 58 (15.52%)	
occurrences (all)	4	10	
Urinary tract infection			
subjects affected / exposed	8 / 64 (12.50%)	3 / 58 (5.17%)	
occurrences (all)	9	4	
Upper respiratory tract infection			
subjects affected / exposed	4 / 64 (6.25%)	3 / 58 (5.17%)	
occurrences (all)	4	3	
Influenza			
subjects affected / exposed	3 / 64 (4.69%)	3 / 58 (5.17%)	
occurrences (all)	3	4	
Bronchitis			
subjects affected / exposed	3 / 64 (4.69%)	1 / 58 (1.72%)	
occurrences (all)	3	1	

Asymptomatic bacteriuria			
subjects affected / exposed	1 / 64 (1.56%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
Herpes zoster			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Pyelonephritis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Tonsillitis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 58 (3.45%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 64 (4.69%)	1 / 58 (1.72%)	
occurrences (all)	5	1	
Hypercholesterolaemia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 58 (3.45%)	
occurrences (all)	2	2	
Hypocalcaemia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 58 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2014	The purpose of this amendment was • to include the contact details of the assigned Medical Monitor • to change the study design and harmonise the new study design in the document, • to correct the protocol title and typographical errors in the Protocol. • to clarify RGB-03 administration.
01 April 2015	The protocol was amended • with administrative changes, including corrections to typographical errors, Medical Support information, • to clarify weight measurement during Screening Visit, blinding and IMP handling/administration procedure, patient monitoring during IMP administration, • to complete missing measurements during Clinical Laboratory evaluation, • to reflect change in efficacy analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported