Clinical trial results:
A Phase III Randomized, Double Blind, Placebo-controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease

Summary

EudraCT number	2015-001179-36
Trial protocol	PL CZ SK BG
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	RHB-104-01 Clinical Study Report Synopsis (rhb-104-01-csr-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	RHB-104-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951326
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RedHill Biopharma Ltd.
Sponsor organisation address	21 Ha'arba'a St, Tel Aviv, Israel, 6473921
Public contact	Aida Bibliowicz, VP Clinical Affairs EU, RedHill Biopharma Ltd., +972 3-541-3131, aida@redhillbio.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of remission at the 26 week assessment as compared to subjects randomized to receive placebo.

Protection of trial subjects:

Safety data were reviewed by medical monitors, and summary information was reviewed by an external Data Safety Monitoring Board (DSMB) approximately one-third (21 November 2016) and two-thirds (25 July 2017) of the way through the study. On 25 July 2017, the DSMB reviewed the unblinded interim safety and efficacy data and recommended continuing the study through enrolment with no changes to the protocol, investigator's brochure, study conduct, or informed consent form (ICF).

Background therapy:

Subjects were allowed to have anti-TNF background therapy and randomization was performed within strata defined
by whether subjects used protocol permitted anti-TNF agents (yes or no).

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
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	Australia: 11
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	United States: 164
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Serbia: 22
Worldwide total number of subjects	331
EEA total number of subjects	76

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)	326
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were be assessed for study eligibility during the screening visit (Day -42 to -7).
Screening assessments included medical history, CDAI diary collection and assessment, uveitis assessment, 12-lead ECG, hematology, biochemistry, serology, pregnancy test, CRP, TB test, stool sampling for C. difficile and fecal calprotectine and other

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RHB-104 - Active Therapy

Arm description: -

Arm type	Experimental
Investigational medicinal product name	RHB-104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects took 5 capsules bid with food.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo matching RHB-104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects took 5 capsules bid with food

Number of subjects in period 1	RHB-104 - Active Therapy	Placebo
Started	166	165
Completed	87	87
Not completed	79	78
Consent withdrawn by subject	25	26
Physician decision	6	5

Adverse event, non-fatal	29	33
Pregnancy	-	1
Administrative decisions and others	-	5
Lost to follow-up	6	7
Administrative and other reasons	6	-
Protocol deviation	7	1

Baseline characteristics

Reporting groups	
Reporting group title	RHB-104 - Active Therapy
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	RHB-104 - Active Therapy	Placebo	Total
Number of subjects	166	165	331
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Males and females of 18 to 75 years of age			
Units: years			
arithmetic mean	39	39.3	
standard deviation	± 12.51	± 12.56	-
Gender categorical Units: Subjects			
Female	75	67	142
Male	91	98	189
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	0	1	1
Black or African American	8	12	20
White	156	150	306
Other	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	6	3	9
Non Hispanic or Latino	160	162	322
Baseline Crohn's Disease Activity Index (CDAI) Score Units: Units on a Scale			
arithmetic mean	297.77	293.44	
standard deviation	± 57.02	± 53.18	-

End points

End points reporting groups	
Reporting group title	RHB-104 - Active Therapy
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Remission at Week 26	
End point title	Remission at Week 26
End point description:	
Remission was defined as CDAI score of <150; subjects who had CDAI ≥150 or who did not have a CDAI measurement at Week 26 were classified as not having achieved remission.	
End point type	Primary
End point timeframe:	
Week 26	

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	61	37		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel chi-square test
Comparison groups	Placebo v RHB-104 - Active Therapy
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Proportion diference
Point estimate	14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	24

Secondary: Response at Week 26	
End point title	Response at Week 26

End point description:

Response was defined as reduction from baseline of ≥100 in CDAI score; subjects who had a change from baseline to Week 26 in CDAI score which was not a reduction of ≥100 or who did not have a change from baseline to Week 26 in CDAI score were classified as not having experienced response.

End point type	Secondary

End point timeframe:

Week 26

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	73	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Remission at Week 52

End point title	Remission at Week 52

End point description:

Remission at Week 52 was defined CDAI score of <150 at Week 52. Subjects who had a CDAI score ≥150 or who did not have a CDAI measurement at Week 52 were classified as not having achieved remission.

End point type	Secondary

End point timeframe:

Week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	47	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Remission Week 26 through Week 52

End point title	Durable Remission Week 26 through Week 52

End point description:

End point type	Secondary

End point timeframe:

Week 26 through Week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	33	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Early Remission Week 16

End point title	Early Remission Week 16

End point description:

Subjects who had a CDAI ≥150 or who did not have a CDAI measurement at Week 16 were classified as not having achieved remission.

End point type	Secondary

End point timeframe:

Week 16

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	70	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Steroid-Free Remission Week 52

End point title	Steroid-Free Remission Week 52

End point description:

Steroid-free remission Week 52 was defined as a subject having a CDAI score of <150, and subject must have been maintained off steroids for at least 3 weeks (ie., by Week 49) to be determined to be in steroid-free remission at Week 52.
Subjects who had a CDAI measurement ≥150 or who did not have a CDAI measurement at Week 52 or who were not off steroids by Week 49 were classified as not having achieved remission.

End point type	Secondary

End point timeframe:

Week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: Subjects	11	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Remission

End point title	Time to Remission

End point description:

Time to remission = [date of first observed remission (CDAI score < 150) – date of first dose or date of randomization if not dosed + 1] / 7 days. Subjects who never experienced remission during the study were censored at the date of their last CDAI assessment. Percentages were based on the number of subjects in the population.

End point type	Secondary

End point timeframe:

Baseline through week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	78		
Units: Weeks				
number (confidence interval 95%)	12.1 (8.43 to 12.71)	19.9 (13 to 52.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Remission

End point title	Duration of Remission

End point description:

Duration of remission was defined as the number of weeks the subject was in remission (CDAI score <150). It was calculated as the first date following remission at which CDAI was ≥150 minus the date of first remission, plus 1 day, divided by 7. Subjects who experienced remission and continued to be in remission at the time of their last CDAI assessment were censored at the date of their last CDAI assessment.

End point type	Secondary

End point timeframe:

Baseline through week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	78		
Units: Weeks				
number (confidence interval 95%)	27.1 (16.14 to 46.86)	16.7 (10.14 to 30.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to Response = [Date of first observed response (a reduction from baseline of ≥100 in CDAI score) – Date of first dose or date of randomization if not dosed + 1] / 7 Days. Subjects who never experienced response during the study were censored at the date of their last CDAI assessment.

End point type	Secondary

End point timeframe:

Baseline through week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	92		
Units: Weeks				
number (confidence interval 95%)	8.3 (8.00 to 9.14)	12.1 (8.14 to 15.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the number of weeks the subjects were in a state of response (a reduction from baseline of ≥100 in CDAI score). It was calculated as the first date after response at

which the reduction from baseline in CDAI was <100 minus the date of first response, plus 1 day, divided by 7. Subjects who experienced response and continued to be in response at the time of their last CDAI assessment were censored at the date of their last CDAI assessment.

End point type	Secondary

End point timeframe:

Baseline through week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	92		
Units: Weeks				
number (confidence interval 95%)	40.1 (22.14 to 52.29)	22.1 (12.14 to 32.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Remission Week 16 through Week 52

End point title	Durable Remission Week 16 through Week 52

End point description:

Durable remission was defined as maintaining CDAI score <150 from Week 16 through Week 52 assessments. Subjects experiencing a CDAI score ≥150 at any visit time point assessment from Week 16 through Week 52 or who had no CDAI measurement Week 16 or Week 52 were classified as not having achieved durable remission.

End point type	Secondary

End point timeframe:

Week 16 through Week 52

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	31	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Early Response at Week 16

End point title	Early Response at Week 16

End point description:

Subjects who had a change from baseline to Week 16 CDAI score which was not a reduction of ≥100 or who did not have a change from baseline to Week 16 in CDAI score were classified as not having experienced a response.

End point type	Secondary

End point timeframe:

Week 16

End point values	RHB-104 - Active Therapy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Subjects	79	60		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time from the first study drug administration to the end of study visit at week 56 (last study drug dose was at week 52).

Adverse event reporting additional description:

The safety analysis set included all subjects who received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	RHB-104

Reporting group description:

RHB-104; a fixed-dose combination of 95 mg clarithromycin, 45 mg rifabutin, and 10 mg clofazimine. The target dose of RHB-104 was 5 capsules administered bid via oral administration.

Reporting group title	Placebo

Reporting group description:

Placebo is a capsule with a similar appearance as RHB-104. Dosage was 5 capsules bid via oral administration.

Serious adverse events	RHB-104	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 166 (18.67%)	31 / 165 (18.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intestinal anastomosis complication			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
noncardiac chest pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	10 / 166 (6.02%)	8 / 165 (4.85%)	
occurrences causally related to treatment / all	10 / 10	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 166 (1.81%)	4 / 165 (2.42%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 166 (1.81%)	2 / 165 (1.21%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 166 (0.60%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 166 (0.00%)	3 / 165 (1.82%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			

subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	RHB-104	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 166 (87.35%)	135 / 165 (81.82%)	
Investigations			
Weight decreased			
subjects affected / exposed	6 / 166 (3.61%)	4 / 165 (2.42%)	
occurrences (all)	6	4	
Weight increased			
subjects affected / exposed	2 / 166 (1.20%)	7 / 165 (4.24%)	
occurrences (all)	2	7	
Hepatic enzyme increased			

subjects affected / exposed	5 / 166 (3.01%)	0 / 165 (0.00%)	
occurrences (all)	5	0	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 166 (9.64%)	17 / 165 (10.30%)	
occurrences (all)	16	17	
Dizziness			
subjects affected / exposed	5 / 166 (3.01%)	5 / 165 (3.03%)	
occurrences (all)	5	5	
Dysgeusia			
subjects affected / exposed	7 / 166 (4.22%)	19 / 165 (11.52%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 166 (6.02%)	6 / 165 (3.64%)	
occurrences (all)	10	6	
Leukopenia			
subjects affected / exposed	4 / 166 (2.41%)	1 / 165 (0.61%)	
occurrences (all)	4	1	
Neutropenia			
subjects affected / exposed	4 / 166 (2.41%)	0 / 165 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 166 (5.42%)	6 / 165 (3.64%)	
occurrences (all)	9	6	
Fatigue			
subjects affected / exposed	8 / 166 (4.82%)	4 / 165 (2.42%)	
occurrences (all)	8	4	
Oedema peripheral			
subjects affected / exposed	4 / 166 (2.41%)	2 / 165 (1.21%)	
occurrences (all)	4	2	
Peripheral swelling			
subjects affected / exposed	4 / 166 (2.41%)	1 / 165 (0.61%)	
occurrences (all)	4	1	
Gastrointestinal disorders			

Crohn's disease			
subjects affected / exposed	21 / 166 (12.65%)	25 / 165 (15.15%)	
occurrences (all)	21	25	
Abdominal pain			
subjects affected / exposed	24 / 166 (14.46%)	19 / 165 (11.52%)	
occurrences (all)	24	19	
Nausea			
subjects affected / exposed	22 / 166 (13.25%)	12 / 165 (7.27%)	
occurrences (all)	22	12	
Diarrhoea			
subjects affected / exposed	11 / 166 (6.63%)	8 / 165 (4.85%)	
occurrences (all)	11	8	
Vomiting			
subjects affected / exposed	12 / 166 (7.23%)	7 / 165 (4.24%)	
occurrences (all)	12	7	
Abdominal tenderness			
subjects affected / exposed	4 / 166 (2.41%)	9 / 165 (5.45%)	
occurrences (all)	4	9	
Abdominal distension			
subjects affected / exposed	8 / 166 (4.82%)	3 / 165 (1.82%)	
occurrences (all)	8	3	
Dry mouth			
subjects affected / exposed	6 / 166 (3.61%)	3 / 165 (1.82%)	
occurrences (all)	6	3	
Dyspepsia			
subjects affected / exposed	7 / 166 (4.22%)	2 / 165 (1.21%)	
occurrences (all)	7	2	
Flatulence			
subjects affected / exposed	7 / 166 (4.22%)	25 / 165 (15.15%)	
occurrences (all)	7	2	
Small intestinal obstruction			
subjects affected / exposed	4 / 166 (2.41%)	4 / 165 (2.42%)	
occurrences (all)	4	4	
Tooth discolouration			
subjects affected / exposed	7 / 166 (4.22%)	0 / 165 (0.00%)	
occurrences (all)	7	0	

Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 166 (1.20%)	4 / 165 (2.42%)	
occurrences (all)	2	4	
Abdominal pain lower			
subjects affected / exposed	0 / 166 (0.00%)	4 / 165 (2.42%)	
occurrences (all)	0	4	
Constipation			
subjects affected / exposed	4 / 166 (2.41%)	0 / 165 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 166 (3.01%)	2 / 165 (1.21%)	
occurrences (all)	5	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 166 (0.60%)	5 / 165 (3.03%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	7 / 166 (4.22%)	17 / 165 (10.30%)	
occurrences (all)	7	1	
Skin discolouration			
subjects affected / exposed	6 / 166 (3.61%)	0 / 165 (0.00%)	
occurrences (all)	6	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	42 / 166 (25.30%)	2 / 165 (1.21%)	
occurrences (all)	42	2	
Haematuria			
subjects affected / exposed	1 / 166 (0.60%)	6 / 165 (3.64%)	
occurrences (all)	1	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 166 (1.81%)	5 / 165 (3.03%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	16 / 166 (9.64%)	7 / 165 (4.24%)	
occurrences (all)	16	7	
Back pain			
subjects affected / exposed	4 / 166 (2.41%)	8 / 165 (4.85%)	
occurrences (all)	4	8	
Myalgia			
subjects affected / exposed	5 / 166 (3.01%)	3 / 165 (1.82%)	
occurrences (all)	5	3	
Pain in extremity			
subjects affected / exposed	7 / 166 (4.22%)	1 / 165 (0.61%)	
occurrences (all)	7	1	
Neck pain			
subjects affected / exposed	1 / 166 (0.60%)	4 / 165 (2.42%)	
occurrences (all)	1	4	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	4 / 166 (2.41%)	14 / 165 (8.48%)	
occurrences (all)	4	14	
Upper respiratory tract infection			
subjects affected / exposed	8 / 166 (4.82%)	9 / 165 (5.45%)	
occurrences (all)	8	9	
Influenza			
subjects affected / exposed	6 / 166 (3.61%)	10 / 165 (6.06%)	
occurrences (all)	6	10	
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 166 (4.22%)	9 / 165 (5.45%)	
occurrences (all)	7	9	
Rash			
subjects affected / exposed	8 / 166 (4.82%)	8 / 165 (4.85%)	
occurrences (all)	8	8	
Urinary tract infection			
subjects affected / exposed	7 / 166 (4.22%)	5 / 165 (3.03%)	
occurrences (all)	7	5	
Bronchitis			

subjects affected / exposed	5 / 166 (3.01%)	3 / 165 (1.82%)	
occurrences (all)	5	3	
Gastroenteritis			
subjects affected / exposed	4 / 166 (2.41%)	3 / 165 (1.82%)	
occurrences (all)	4	3	
Pneumonia			
subjects affected / exposed	2 / 166 (1.20%)	4 / 165 (2.42%)	
occurrences (all)	2	4	
Anal abscess			
subjects affected / exposed	1 / 166 (0.60%)	4 / 165 (2.42%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 166 (3.01%)	1 / 165 (0.61%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2016	Major changes in the Version 9.0 were as follows: • Adequate time to demonstrate lack of efficacy in baseline anti-TNF agents was reflected. • Increased estimated number of subjects and participating centers in the study. • Reference to the open-label rescue study was made. • Clarification due to allowance of colonoscopies without biopsy as per investigator requests. • Addition of SES-CD alongside CDEIS as an exploratory outcome measure of endoscopic changes to be assessed in those subjects who consented to colonoscopy.
29 March 2017	Major changes in the Version 10.0 were as follows: • Endpoints clarified to represent those clinically most relevant after the primary objective as key secondary objectives, followed by selected other supportive objectives and finally other exploratory objectives. • Updates to the exclusion criteria were made to include quinolones in the list of medications that caused QT prolongation or Torsades de Pointe. • Clarification that subjects not in remission at Week 26, could elect to continue participation in the RHB-104-01 study, and would remain in the RHB-104-01 study until study drug administration in the RHB-104-04 study, if applicable. This allowed for subjects to transition into the RHB-104-04 study after Week 26 in cases where the RHB-104-04 study was not yet IRB approved and clarified that AEs from the RHB 104 01 would be captured until the day before the start of dosing in RHB-104-04. • Clarification that minimum overall compliance had to be approximately 80%, upon which a subject could be discontinued from treatment after a discussion with the medical monitor. • Clarification that subject would be considered a treatment failure in the steroid-free remission analysis if the subject experienced a worsening of disease activity during the taper, and further steroid dose decreases were suspended, and/or the oral corticosteroid dose increased. • Clarification that the administration of the morning dose from a newly dispensed treatment bottle would not be considered a protocol deviation. The study drug administration
29 September 2017	Major changes in Protocol Version 11.0 were as follows: • It reflected curtailment of study recruitment and representation of power as initial estimates were overly conservative did not account for accrual trends. Curtailment to a target sample size of approximately 324 subjects would effectively provide 86% of the necessary sample size while still maintaining statistical power of over 80% with a treatment effect of 15%. • Some additional sensitivity analyses were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported