Clinical trial results:
A Multi-arm, Phase II, Open-Label, Multicentre Study to Assess the Preliminary Efficacy of RXC004 in Monotherapy and in Combination with Nivolumab, in Patients with Ring Finger Protein 43 (RNF43) or R-spondin (RSPO) Aberrated, Metastatic, Microsatellite Stable, Colorectal Cancer who have Progressed following Therapy with Current Standard of Care

Summary

EudraCT number	2020-003132-24
Trial protocol	ES
Global end of trial date	02 April 2024

Results information

Result version number	v1 (current)
This version publication date	11 April 2025
First version publication date	11 April 2025

Trial information

Trial identification

Sponsor protocol code	RXC004/0002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04907539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Redx Pharma Limited
Sponsor organisation address	Block 33, Mereside, Alderley Park, Alderley Edge, Cheshire, United Kingdom,
Public contact	Craig Tilston, Redx Pharma Limited, +44(0) 7787983638, c.tilston@redxpharma.com
Scientific contact	Craig Tilston, Redx Pharma Limited, +44(0) 7787983638, c.tilston@redxpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-tumour activity of RXC004 monotherapy and RXC004 + Nivolumab.

Protection of trial subjects:

The study was conducted in accordance with the protocol and Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH Good Clinical Practice (GCP) Guidelines and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2021
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	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	25
EEA total number of subjects	5

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)	17
From 65 to 84 years	8

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 08 November 2021 to 02 April 2024 at multiple centers in 4 countries (South Korea, Spain, United Kingdom and United States of America).

Pre-assignment

Screening details:

Patients who met the inclusion criteria, and none of the exclusion criteria were enrolled to the study. All study assessments were performed as per the Schedule of Assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: RXC004 Monotherapy

Arm description:

Patients received 2 mg of RXC004 once daily orally.

Arm type	Experimental
Investigational medicinal product name	RXC004
Investigational medicinal product code	RXC004
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were administered with 2 mg of RXC004 as a monotherapy once daily.

Arm title	Arm B: RXC004+Nivolumab

Arm description:

Patients received 1.5 mg of RXC004 once daily orally along with the combination of 480 mg of Nivolumab once every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	RXC004
Investigational medicinal product code	RXC004
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were administered with 2 mg of RXC004 as a monotherapy once daily.

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Nivolumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Intravenous drip use

Dosage and administration details:

Patients were administered with 480 mg of Nivolumab once in 4 weeks in combination with RXC004.

Number of subjects in period 1	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab
Started	17	8
Completed	2	5
Not completed	15	3
Consent withdrawn by subject	1	-
Death	14	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: RXC004 Monotherapy
Reporting group description:	
Patients received 2 mg of RXC004 once daily orally.	
Reporting group title	Arm B: RXC004+Nivolumab
Reporting group description:	
Patients received 1.5 mg of RXC004 once daily orally along with the combination of 480 mg of Nivolumab once every 4 weeks.	

Reporting group values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab	Total
Number of subjects	17	8	25
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)	13	4	17
From 65-84 years	4	4	8
85 years and over	0	0	0
Age categorial	0	0	0
Age continuous Units: years			
median	53.4	64.8	
standard deviation	± 13.87	± 7.78	-
Gender categorical Units: Subjects			
Female	8	5	13
Male	9	3	12
Ethnicity Units: Subjects			
Not Hispanic or Latino	14	6	20
Not stated	1	1	2
Unknown	1	0	1
Other	1	1	2

End points

End points reporting groups

Reporting group title	Arm A: RXC004 Monotherapy
Reporting group description:	
Patients received 2 mg of RXC004 once daily orally.	
Reporting group title	Arm B: RXC004+Nivolumab
Reporting group description:	
Patients received 1.5 mg of RXC004 once daily orally along with the combination of 480 mg of Nivolumab once every 4 weeks.	

Primary: RXC004 Monotherapy (Arm A): Disease Control Rate (DCR) Using Each Patient's Best Overall Response (BOR) According to Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST 1.1)

End point title	RXC004 Monotherapy (Arm A): Disease Control Rate (DCR) Using Each Patient's Best Overall Response (BOR) According to Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST 1.1)[1][2]

End point description:

The anti-tumour activity of RXC004 monotherapy was evaluated. DCR was defined as the percentage of patients with a BOR of either complete response (CR), partial response (PR) or stable disease (SD) for at least 16 weeks post baseline. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumour assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may have impacted outcome were excluded from the population.

End point type	Primary

End point timeframe:

Up to 28 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for Arm A only.

End point values	Arm A: RXC004 Monotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage of patients				
number (confidence interval 90%)	18.2 (3.33 to 47.01)			

Statistical analyses

No statistical analyses for this end point

Primary: RXC004+Nivolumab Combination Therapy (Arm B): Objective Response Rate (ORR) Using Each Patient's BOR According to RECIST 1.1

End point title	RXC004+Nivolumab Combination Therapy (Arm B): Objective Response Rate (ORR) Using Each Patient's BOR According to RECIST 1.1[3][4]

End point description:

The anti-tumour activity as a combination therapy of RXC004 +nivolumab was evaluated. ORR was defined as the percentage of patients with a BOR of CR or PR based on local investigator assessment, as defined in RECIST 1.1. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumour assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may have impacted outcome were excluded from the population.

End point type	Primary

End point timeframe:

Up to 28 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this end point.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for Arm B only.

End point values	Arm B: RXC004+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of patients				
number (confidence interval 90%)	14.3 (0.73 to 52.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Percentage Change in Tumor Size

End point title	Best Percentage Change in Tumor Size

End point description:

The preliminary efficacy of RXC004 monotherapy and combination therapy of RXC004 + nivolumab was evaluated. The best percentage change in tumor size was determined at a patient level. Percentage change in tumor size was derived at each visit by the percentage change from baseline in the sum of diameters of target lesions. The best percentage change in tumor size was the patients value representing the largest decrease (or smallest increase) from baseline in tumor size. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumor assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may impact outcome were excluded from the population.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: Percentage change in tumor size				
median (full range (min-max))	9.34 (-11.8 to 59.8)	0.00 (-40.4 to 39.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The preliminary efficacy of RXC004 monotherapy and combination therapy of RXC004 + nivolumab was evaluated. PFS was defined as the time from first dose of study treatment until the date of disease progression or death (by any cause in the absence of progression). Full analysis set consisted of all patients who were enrolled and received at least one dose of study drug (RXC004). In the data presentation table, the arbitrary value, 999.999, represented the estimates that were not calculable as there were insufficient number of patients with evaluable events as per methodology specified in Statistical Analysis Plan (SAP).

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: Months				
median (confidence interval 95%)	2.0 (1.31 to 2.33)	3.9 (1.58 to 999.999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The preliminary efficacy of RXC004 monotherapy and combination therapy of RXC004 + nivolumab was evaluated. The DOR was defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumor assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may have impacted outcome were excluded from the population. DOR was not calculated as no patient was analysed for this endpoint due to absence of any patient with a complete response (CR); only 1 patient had a partial response (PR). As pre-specified in the SAP that after the review of the available data, DOR would not be summarized and listed.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - No patient was analysed for this endpoint

[6] - No patient was analysed for this endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: RXC004 Monotherapy (Arm A): Objective Response Rate (ORR) Using Investigator Assessments According to RECIST 1.1

End point title	RXC004 Monotherapy (Arm A): Objective Response Rate (ORR) Using Investigator Assessments According to RECIST 1.1[7]

End point description:

The preliminary efficacy of RXC004 monotherapy was evaluated. ORR was defined as the percentage of patients with a BOR of CR or PR based on local investigator assessment as defined in RECIST 1.1. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumour assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may have impacted outcome were excluded from the population.

End point type	Secondary

End point timeframe:

Up to 28 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for Arm A only.

End point values	Arm A: RXC004 Monotherapy			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage of patients				
number (confidence interval 90%)	0 (0.00 to 23.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: RXC004 + Nivolumab Combination Therapy (Arm B): Disease Control Rate Using Investigator Assessments According to RECIST 1.1

End point title	RXC004 + Nivolumab Combination Therapy (Arm B): Disease Control Rate Using Investigator Assessments According to RECIST 1.1[8]

End point description:

The preliminary efficacy of combination therapy of RXC004 + nivolumab was evaluated. DCR was defined as the percentage of patients with a BOR of either CR, PR or SD for at least 16 weeks post baseline. Evaluable set consisted of all patients who received radiographic assessment at baseline (with measurable disease according to RECIST 1.1), received at least 4 weeks of study treatment and at least 1 post-dose radiographic tumour assessment or progressed or died ahead of the first radiographic assessment. Patients with important protocol deviations that may have impacted outcome were excluded from the population.

End point type	Secondary

End point timeframe:

Up to 28 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was applicable for Arm B only.

End point values	Arm B: RXC004+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of patients				
number (confidence interval 90%)	57.1 (22.53 to 87.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The preliminary efficacy of RXC004 monotherapy and combination therapy of RXC004 + nivolumab was evaluated. OS is defined as the time from first day of study treatment until death due to any cause. Full

analysis set consisted of all patients who were enrolled and received at least one dose of study drug (RXC004). The arbitrary value, 999.999, indicated that due to insufficient follow-up information, the median for Arm B was not reached and therefore estimates were not calculable as per methodology specified in the SAP.

End point type	Secondary

End point timeframe:

Up to 28 months

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: Months				
median (confidence interval 95%)	4.8 (1.3 to 6.5)	999.999 (1.7 to 999.999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)

End point description:

The pharmacokinetic (PK) (Cmax) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated. The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
The number analyzed "nA" for Arm A and "nB" for Arm B refer to the number of patients included in analysis in specific arms and specific time points.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length) and Cycle 1 Day 15 (28-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1 (nA=16; nB=8)	65.2 (± 62.0)	56.5 (± 56.4)		
Cycle 1 Day 15 (nA=11; nB=7)	80.0 (± 66.8)	79.4 (± 42.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax)

End point title	Time to Maximum Plasma Concentration (Tmax)

End point description:

The PK (Tmax) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated.
The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
The number analyzed "nA" for Arm A and "nB" for Arm B refer to the number of patients included in analysis in specific arms and specific time points.

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length) and Cycle 1 Day 15 (28-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: Hour (h)				
median (full range (min-max))				
Cycle 0 Day 1 (nA=16; nB=8)	2.07 (0.983 to 4.18)	1.95 (0.933 to 2.12)		
Cycle 1 Day 15 (nA=11; nB=7)	1.35 (0.517 to 6.12)	1.98 (1.02 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration Across the Dosing Interval (Cmin)

End point title	Minimum Observed Concentration Across the Dosing Interval (Cmin)

End point description:

The PK (Cmin) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated.
The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 1 Day 15 (28-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15	12.8 (± 65.8)	17.2 (± 49.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Rate Constant (λz)

End point title	Terminal Rate Constant (λz)

End point description:

The PK (λz) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated. The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: 1/hour				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1	0.0769 (± 73.3)	0.0540 (± 29.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t½)

End point title	Terminal Half-life (t½)

End point description:

The PK (t½) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated. The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: hour (h)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1	9.02 (± 73.3)	12.2 (± 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Zero to Infinity(AUC0-∞)

End point title	Area Under the Plasma Concentration-time Curve from Zero to Infinity(AUC0-∞)

End point description:

The PK (AUC0-∞) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated.
The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: hour*nanogram/milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1	733 (± 48.9)	749 (± 45.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Plasma Clearance After Oral Administration (CL/F)

End point title	Total Plasma Clearance After Oral Administration (CL/F)

End point description:

The PK (CL/F) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated.
The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: milliliter per hour (mL/h)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1	2730 (± 48.9)	2000 (± 45.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution After Oral Administration (Vz/F)

End point title	Apparent Volume of Distribution After Oral Administration (Vz/F)

End point description:

The PK (Vz/F) of RXC004 in monotherapy and in combination therapy with nivolumab was evaluated.
The PK Analysis Set included all patients in the full analysis set with at least 1 blood sample.
For the geometric coefficient of variation (CV), the unit of measure was percentage (%).

End point type	Secondary

End point timeframe:

On Cycle 0 Day 1 (3–7-day cycle in length)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: milliliter (mL)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1	32300 (± 89.6)	35800 (± 22.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Adverse Events (AEs)

End point title	Number of Patients with Adverse Events (AEs)

End point description:

The safety and tolerability of RXC004 monotherapy and RXC004+ nivolumab combination was evaluated. The National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) Grade refers to the severity of the AE. The CTCAE displays Grades 1-5 with unique clinical descriptions of severity for each AE based on general guideline: Grade 1 Mild; asymptomatic/mild symptoms; clinical/diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local/noninvasive intervention indicated; limiting age-appropriate instrumentally. Grade 3 Severe/medically significant but not immediately life threatening; hospitalization/prolongation of hospitalization indicated; disabling; limiting selfcare ADL; Grade 4: Life-threatening, urgent intervention required; Grade 5: Death related to AE. The safety analysis set consisted of all patients who were enrolled and received at least 1 dose of RXC004.
Perm=Permanent, Disc=discontinuation, Inter=Interruption, Reduc=reduction.

End point type	Secondary

End point timeframe:

From time of signature of informed consent form throughout the treatment period and until 30 days after the last dose of RXC004 (forRXC004 monotherapy only) or 90 days after the last dose of Nivolumab (for RXC004 + nivolumab) (up to 28 months)

End point values	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	8		
Units: patients				
number (not applicable)				
Treatment emergent adverse events (TEAE)	17	8		
RXC004 Related TEAE	14	8		
Nivolumab Related TEAE	1	5		
Grade >=3 TEAE	9	5		
RXC004 Related Grade>=3 TEAE	3	4		
Nivolumab Related Grade>=3 TEAE	0	2		
Serious TEAE	3	5		
RXC004 Related Serious TEAE	2	4		
Nivolumab Related Serious TEAE	0	2		
TEAE Leading to Death	0	1		
TEAE Leading to Perm Disc or Reduc/Inter of RXC004	10	7		
TEAE Leading to Perm Disc RXC004	2	3		
TEAE Leading to Reduc of RXC004	3	4		
TEAE Leading to Inter of RXC004	8	3		

TEAE Leading to Perm Disc or Inter of Nivolumab	0	5		
TEAE Leading to Perm Disc Nivolumab	0	3		
TEAE Leading to Inter of Nivolumab	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of signature of ICF throughout the treatment period and until 30 days after the last dose of RXC004 (for RXC004 monotherapy only) or 90 days after the last dose of Nivolumab (for RXC004 + nivolumab) (up to 28 months).

Adverse event reporting additional description:

The safety analysis set consisted of all patients who were enrolled and received at least one dose of study drug (RXC004).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Arm A: RXC004 Monotherapy

Reporting group description:

Patients received 2 mg of RXC004 monotherapy once daily orally.

Reporting group title	Arm B: RXC004+Nivolumab

Reporting group description:

Patients received 1.5 mg of RXC004 once daily along with the combination of 480 mg of Nivolumab every 4 weeks orally.

Serious adverse events	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	5 / 8 (62.50%)	
number of deaths (all causes)	14	3	
number of deaths resulting from adverse events	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A: RXC004 Monotherapy	Arm B: RXC004+Nivolumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	8 / 8 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Chills			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)	4 / 8 (50.00%)	
occurrences (all)	2	5	
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Pyrexia			

subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vulvovaginal dryness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 17 (5.88%)	3 / 8 (37.50%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Mental status changes			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)		
occurrences (all)	1	1		
Amylase increased				
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)		
occurrences (all)	2	0		
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)		
occurrences (all)	2	1		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)		
occurrences (all)	1	1		
Blood bilirubin increased				
subjects affected / exposed	2 / 17 (11.76%)	3 / 8 (37.50%)		
occurrences (all)	2	5		
Blood creatinine increased				
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)		
occurrences (all)	0	2		
Blood fibrinogen increased				
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)		
occurrences (all)	0	1		
C-reactive protein increased				
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)		
occurrences (all)	2	0		
Carcinoembryonic antigen increased				
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)		
occurrences (all)	1	0		
Ejection fraction decreased				
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)		
occurrences (all)	0	1		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)		
occurrences (all)	1	0		
Gastric pH decreased				

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Protein urine present			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Urine calcium decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vitamin D decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	2 / 17 (11.76%)	4 / 8 (50.00%)	
occurrences (all)	3	4	
Injury, poisoning and procedural complications			
Stoma prolapse			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dysgeusia			

subjects affected / exposed	9 / 17 (52.94%)	6 / 8 (75.00%)	
occurrences (all)	11	7	
Headache			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Lethargy			
subjects affected / exposed	1 / 17 (5.88%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Loss of consciousness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Neurotoxicity			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Seizure			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vocal cord paralysis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 17 (23.53%)	1 / 8 (12.50%)	
occurrences (all)	5	2	
Lymphopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Abdominal pain upper			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	3 / 17 (17.65%)	2 / 8 (25.00%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	4 / 17 (23.53%)	5 / 8 (62.50%)	
occurrences (all)	6	7	
Dyspepsia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	9 / 17 (52.94%)	4 / 8 (50.00%)	
occurrences (all)	15	8	
Vomiting			
subjects affected / exposed	4 / 17 (23.53%)	3 / 8 (37.50%)	
occurrences (all)	10	3	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypertransaminasaemia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Jaundice			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Portal vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 17 (11.76%)	4 / 8 (50.00%)	
occurrences (all)	2	4	
Dermatitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Nail discolouration			
subjects affected / exposed	0 / 17 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Nail disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nail ridging			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Onychoclasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Coccydynia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Osteomyelitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinitis			

subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 17 (47.06%)	5 / 8 (62.50%)	
occurrences (all)	10	6	
Hyperammonaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	4	
Hypomagnesaemia			
subjects affected / exposed	3 / 17 (17.65%)	2 / 8 (25.00%)	
occurrences (all)	3	2	

Hyponatraemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	2	2	
Malnutrition			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2021	Version 4.0: Dose of RXC004 in Arm A updated to 2 mg QD, due to data from Phase 1 study and Safety Review Committee recommendations. RXC004 background, risk/benefit, dose rationale and dose modification sections also updated with most recent data from Phase 1 dose escalation study. Inclusion criteria for entry into the combination treatment phase in Arm A added, to clarify when crossover to combination treatment can occur. Acceptable methods of contraception in the lifestyle consideration updated to be consistent with the Clinical Trial Facilitation Group (CTFG) recommendations for highly effective methods of contraception in Sub section Contraception of Section Lifestyle Consideration. A new section-Appendix: Management of colitis events was added presenting the Management plan for RXC004 related diarrhoea/colitis events added after safety review of data from the Phase 1 study. Several items have been added to the protocol as a result of the COVID-19 vaccination risk assessment. Several changes were made in Schedule of Assessment (SOA). Section Dysgeusia, SOA for Arms A and B, Objectives and Endpoints and Appendix Dysgeusia treatment guidelines were updated. Details of a Safety Monitoring Committee for Redx Phase 2 RCX004 studies added to protocol to aid patient safety monitoring. Additional language added to sample size determination to ensure that the decision for stopping development is not based purely on patients with RNF43 mutation or RSPO fusions alone. In the section Background, the subsection Nivolumab was updated in Nivolumab toxicity management guidelines. Section Inclusion criteria and Section efficacy assessment were updated: Language about collection of scans preformed before consent moved from Inclusion criteria #4 and added into section Tumor assessment so that availability of theses scans does not affect patient eligibility for the study.
14 September 2021	Version 5.0: The following updates were made to the eligibility criteria: a) Exclusion criteria updated to exclude patients with QTcF >470 ms; b) Creatinine clearance (CLcr) inclusion criteria and monitoring added to enable future population PK analysis of effect of CLcr on PK of RXC004. Guidelines for management of colitis events updated after Information Brochure (IB) was updated. Dose modification tables prohibited medications and safety labs also updated accordingly. Discontinuation of RXC004 and nivolumab (for patients on the combination) for grade 3 colitis events added as per MHRA request. RXC004 background, risk assessment, and dose justification were updated. Adverse Events of Potential Interest (AEPI) identified for monitoring: bone toxicities and colitis events were updated in Section AEPI. In section Contraception, contraception requirements updated to include the definition of sexual abstinence, as per MHRA request. Clarification for treating patients after RECIST 1.1 progression added in Section Discontinuation of Study Treatment. RXC004 fasting requirements from section Meals and Dietary Restrictions added to SOA footnotes and RXC004 handling instructions for clarity. The section, Prohibited medications, was updated. Restrictions on the use of concomitant CYP3A4 inhibitors and inducers updated to include 2 weeks prior to first dose of study treatment, as well as throughout the study treatment. The Dose modification section, Appendix J, maximum 14 days RXC004 interruption without Sponsor approval's language removed. Language also amended to allow Microsatellite instability status of patients to be confirmed at the central laboratory. Ability of patients to enrol in concomitant COVID-19 vaccination studies removed as per MHRA request. Dysgeusia dose modifications from Table 10 and added to Table 9 Retention of ECG traces added to programme initiative to enable future QT investigations if required. Arm A primary endpoint updated.

13 January 2022	Version 6.0: Section Inclusion criteria creatinine clearance amended to ≥60mL/min instead of > 60mL/min following FDA advice. RXC004 related colitis management guideline was revised to clarify the maximum time a patient with Grade 1 colitis can continue RXC004 at a lower dose before switching to Grade 2 management and to clarify the maximum time that RXC004 treatment can be held before permanent discontinuation, following FDA advice in Appendix J. In Table Dose Modification and Stopping Criteria of Appendix I, dose modification table was revised if a patient has >5kg weight loss associated with dysgeusia and dysgeusia treatment guidelines modified to clarify management options. Tables for Dose Modification and Stopping Criteria and Table for Guidance for dose reductions for RXC004-related adverse events were updated where dose modification table was revised to include permanent discontinuation of RXC004 in the event of a RXC004 related Grade 4 event. Several changes were made in SOA. Echocardiography monitoring plan was revised.
19 August 2022	Version 7.0: In section Justification for Doses of RXC004 and Nivolumab and its subsections Investigational Products, Dose Modification, The RXC004 dose to be used in combination therapy (1.5 mg QD) has been defined and justified by updated and new text, to support combination therapy. Supporting information has been added on the dose regimen and dose reductions. Details of allocation of patients to Arm A or Arm B by randomisation once Arm B has started enrolment have been added in Sections SOA, Overall Design and Randomisation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported