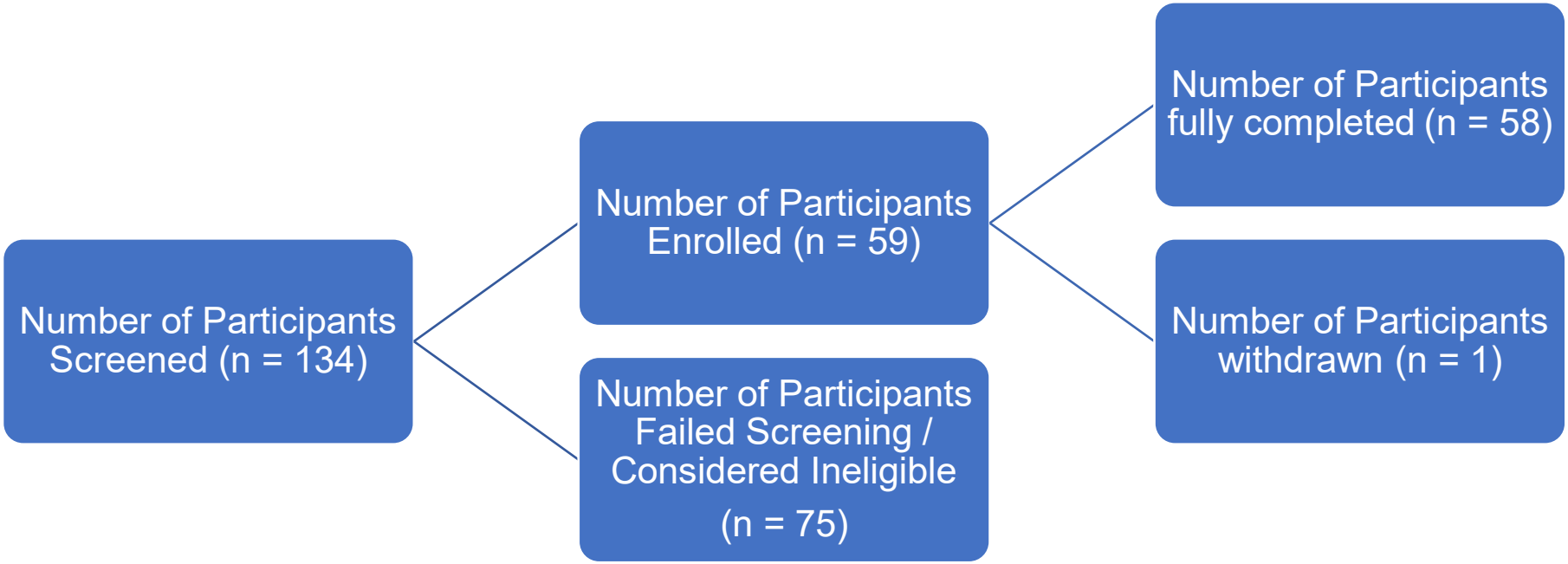
Participant Flow



Baseline Characteristics

Summary of Participant Demographics – Part A (SAD) (Safety Set)

Parameter	Statistic	Placebo (N=12)	RXC008 10 mg (Cohort 1) (N=4)	RXC008 30 mg (Cohort 2) (N=4)	RXC008 100 mg (Cohort 3) (N=4)	RXC008 300 mg (Cohort 4) (N=4)	RXC008 600 mg (Cohort 5) (N=4)	RXC008 1000 mg (Cohort 6) (N=4)	RXC008 Overall (N=24)	Overall (N=36)
Gender:										
Male	n (%)	12 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	24 (100.0)	36 (100.0)
Ethnicity:										
Not Hispanic or Latino	n (%)	12 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	24 (100.0)	36 (100.0)
Race										
Black Or African American	n (%)	0	0	0	0	0	0	2 (50.0)	2 (8.3)	2 (5.6)
Asian	n (%)	0	0	0	1 (25.0)	0	0	0	1 (4.2)	1 (2.8)
White	n (%)	11 (91.7)	4 (100.0)	4 (100.0)	2 (50.0)	4 (100.0)	4 (100.0)	2 (50.0)	20 (83.3)	31 (86.1)
Other	n (%)	1 (8.3)	0	0	1 (25.0)	0	0	0	1 (4.2)	2 (5.6)
Age (yrs)	Mean	39.1	33.8	38.0	37.5	39.0	44.0	34.8	37.8	38.3
	SD	6.20	13.77	8.25	3.42	6.38	3.16	11.53	8.40	7.67
	Median	40.0	32.5	39.0	37.0	40.5	43.5	32.5	40.0	40.0
	Min-Max	26 - 46	20 - 50	29 - 45	34 - 42	30 - 45	41 - 48	24 - 50	20 - 50	20 - 50
Height (m)	Mean	1.791	1.815	1.815	1.768	1.790	1.813	1.760	1.793	1.793
	SD	0.0617	0.0387	0.1297	0.0538	0.0416	0.0275	0.0424	0.0622	0.0611
	Median	1.815	1.815	1.770	1.775	1.790	1.815	1.765	1.800	1.800
	Min-Max	1.70 - 1.87	1.77 - 1.86	1.72 - 2.00	1.70 - 1.82	1.74 - 1.84	1.78 - 1.84	1.71 - 1.80	1.70 - 2.00	1.70 - 2.00
Weight (kg)	Mean	82.79	79.65	91.35	84.60	82.48	86.25	83.48	84.63	84.02
	SD	13.608	11.952	18.780	12.897	13.511	9.695	7.528	11.977	12.379
	Median	81.75	75.45	84.60	87.10	82.95	89.50	82.15	84.70	84.35
	Min-Max	55.6 - 101.9	70.6 - 97.1	77.3 - 118.9	66.8 - 97.4	65.5 - 98.5	72.5 - 93.5	76.5 - 93.1	65.5 - 118.9	55.6 - 118.9
BMI (kg/m^2)	Mean	25.689	24.188	27.475	26.953	25.625	26.205	26.908	26.225	26.047

Parameter	Statistic	Placebo (N=12)	RXC008 10 mg (Cohort 1) (N=4)	RXC008 30 mg (Cohort 2) (N=4)	RXC008 100 mg (Cohort 3) (N=4)	RXC008 300 mg (Cohort 4) (N=4)	RXC008 600 mg (Cohort 5) (N=4)	RXC008 1000 mg (Cohort 6) (N=4)	RXC008 Overall (N=24)	Overall (N=36)
	SD	3.1362	3.5556	1.7086	2.6983	3.0610	2.2748	1.4176	2.5235	2.7096
	Median	25.750	23.675	27.175	27.650	25.890	27.010	26.815	26.710	26.540
	Min-Max	18.79 - 29.82	20.41 - 28.99	25.83 - 29.72	23.11 - 29.40	21.63 - 29.09	22.88 - 27.92	25.27 - 28.73	20.41 - 29.72	18.79 - 29.82

Treatment: Single dose of RXC008 oral capsule or placebo in the fasted state.
Percentages calculated from the number of participants in the Safety Set within a treatment group.
BMI = body mass index, SAD = single ascending dose.

Summary of Participant Demographics – Part B (MAD) (Safety Set)

Parameter	Statistic	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
Gender:							
Male	n (%)	6 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	17 (100.0)	23 (100.0)
Ethnicity:							
Not Hispanic or Latino	n (%)	6 (100.0)	5 (83.3)	3 (60.0)	6 (100.0)	14 (82.4)	20 (87.0)
Hispanic or Latino	n (%)	0	1 (16.7)	2 (40.0)	0	3 (17.6)	3 (13.0)
Race							
Black Or African American	n (%)	2 (33.3)	1 (16.7)	0	0	1 (5.9)	3 (13.0)
Asian	n (%)	0	0	0	1 (16.7)	1 (5.9)	1 (4.3)
White	n (%)	4 (66.7)	5 (83.3)	3 (60.0)	4 (66.7)	12 (70.6)	16 (69.6)
Other	n (%)	0	0	2 (40.0)	1 (16.7)	3 (17.6)	3 (13.0)
Age (yrs)	Mean	36.5	34.8	34.0	38.5	35.9	36.0
	SD	7.87	10.40	7.91	9.46	9.03	8.57
	Median	34.0	39.0	32.0	41.5	39.0	39.0
	Min-Max	28 - 50	21 - 47	26 - 45	25 - 47	21 - 47	21 - 50
Height (m)	Mean	1.758	1.778	1.778	1.778	1.778	1.773
	SD	0.0449	0.0788	0.0363	0.1157	0.0803	0.0723
	Median	1.750	1.800	1.770	1.795	1.770	1.770
	Min-Max	1.72 - 1.84	1.67 - 1.86	1.73 - 1.83	1.58 - 1.90	1.58 - 1.90	1.58 - 1.90
Weight (kg)	Mean	78.00	78.38	88.36	85.27	83.75	82.25
	SD	6.626	12.376	3.097	14.359	11.533	10.647
	Median	75.60	72.80	88.00	82.25	85.60	81.90
	Min-Max	72.0 - 89.5	69.0 - 100.5	85.6 - 93.1	71.7 - 106.0	69.0 - 106.0	69.0 - 106.0
BMI (kg/m^2)	Mean	25.258	24.787	27.972	26.943	26.485	26.165
	SD	2.3713	3.4472	1.2821	3.3744	3.0877	2.9180

Parameter	Statistic	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
	Median	24.675	24.465	28.090	28.730	27.230	26.750
	Min-Max	22.71 - 28.57	20.52 - 30.01	26.70 - 29.72	20.84 - 29.36	20.52 - 30.01	20.52 - 30.01

Treatment: Once daily dosing of RXC008 oral capsule or placebo for 14 days in the fasted state.
Percentages calculated from the number of participants in the Safety Set within a treatment group.
BMI = body mass index, MAD = Multiple ascending dose.

Outcome Measures

Note: there are no data presented for RXC008 plasma PK parameters as there were insufficient samples above the LoQ available in order to determine and calculate PK parameters accordingly.

Summary of Plasma Metabolite REDX11246 PK Parameters – Part A (SAD) (PK Set)

Treatment	Study Day	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)
RXC008 10 mg (Cohort 1) (N=4)	Insufficient quantifiable plasma REDX11246 concentrations.				
RXC008 30 mg (Cohort 2) (N=4)	Day 1	n	4	4	4
		Geo. Mean	0.310	1.00[1]	2.77
		Geo. CV%	31.2	1.00-6.00[2]	12.7
RXC008 100 mg (Cohort 3) (N=4)	Day 1*	n	3	3	3
		Geo. Mean	0.729	1.00[1]	3.90
		Geo. CV%	22.9	1.00-1.00[2]	18.6
RXC008 300 mg (Cohort 4) (N=4)	Day 1	n	4	4	4
		Geo. Mean	0.545	2.00[1]	4.16
		Geo. CV%	55.2	1.00-4.00[2]	23.0
RXC008 600 mg (Cohort 5) (N=4)	Day 1	n	4	4	4
		Geo. Mean	0.661	1.00[1]	5.28
		Geo. CV%	69.9	1.00-4.00[2]	53.6
RXC008 1000 mg (Cohort 6) (N=4)	Day 1	n	4	4	4
		Geo. Mean	1.13	1.00[1]	7.51
		Geo. CV%	42.6	1.00-2.00[2]	28.3

[1]= median T_{max}

[2] = min-max T_{max}

Treatment: Single dose of RXC008 oral capsule in the fasted state.

Lower LoQ – 0.198 ng/mL (Cohorts 1, 2, 4 and 5) and 0.199 ng/mL (Cohorts 3 and 6). Values below lower LoQ imputed as 0 at prefirst dose and as lower LoQ /2 for postdose timepoints.
* Participants with all PK metabolite values below lower LoQ are not included in the summary statistics and therefore the magnitude of exposure at this dose may be over estimated and the variability underestimated.
Geo. = geometric, LoQ = limit of quantification, PK = pharmacokinetic, SAD = single ascending dose.

Summary of Plasma Metabolite REDX11246 PK Parameters – Part B (MAD) (PK Set)

Treatment	Study Day	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)
RXC008 30 mg (Cohort 3) (N=6)	Day 1*	n	5	5	5
		Geo. Mean	0.363	2.00[1]	3.05
		Geo. CV%	37.6	1.00-6.00[2]	14.6
	Day 11*	n	4	4	4
		Geo. Mean	0.349	1.00[1]	2.25
		Geo. CV%	21.7	1.00-6.00[2]	48.8
RXC008 100 mg (Cohort 1) (N=5)	Day 1*	n	3	3	3
		Geo. Mean	0.386	2.00[1]	3.70
		Geo. CV%	60.4	1.00-4.00[2]	38.1
	Day 11*	n	3	3	3
		Geo. Mean	0.380	2.00[1]	3.87
		Geo. CV%	33.9	2.00-2.00[2]	42.5
RXC008 300 mg Cohort 2) (N=6)	Day 1	n	6	6	6
		Geo. Mean	0.359	2.00[1]	3.15
		Geo. CV%	44.9	0.50-4.00[2]	34.3
	Day 11	n	6	6	6
		Geo. Mean	0.538	2.00[1]	4.45
		Geo. CV%	28.2	1.00-2.00[2]	30.3

[1]= median T_{max}

[2] = min-max T_{max}

Treatment: Once daily dosing of RXC008 oral capsule for 14 days in the fasted state.
Lower LoQ – 0.199 ng/mL. Values below lower LoQ imputed as 0 at pre-first dose and as lower LoQ/2 for post-dose time-points.
Participant 01-02-023 of Cohort 3 withdrew from the study on Day 11.
* Participants with all PK metabolite values below lower LoQ are not included in the summary statistics and therefore the magnitude of exposure at this dose may be over estimated and the variability under estimated.

Geo. = geometric, LoQ = limit of quantification, MAD = multiple ascending dose.

Summary of Ileum and Colon Tissue RXC008 Concentration Data – Part B (MAD) (PK Set)

Treatment	Site	Time-point (Post-Dose)	nq[a]	n	RXC008 Concentration (ng/g)							
					Mean	SD	Geo. Mean	Geo. SD	Geo. %CV	Min	Median	Max
RXC008 30 mg	Ileum, Terminal	Day 14	4	5	1430	1410	362	18.9	7494.8	2.53	1060	3160
(Cohort 3)	Colon, Ascending	Day 14	5	5	4120	7760	661	11.6	2003.8	21.5	444	17900
(N=6)	Colon, Descending	Day 14	5	5	1000	1130	347	9.41	1231.3	8.69	461	2760
RXC008 100 mg	Ileum, Terminal	Day 14	5	5	16600	17400	4710	14.9	3844.7	49.8	11400	42300
(Cohort 1)	Colon, Ascending	Day 14,	5	5	9690	13000	3910	6.05	495.0	235	6370	32500
(N=5)	Colon, Descending	Day 14,	5	5	918	987	621	2.59	121.5	247	707	2640
RXC008 300 mg	Ileum, Terminal	Day 14	6	6	32700	34800	4210	30.8	35663.3	53.0	26900	78300
(Cohort 2)	Colon, Ascending	Day 14	6	6	24700	36700	4830	12.0	2180.0	187	7030	92900
(N=6)	Colon, Descending	Day 14	6	6	2500	3140	1150	4.48	290.8	201	1530	8530

Treatment: Once daily dosing of RXC008 oral capsule for 14 days in the fasted state.
Day 14 samples were post-dose.
Values below lower LoQ imputed as lower LoQ/2 for post-dose time-points.
[a] nq = Number of participants with quantifiable concentrations (≥ lower LoQ).
Participant 01-02-023 withdrew from the study on Day 11.
Geo. = geometric, LoQ = limit of quantification, MAD= multiple ascending dose

Adverse Events

Part A (SAD): No participant reported any TEAEs.

Part B (MAD): There were no severe AEs, SAEs, events leading to death or withdrawal during Part B of the study.

A total of 19 TEAEs were reported by 10 (43.5%) participants following oral doses of RXC008 30 mg, 100 mg and 300 mg or placebo once daily for 14 days. All events were mild or moderate with the majority considered not related to study drug. Related events included decreased appetite, which was reported by 1 (4.3%) participant overall following treatment with 30 mg RXC008. The most commonly occurring event (related or not) in Part B was procedural related rectal haemorrhage, reported by 2 (8.7%) participants overall. Review of the TEAE profiles for Part B demonstrated no treatment, or dose related trends in TEAEs following study treatment.

One (1) (4.3%) participant overall had a clinically significant increase in ALT following 30 mg RXC008 that was reported as an AE. The event was mild and not related to study treatment.

Summary of TEAEs – Part B (MAD) (Safety Set)

	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
Number of TEAEs	4	10	4	1	15	19
Number of Study Drug-Related TEAEs	0	1	0	0	1	1
Number of Study Procedure-Related AEs	1	2	4	1	7	8
Number (%) of Participants Reporting at Least One:						
TEAE	3 (50.0)	4 (66.7)	2 (40.0)	1 (16.7)	7 (41.2)	10 (43.5)
Study Procedure-Related AE	1 (16.7)	2 (33.3)	2 (40.0)	1 (16.7)	5 (29.4)	6 (26.1)
Serious TEAE	0	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0
Number (%) of Participants with TEAE by Severity:						
Mild	2 (33.3)	2 (33.3)	1 (20.0)	1 (16.7)	4 (23.5)	6 (26.1)
Moderate	1 (16.7)	2 (33.3)	1 (20.0)	0	3 (17.6)	4 (17.4)
Severe	0	0	0	0	0	0

	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
Number (%) of Participants with TEAE by Relationship to Study Drug:						
Definitely Related	0	0	0	0	0	0
Probably Related	0	0	0	0	0	0
Possibly Related	0	1 (16.7)*	0	0	1 (5.9)*	1 (4.3)*
Unlikely Related	0	0	0	0	0	0
Not Related	3 (50.0)	3 (50.0)	2 (40.0)	1 (16.7)	6 (35.3)	9 (39.1)

* One (1) participant (01-02-019) reported decreased appetite following treatment with 30 mg RXC008 considered possibly related to study drug

Treatment: Once daily dosing of RXC008 oral capsule or placebo for 14 days in the fasted state.
A participant with multiple AEs is counted only once at the maximum level of severity or the strongest relationship to study drug within a treatment group.
Percentages calculated from the number of participants in the Safety Set within a treatment group.
Study drug-related AEs defined as having a causality of definitely related, probably related, or possibly related.
AE(s) = adverse event(s), MAD = multiple ascending dose, TEAE = treatment-emergent adverse event.

Summary of TEAEs by Preferred Term – Part B (MAD) (Safety Set)

Preferred Term	Number of Events / Number (%) of Participants					
	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
Number of TEAEs	**4**	**10**	**4**	**1**	**15**	**19**
Rectal haemorrhage	1 / 1 (16.7)	0	1 / 1 (20.0)	0	1 / 1 (5.9)	2 / 2 (8.7)
Abdominal pain upper	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Alanine aminotransferase increased	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Decreased appetite	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Dizziness	0	0	1 / 1 (20.0)	0	1 / 1 (5.9)	1 / 1 (4.3)
Dry skin	1 / 1 (16.7)	0	0	0	0	1 / 1 (4.3)
Foot fracture	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Gingival ulceration	0	1 / 1 (16.7)	0	0	1 / 1 5.9)	1 / 1 (4.3)

Preferred Term	Number of Events / Number (%) of Participants					
	Placebo (N=6)	RXC008 30 mg (Cohort 3) (N=6)	RXC008 100 mg (Cohort 1) (N=5)	RXC008 300 mg (Cohort 2) (N=6)	RXC008 Overall (N=17)	Overall (N=23)
Headache	1 / 1 (16.7)	0	0	0	0	1 / 1 (4.3)
Medical device site rash	0	0	0	1 / 1 (16.7)	1 / 1 (5.9)	1 / 1 (4.3)
Nasal congestion	1 / 1 (16.7)	0	0	0	0	1 / 1 (4.3)
Nausea	0	0	1 / 1 (20.0)	0	1 / 1 (5.9)	1 / 1 (4.3)
Non-cardiac chest pain	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Oropharyngeal pain	0	2 / 1 (16.7)	0	0	2 / 1 (5.9)	2 / 1 (4.3)
Presyncope	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)
Rash	0	0	1 / 1 (20.0)	0	1 / 1 (5.9)	1 / 1 (4.3)
Skin fissures	0	1 / 1 (16.7)	0	0	1 / 1 (5.9)	1 / 1 (4.3)

Treatment: Once daily dosing of RXC008 oral capsule or placebo for 14 days in the fasted state.
A participant is counted only once per preferred term within a treatment group.
Percentages calculated from the number of participants in the Safety Set within a treatment group.
MedDRA version 26.1.
MAD = multiple ascending dose