Clinical Study Protocol

Protocol Title:	A Modular multi-Arm, Phase 1, Adaptive Design Study to Evaluate the Safety and Tolerability of RXC004, Alone and in Combination with Anti-cancer Treatments, in Patients with Advanced Malignancies
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Study Phase:	Phase 1
Sponsor:	Redx Pharma plc Block 33 Mereside, Alderley Park Alderley Edge, Cheshire SK10 4TG, UK
Medical Monitor	[redacted]
Principal Investigator:	[redacted]

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SIGNATURES

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PROTOCOL NO: RXC004/0001

[redacted] Sep 16, 2022

[redacted] Signature Date

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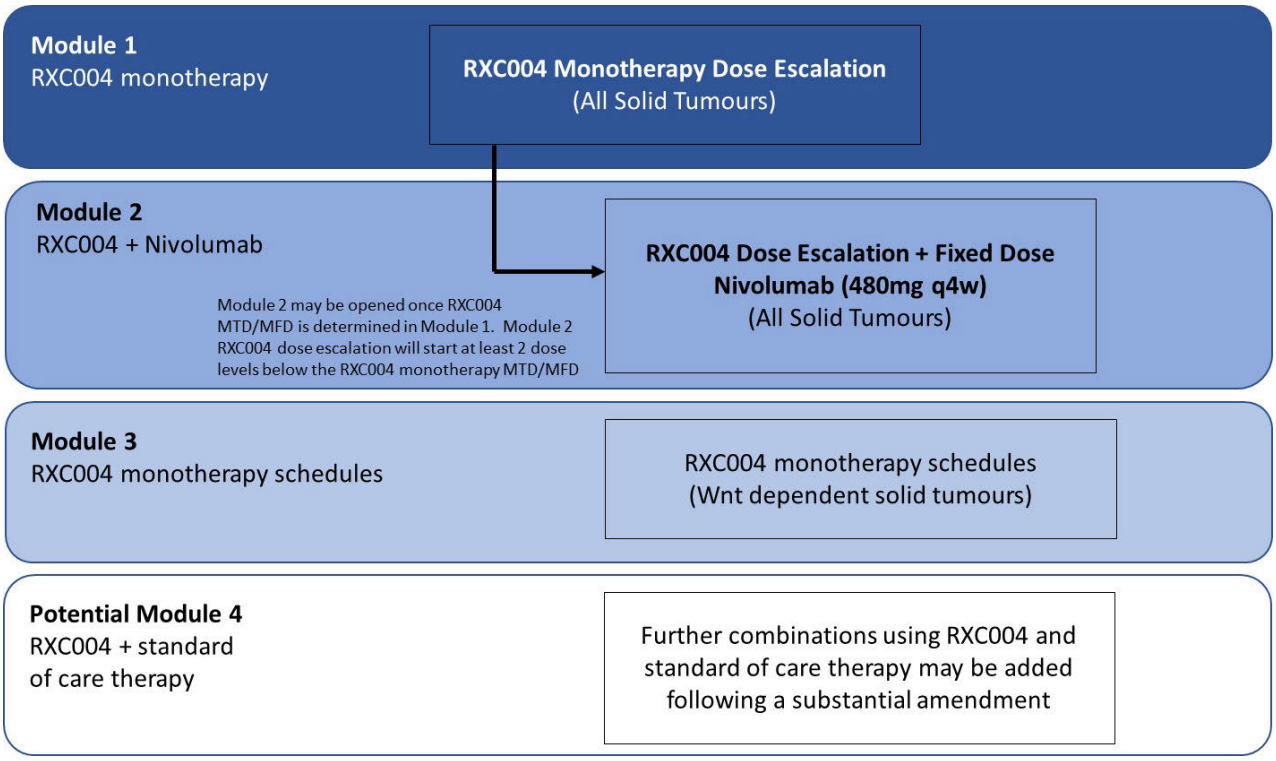
Overview of Study



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Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Adenomatous polyposis coli
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{ss}	Area under the curve at steady state
BAD	Biologically active dose
BCG	Bacillus Calmette–Guérin vaccine
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CBP	CREB binding protein
CFR	Code of Federal Regulations
CHL	Classical Hodgkin's lymphoma
CIOMS	Council for International Organisations of Medical Sciences
C_{max}	Maximum plasma concentration
CMO	Chief Medical Officer
CPMP	Committee for proprietary medicinal products
CR	Complete response
CRF	Case report form (electronic/paper)
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised tomography
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
DC	Dendritic cell
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSH	Dishevelled
ECG	Electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Co-operative Oncology group
EDC	Electronic data capture
EF	Ejection fraction
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTIH	First time in human
Fz	Frizzled co-receptor
GCP	Good Clinical Practice
GCSF	Granulocyte-colony stimulating factor
GEJ	Gastro-oesophageal junction
GI	Gastro-intestinal
GnRH	Gonadotropin-releasing hormone
GSK3β	Glycogen synthase kinase 3β
HDPE	High-density polyethylene
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional Review Board
IUD	Intra-uterine device
LH	Luteinising hormone
LoF	Loss of function
LRP5/6	Low-density lipoprotein receptor-related protein 5/6
LRV	Lower reference value
mAbs	Monoclonal antibodies
MAD	Multiple ascending dose
MBAD	Minimal biologically active dose
MDSC	Myeloid-derived suppressor cell
MFD	Maximum feasible dose
MHRA	Medicines and Healthcare products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MMTV	Mouse mammary tumour virus
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaulable
NK	Natural killer
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PD	Progression of disease
PD-1	Programmed death receptor-1
PDAC	Pancreatic ductal adenocarcinoma
PI	Principal investigator
pIC_{50}	Negative log of half maximal inhibitory concentration
PFS	Progression-free survival
PK	Pharmacokinetics
PDL 1	Programmed death-ligand 1
PoC	Proof of concept (defined as evidence of clinical benefit, such as reduction in tumour size)
PoM	Proof of mechanism (defined as evidence that the compound has a potential mechanism of action in humans such as inhibition of target enzyme or receptor)
PoP	Proof of principle (defined as proof of not only engagement with the biological target but also that the downstream consequneces of this target action have changed)
PORCN	Protein-serine O-palmitoleoyltransferase porcupine
PR	Partial response
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RNF43	Ring finger protein 43
SAE	Serious adverse event
SAD	Single ascending dose
SAP	Statistical Analysis Plan
SCCHN	Squamous-cell carcinoma of the head and neck
SD	Stable disease

Abbreviation or special term	Explanation
SDV	Source data verification
SFRP	Secreted frizzled-related protein
SoC	Standard of care
SOP	Standard operating procedures
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TGI	Tumour growth inhibition
TIL	Tumour infiltrating lymphocytes
T_{max}	Maximum plasma concentration
$T_{½}$	The time taken for any concentration point in the elimination phase to fall to half its value
TL	Target lesion
TV	Target value
UK	United Kingdom
ULN	Upper limit of normal
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

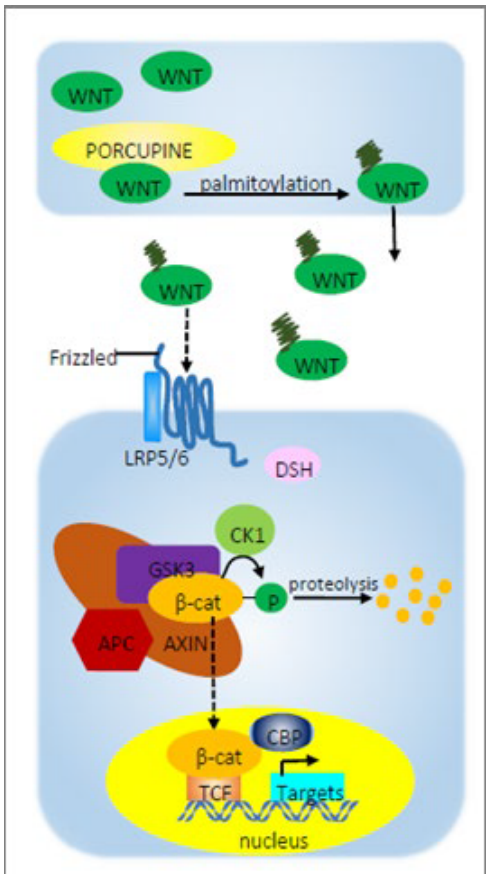
1 INTRODUCTION – CORE

1.1 Investigational Agent

The investigational agent RXC004 is a novel, small-molecule inhibitor of the membrane bound protein-serine O-palmitoleoyltransferase porcupine (PORCN). PORCN is required for the post-translational modification of all Wnts ligands and is vital for Wnt secretion and initiation of downstream canonical and non-canonical signalling. {Herr, 2012 Ref 16}

The Wnt signaling pathway plays an instrumental role in animal development and in the regulation of cellular proliferation, migration, morphology, apoptosis, differentiation, and stem cell self-renewal. Dysregulation and aberrant activation of the Wnt pathway is known to play a critical role in the development of a variety of malignancies {Logan, 2004 Ref 24}.
The interaction between porcupine and the canonical Wnt pathway is illustrated in Figure 1.

Figure 1: Interaction Between Porcupine and the Canonical Wnt Pathway



PORCN is required for the post-translational modification of all Wnt proteins, and is vital for Wnt secretion.The Wnt pathway is initiated by the binding of Wnt glycoproteins to co-receptors frizzled (Fz) and low-density lipoprotein receptor-related protein (LRP) 5 or 6 resulting in the phosphorylation of dishevelled (DSH), which in turn recruits a destruction complex comprising axin, adenomatous polyposis coli (APC) and glycogen synthase kinase 3β (GSK3β) to the cell membrane. The movement of these proteins inhibits the phosphorylation of β-catenin allowing β-catenin to accumulate near the cell nucleus and induces the transcription of target genes.

Aberrant activation of the pro-survival Wnt signalling pathway is a key determinant in numerous cancers {Nusse, 2012 Ref 31} and therefore constituents of this pathway are potentially promising therapeutic targets.{Artem Blagodatski1†, 2014 Ref 2}

The investigational agent RXC004 is a novel, orally bioavailable small-molecule inhibitor of porcupine (PORCN). The mechanism of action of RXC004 provides the potential to afford monotherapy efficacy as well as efficacy in combination (either via synergistic or additive effects) with a number of anti-cancer treatments. This study is, therefore, an adaptive modular study in design, allowing evaluation of the safety, tolerability, PK and anti-tumour activity of

RXC004 at increasing doses, initially as monotherapy and then in combination with different anti-cancer treatments, in patients with advanced malignancies.

1.2 Disease Linkage

1.2.1 Genetic Alterations in the Wnt Pathway in Colorectal, Gastric and Pancreatic Cancers

Recurrent chromosome rearrangements involving members of the R-Spondin (RSPO) family, RSPO2 and RSPO3, have been described in colorectal cancer (CRC). {Seshagiri, 2012 Ref 36} The rearrangements result in fusion transcripts that drive marked overexpression of the RSPO gene. RSPOs are secreted proteins that act as ligands for the leucine rich repeat containing G-protein coupled receptor LRP family (LRP 4/5/6). RSPO binding to LRPs potentiates Wnt signalling by sequestering the E3 ubiquitin ligases RNF43 and ZNRF3, resulting in the accumulation of Fz/LRP-receptor complexes at the cell membrane. All reported RSPO-fusion events in CRCs are mutually exclusive of APC mutations and other activating mutations in the Wnt pathway, indicating RSPO rearrangements are likely key genetic drivers in CRC. RSPO proteins can stabilise cytosolic β-catenin and dramatically synergize with Wnt ligands resulting in increased pathway activity.{Seshagiri, 2012 Ref 36;de Lau, 2014 Ref 6}

Redx has demonstrated an anti-proliferative effect of RXC004 in the SNU-1411 cell line, a human CRC cell line containing an RSPO fusion. RNF43 is an integral membrane E3 ubiquitin ligase that promotes degradation of Fz receptors (Figure 1). A number of mutations in this ligase have been identified in cancer patients and are predicted to result in RNF43 LoF leading to increased Fz expression at the cell surface and elevated Wnt signalling. A significant incidence of RNF43 mutations has been reported in CRC, gastric and pancreatic cancers. Sensitivity to PORCN inhibitors has been demonstrated in tumour cell lines with RNF43 LoF mutations.{Madan, 2016 Ref 26}

This sensitivity has been corroborated in *in vivo* studies; Redx has also demonstrated efficacy of RXC004 in a CAPAN 2 xenograft study (Section 1.3.1) that carries an RNF43 loss of function mutation.

Bioinformatics analysis of The Cancer Genome Atlas (TCGA) and cBioPortal databases has confirmed that the RNF43 mutation prevalence in pancreatic cancer is around 4%. Due to this low incidence it is likely that patient selection for this indication will require Redx to be part of a larger platform based trial. Redx is actively engaged with the Precision Panc initiative (a

UK wide pancreatic cancer trial led by CRUK). In gastric cancer and CRC, bioinformatics has revealed a higher incidence of RNF43 mutation: approximately 9% and 6%, respectively. In addition, RSPO fusions are found in approximately 10% of CRC, thus genetic alteration of upstream Wnt pathway is likely to occur in ~16% of CRC in total Redx has developed assays in order to detect RNF43 LoF mutations and RSPO fusions in patients tumour samples (seee Section 5.4.2.4 for more details)

As discussed above, RXC004 has shown efficacy in both RNF43 LoF and RSPO fusion human xenograft models. As part of these pre-clinical studies it was observed that RXC004 did not show a clear dose-repose relationship when a caliper measurement was used for study endpoint. The calipers measure simply the size of the tumour in the mouse similar to a RECIST scan in a cancer patient. In addition to the caliper measurement Redx has also conducted IHC analysis on these RSPO fusion tumours. By IHC, a clear dose-response relationship was shown on Ki67 staining, which shows an antiproliferative effect of RXC004. In addition to the dramatic dose-dependent reduction in tumour cell proliferation, RXC004 also resulted in a striking change in cell morphology. By Alcian blue staining, RXC004 treatment was shown to increase the presence of mucins in the extracellular space in a dose-dependent manner. Redx believes that this increase in mucin in the tumour microenvironment is responsible for the lack of dose response in the caliper tumour volume measurement in this model. A RECIST measurement on tumour size maybe confounded if this cell differentiation and increase in mucus production in the tumour microenvironment results in a lack of tumour area shrinkage. For these reasons, DCR is the primary endpoint for the RXC004 monotherapy arm because it is possible that RXC004 efficacy could result in prolonged stable disease rather than tumour shrinkage. As complete ablation of tumour cell proliferation has been observed in pre-clinical models, this mechanism of action could still lead to patient benefit, increased progression free survival and ultimately an overall survival benefit for the patient.

1.2.2 Wnt Signalling and Biliary Tract Cancer

Patient samples from biliary-tract cancer (BTC) patients have been shown to have high expression of both Wnt ligands and Fz receptors. {Boulter, 2015 Ref 3} In addition to this high expression, there are no reports of downstream pathway mutations that would render these patients resistant to PORCN inhibition. BTC cell-line xenograft models in mice and chemically induced models of cholangioma in rats have been demonstrated to be sensitive to PORCN inhibition.

1.2.3 Wnt Pathway in Other Cancers

In addition to the upstream genetic mutations in the Wnt pathway and increased Wnt ligand production described above in gastric, pancreatic, colorectal and biliary tract cancers, there is also a potentially much wider role for PORCN inhibition in other solid tumours.

Abnormal expression of regulatory proteins in the pathway by epigenetic alteration has been described. For example, the reduced activity or absence of extracellular Wnt antagonists, the secreted frizzled-related proteins (SFRPs), has been reported in colorectal, breast, prostate, and lung cancers and thus evidence exists for therapeutic utility of a PORCN inhibitor in a wider range of solid tumours.{Caldwell, 2004 Ref 4;Lee, 2004 Ref **23**;Suzuki, 2004 Ref 42;Fukui, 2005 Ref 10;Zou, 2005 Ref 51}.

In addition, although it could be assumed that mutations downstream in the Wnt pathway, such as APC mutations (prevalent in up to 90% of CRC) would render tumours resistant to PORCN inhibition, evidence in the literature exists to suggest such patients may also benefit from a reduction in ligand drive *via* PORCN inhibition.{Voloshanenko, 2013 Ref 47} A small-molecule PORCN inhibitor in CRC cell lines bearing APC mutations resulted in decreased pathway activation, anti-proliferative effects and reduced cell viability. These data suggest patients with cancers bearing downstream mutations in the Wnt pathway, traditionally expected to be insensitive to PORCN inhibitors may well in fact receive therapeutic benefit from treatment with a PORCN inhibitor.

1.2.4 Wnt Pathway as an Immune Oncology Target

There is strong scientific rationale, from both pre-clinical and clinical studies, that Wnt pathway activity drives the immune evasion of tumours.{Spranger, 2018 Ref 41;Wang, 2018 Ref 48} Porcupine inhibition has the potential to block two of the five critical mechanisms of tumour-cell immune evasion. High β-catenin protein levels (i.e. high Wnt pathway activation) were also recently reported to correlate with lack of immune signature across 22 different cancer types. {Luke, 2019 Ref 25} The lack of immune signature has been linked to a lack of response to immune checkpoint inhibitors (such as anti-PD-1). Redx has demonstrated efficacy by an immune system-mediated mechanism with RXC004 in combination with an anti-PD1 antibody in a CT26 mouse syngeneic CRC tumour model. RXC004/anti-PD-1 combination therapy results in a significant decrease in Treg cells and a significant increase in the cytotoxic T cell to Treg cell ratio in this model compared to either agent alone. In addition, RXC004 has monotherapy efficacy in the B16 melanoma mouse syngeneic model. This efficacy is dependent on an intact immune system and correlates with RXC004 causing a decrease in myeloid derived suppressor cells (MDSCs) in the tumours of this model.

As described above, blockade of Wnt by RXC004 would be expected therefore to reverse Wnt induced immune evasion in the tumour microenvironment and result in a decrease in MDSCs

and Tregs and an increase in CD8 T cells. In a patient with PDL1 +ve disease then in order for these newly acquired CD8 T cells to function optimally an anti-PD1/antiPDL1 immunotherapy will be required and therefore in these PDL1 +ve patients we would expect to see synergy between the action of RXC004 to bring in the T cells to the TME and the anti-PD(L)1 agent to release the inhibition on these T cells.

1.2.5 Clinical Precedence with Target

As of yet there are no Wnt pathway inhibitors approved for therapeutic use. A number of companies are investigating porcupine inhibitors in Phase 1/2 clinical trials, these compounds are;: WNT974, ETC-159 and XNW7201, CGX1321. (Table 1)

Data from the completed Phase 1, open-label trial of WNT974, administered in monotherapy have recently been published (NCT01351103). {Rodon, 2021 Ref 35} In this study, 94 patients received oral WNT974 at doses of 5–30 mg QD, plus intermittent dosing schedules. AEs suspected to be related to study treatment were reported for 75 patients (80%), with the most common (≥20%) being dysgeusia (44 patients; 47%), decreased appetite (27 patients; 29%), and nausea (23 patients; 24%). Six patients (6.4%) experienced seven bone-related disorders, five of which were suspected to be related to study treatment: osteoporosis, pathological fracture, osteopenia, and two Grade 3 spinal fractures. No OR evaluation criteria in solid tumors (RECIST) responses were reported but 15 patients (16%) had stable disease (median duration 19.9 weeks). In the expansion cohort, SD was observed in 10/28 patients (36%), which was enriched in patients with RNF43 mutations.

WNT974 is also being evaluated in an ongoing Phase 1 dose-escalation study (NCT01351103) in combination with spartalizumab, an anti-PD1 antibody.{Janku, 2020 Ref 19} At the time of the last report, 32 patients with advanced/metastatic solid tumours have been enrolled including cutaneous melanoma, uveal melanoma, lung SCC, HNSCC, pancreatic cancer, cervical cancer and TNBC. Seventeen patients (melanoma, lung SCC, HNSCC) were refractory (best response was PD) to prior anti-PD1. WNT974 was administered orally QD and administered either on Days 1-8 or 1-15 in Cycle 1 (28-day cycle) only or in Cycles 1-4. Spartalizumab was administered at 400 mg QD every 28 days starting on Day 1. The safety of the combination was largely consistent with either agent administered as monotherapy. Two DLTs were reported (Grade 2 spinal compression fracture [study Day 9] after 2.5 mg Day 1-8 Cycles 1-4) and Grade 3 arthralgia (2.5 mg Days1-15 Cycle 1 only). No MTD had been established.{Janku, 2020 Ref 19}
The DCR (SD + PR + CR) reported was 41% (13/32), which included 12 patients who achieved SD and one (TNBC) who achieved a PR. Of patients who received prior anti-PD1, 47% achieved SD (9/19). The majority of these patients were refractory to prior anti-PD1 treatment (17/19). All five patients with uveal melanoma achieved durable SD of > 24 weeks duration.

The study is ongoing with further recruitment of uveal melanoma patients planned in addition to evaluating whether AXIN2 mRNA levels may be predictive of clinical benefit.

Phase 1a safety data from an ongoing FTIM clinical study of the small molecule PORCN inhibitor ETC-159 (NCT02521844), were presented in a poster at the ASCO 2017 annual meeting {Ng, 2017 #10270}. Twenty advanced solid tumour patients were treated in the dose-escalation phase (1–40 mg ETC-159, QOD in a 28-day cycle). Two DLTs were reported (hyperbilirubinemia at 16 mg and a skeletal fragility fracture at 30 mg) and the most common AEs (irrespective of causality) were anorexia (30%), fatigue (30%), vomiting (30%), dysgeusia (30%), increased β-CTX (30%), nausea (20%) and constipation (20%). In the 30 mg cohort, two of five patients experienced bone-fragility fractures (one of these was classed as a DLT while the other was outside the DLT period) and four out of five patients experienced a doubling from baseline and increase to >1000 pg/mL in serum β-CTX levels. These patients with increased β-CTX (defined as a doubling from baseline to a level above 1000 pg/mL) were given bone protective treatments (denosumab or bisphosphonate), which normalised β-CTX levels. The MTD was therefore declared at 30 mg. Efficacy analysis in the first twenty patients showed that five had SD.

CGX1321 (Curegenix Inc) is a porcupine inhibitor in Phase 1 development in Asia as monotherapy in advanced solid tumours and in Phase 1b in combination with pembrolizumab in patients with advanced GI tumours (CRC, gastric, pancreatic, bile duct, hepatocellular, oesophageal and GI cancers). No clinical data have been reported to date on CGX1321.

Table 1 Wnt Pathway Clinical Trials

PORCN Inhibitor	Global Status, Trial ID, Location	Tumor Type	Drugs tested	Patient segment	Prior SoC treatment
CGX-1321	Phase1/1b (recruiting) NCT02675946, US and OUS	Colorectal, esophageal, gastric, liver, pancreatic, unspecific solid tumors	CGX-1321; pembrolizumab[1]	Second line Stage III, IV	Patients who have relapsed, are refractory to, or are not considered medically suitable to receive SoC treatment.
	Phase 1 (recruiting) NCT03507998, OUS	Colorectal, esophageal, gastric, liver, pancreatic, unspecified solid tumors[2]	CGX-1321	Second line Stage III, IV	Histologically diagnosed tumors that have relapsed, are refractory to, or are not considered medically suitable to receive SoC treatment.
ETC-159	Phase 1a/b (recruiting) NCT02521844, US and OUS	Colorectal, endometrial, ovarian, unspecified solid tumors	ETC-159; pembrolizumab[1]	RSPO fusion for MMS colorectal cancer; MMS-ovarian, MMS-endometrial Second line Stage III, IV	Histologically or cytologically confirmed advanced or metastatic tumors, that are unresectable solid malignancies, and that are refractory, intolerant or not suitable to available treatment.
WNT-974/ LGK-974	Phase 1 (recruiting) NCT01351103, US and OUS	Breast, cervical, colorectal, esophageal, head/neck, lung, non-small-cell, melanoma, pancreatic[2]	LGK-974; spartalizumab[1,5]	BRAF, HER2-negative, Second line Stage II, III, IV, triple receptor-negative	Patients who have progressed despite standard therapy or for which no effective standard therapy exists.
	Phase 1b/2 (completed) NCT02278133, US and OUS	Colorectal[2]	LGK-974, cetuximab[3], encorafenib[4]	BRAF second line Stage IV	Patients with BRAFV600-mutant KRAS wild type with RNF43 mutation and/or RSPO fusion in metastatic colorectal cancer who have progressed after at

					least one prior SoC regimen or are intolerant to irinotecan-based regimens.
XNW-7201	Phase 1 (recruiting) NCT03901950, OUS	Unspecified solid tumors	XNW-7201	Second line Stage III Stage IV	Patients with histologically or cytologically confirmed advanced solid tumors after failure of SoC, or intolerability to SoC, or with no SoC.

[1]Anti-PD-1 antibody; [2] includes evaluation of PORCN in tumors with aberrations in the WNT signalling pathway (RSPO fusion or RNF43); [3] EGFR antagonist; [4] BRAF kinase inhibitor; [5]Unapproved product; US = United States; MMS = microsatellite stable; OUS = Out of the United States, SoC=standard of care.

1.2.6 Tolerability of Targeting Porcupine

An update of the tolerability of RXC004 in the current study can be found in Section 1.7.1.2. The safety profile of RXC004 monotherapy is similar to that reported for two other porcupine inhibitors, ETC-159 and WNT974, in clinical trials, which demonstrated a tolerable safety profile for this pharmacological class at doses with confirmed Wnt pathway inhibition, as described in Section 1.2.5. {Janku, 2020 Ref 19;Ng, 2017 #10831}(Janku et al 2015 Ref 18, Rodon Ref **35** and Ng et al 2017 Ref 30)

As well as having a role in tumour development the Wnt pathway is involved in tissue homeostasis in the GI tract and in bone. Pre-clinical studies have demonstrated a therapeutic margin between the exposure levels required for anti-cancer efficacy and the emergence of on-target GI side effects with porcupine inhibitors. This is in contrast to other approaches targeting the Wnt pathway such as tankyrase inhibition, in which the therapeutic window was shown to be <1. {Zhong, 2016 Ref 50}

1.3 Non-clinical Information and Correlative Studies

1.3.1 Pre-clinical Primary Pharmacology Studies

In vitro cellular assays were used to define the Wnt pathway inhibitory activity of RXC004. RXC004 was tested for its ability to reduce production of Wnt ligand from Wnt producing mouse L-cells. The amount of Wnt released from these cells was then quantitated by use of a reporter assay. Reporter cells are transfected with the luciferase gene under the control of

β-catenin transcriptional response elements. RXC004 was shown to potently inhibit release of Wnt from the mouse L cells; RXC004 had a pIC_{50} of 10.2 in this reporter assay. In addition, it was also demonstrated that addition of exogenous recombinant Wnt ligand had the ability to "rescue" the inhibition of Wnt pathway by RXC004 in this reporter assay which supports that RXC004 is inhibiting Wnt signalling upstream of Wnt ligand production by inhibiting PORCN. To further confirm the mechanism of action of RXC004 Wnt palmitoylation was directly monitored in HEK293 cells. It was demonstrated that 100 nM RXC004 decreased detectable labelled palmitic acid conjugated to Wnt, supporting that RXC004 directly inhibits PORCN.
The anti-proliferative activity of RXC004 was tested in HPAF-II and Capan-2 human pancreatic ductal adenocarcinoma (PDAC) and SNU-1411 human CRC cell lines. HPAF-II and Capan-2 cell lines harbour RNF43 mutations that are predicted to result in LoF of RNF43, while the SNU-1411 cell line harbours a RSPO fusion. RXC004 was shown to be anti-proliferative in Capan-2, HPAF-II and SNU-1411 cell lines with pIC_{50} of 9.4, 8.8 and 8.6, respectively.

Pre-clinical anti-tumour efficacy of RXC004 as a single agent was evaluated in a Capan-2 and a SNU1411 tumour xenograft model, and a gastric cancer PDX model. Both the Capan and the gastric PDX models have RNF43 LoF mutations, The SNU1411 model has an RSPO fusion. In the Capan-2 xenograft model RXC004 caused significant TGI when dosed at 1.5 mg/kg BID, TGI = 65.6%; and at 5 mg/kg QD, TGI= 67.6%. RXC004 was demonstrated to cause tumour regression (-16.9%) when dosed at 5 mg/kg BID in this model. In the gastric cancer PDX model RXC004 caused significant tumour growth inhibition when dosed at 5 mg/kg QD (TGI=49%). In the SNU-1411 model, RXC004 at 1.5 mg/kg QD, 5 mg/kg QD, 1.5 mg/kg BID and 1.5 mg/kg BID 5 on/2 off significantly slowed the growth of SNU-1411 tumours compared with vehicle-treated animals with T/C values of 53.4% ($p<0.05$), 64.0% ($p<0.01$), 58.2% ($p<0.01$) and 64.1% ($p<0.01$), respectively.

In addition to single-agent monotherapy efficacy in gastric, colorectal and pancreatic cancer models, RXC004 has been tested in the immune competent mouse syngeneic models CT26 and B16. Redx has demonstrated efficacy by an immune system-mediated mechanism with RXC004 in combination with an anti-PD1 antibody in the CT26 mouse syngeneic colorectal tumour model. RXC004/anti-PD-1 combination therapy results in a significant decrease in Treg cells and a significant increase in the cytotoxic to Treg T cell ratio compared to either agent alone. In addition, RXC004 has monotherapy efficacy in the B16 melanoma mouse syngeneic model. This efficacy is dependent on an intact immune system and correlates with RXC004 causing a decrease in MDSCs in the tumours of this model.

1.3.2 Pre-clinical Toxicology and Safety Pharmacology Studies

The preclinical safety studies conducted with RXC004 included oral GLP toxicology studies in rats and dogs for up to 28 days, *in vitro* genetic toxicology studies, secondary and safety pharmacology studies and an assessment of phototoxicity.

Oral dosing of RXC004 to rats and dogs for up to one month was associated primarily with dose-dependent effects on the GI tract and bone. Effects on mobility, food consumption and body weight were dose limiting.

In the one-month rat GLP toxicity study, animals were dosed orally with 1, 3 or 5 mg/kg/day. Dose-dependent growth plate dysplasia, reduced trabecular bone, and fractures were variably present in the femur and femoro-tibial joint in both sexes at all dose levels. Decreased bone was present in the sternum of males administered 3 or 5 mg/kg/day and females at all dose levels. Higher marrow fat levels were variably observed in the femur and sternum of both sexes at all dose levels. Degeneration, inflammation, erosion and ulceration were recorded in the large and small intestine of both sexes. Acinar dilatation was present in the prostate of males administered 5 mg/kg/day. At the end of the recovery phase, findings in the small intestines and prostate had fully reversed with partial recovery of the findings in the femur, femoro-tibial joint, and sternum.

In the dog one-month GLP toxicity study, animals were dosed orally with 5, 10, or 15 mg/kg/day. Administration of 15 mg/kg/day RXC004 to dogs was associated with impaired mobility (stiff gait) with intermittent tremors, slow movements, subdued behaviour, and swollen wrist joints noted in several animals. Two female dogs were removed from the study at the end of Week 1, due to the severity of these signs. Bone lesions (growth-plate dysplasia) were considered to be the cause of these observations. At the recovery sacrifice, growth plate dysplasia was still present in the carpus of one male administered 15 mg/kg/day. The dose level of 5 mg/kg/day is considered the 'no-observed AE-level' (NOAEL).

The majority of the findings in both rats and dogs were considered to be related to on-target pharmacology, resulting from inhibition of porcupine and reduction of Wnt pathway signalling.

An *in vivo* cardiovascular assessment was conducted in a group of telemetered beagle dogs. No test article-related effects on ECG, haemodynamics or body temperature were observed following single oral administration of RXC004 up to 50 mg/kg.

RXC004 absorbs light above 290 nm in the UV/visible spectrum and is therefore considered to be potentially phototoxic. RXC004 was not genotoxic *in vitro* in the Ames test or micronucleus assay.

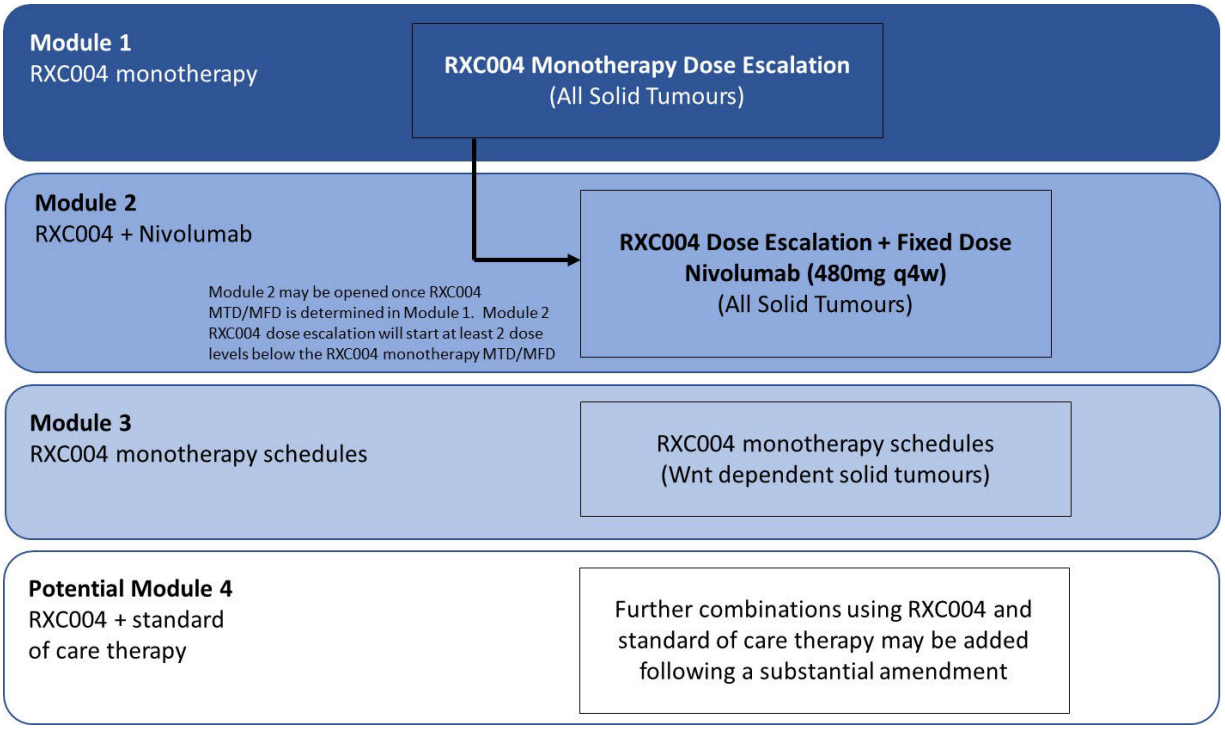
Overall, the results from the toxicology studies support the progression into clinical trials in patients with advanced cancer.

For additional details, please refer to the IB.

1.4 Overall Study Design and Flow Chart

The design is summarised as follows:

Figure 2 Overall Study Design



The study is a modular Phase1, dose-escalation, open-label study to assess the safety, tolerability, PK and preliminary anti-tumour activity of RXC004 in monotherapy and in combination in patients with advanced malignancies.

The study started with the RXC004 monotherapy module (Module 1), a monotherapy dose escalation to identify the MBAD, MTD or MFD in multiple patient cohorts. The recommended RXC004 monotherapy dose for further development was 2 mg QD. A summary of the monotherapy data is provided in Section 1.7.1.2. A RXC004 and nivolumab combination module (Module 2) was added to the protocol using a fixed-dose nivolumab (anti PD-1) monoclonal antibody. Nivolumab will be given at the FDA-approved dose/schedule for MSI-H CRC, while RXC004 will be dose escalated up to a MTD for the combination.

An RXC004 monotherapy scheduling module (Module 3) was added with this amendment. Module 3 will investigate whether alternative dosing schedules are tolerated in selected Wnt pathway activated patients. Two different RXC004 monotherapy schedules will initially be

investigated in Module 3 – 2 mg QD for 4 days, followed by three days off each week (Arm 1), and 2 mg QD for 2 weeks followed by one week off (Arm 2). Additional arms with alternative schedules may be added, after review by the SRC.

Further modules may be added following a substantial protocol amendment to explore the following in patients with locally advanced, unresectable and/or metastatic solid malignancies:

- Combination of RXC004 with SoC therapy
- RXC004 formulation switches
- Potential effects of food on the PK of RXC004

1.5 Blinding

This is an open-label, non-comparative study so blinding is not required.

1.6 Rationale

The mechanism of action of RXC004 provides the potential for monotherapy efficacy but also to combine with a number of anti-cancer treatments, to result in either synergistic or additive activity. This study is, therefore, an adaptive modular study in design, allowing evaluation of the safety, tolerability, PK and anti-tumour activity of RXC004 at increasing doses, initially as monotherapy and then in combination with nivolumab, an anti-PD1 immune-checkpoint inhibitor. Other combinations may be evaluated e.g. RXC004 with SoC chemotherapeutic and/or targeted treatments in patients with advanced malignancies.{Biankin, 2015 Ref 1; Emens, 2016 Ref 8; Sharma, 2016 Ref 38}. Additional modules may be added to explore formulation switches or potential food effects at a later date.

Key aspects of the study, such as the revised starting dose of RXC004 in Module 1 (0.5mg), and the dose escalation and cohort size of all study modules, are based upon the clinical PK data from Patient 001/001(10mg) and also accepted methodology from other porcupine inhibitor Phase 1 oncology studies.{Ivy, 2010 Ref 17}

The collection of samples is included to allow characterisation of the PK of RXC004, and, if appropriate, investigation of the presence of and/or identity of metabolites of RXC004 to allow the Sponsor to fulfil regulatory requirements related to the testing of the safety of RXC004 and its metabolites.

As part of the clinical drug-development programme for RXC004, the Sponsor plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or

non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how this information can be used to bring better drugs to the clinic.

The results from this study will form the basis for decisions regarding future studies.

1.7 Overall Study Benefit-Risk and Ethical Assessment

RXC004, in this current study, is considered to have a positive benefit-risk profile for patients with advanced cancers with high Wnt ligand dependency, when given at doses up to and including 2 mg QD as a monotherapy. RXC004 also has the potential to enhance the activity of immune checkpoint inhibitors e.g. PD-1 or PD-L1 antibodies in patients with advanced cancers.

1.7.1 RXC004 Monotherapy

1.7.1.1 Potential Benefits

Although there can be no certainty of clinical benefit to patients, particularly in this initial study in patients with locally advanced and unresectable or metastatic tumours, non-clinical data with RXC004 support the hypothesis that as a PORCN inhibitor, RXC004 would be expected to have utility as a therapeutic agent initially in advanced malignancies and, in due course, for earlier stages of disease management.

RXC004 monotherapy treatment may offer the potential of clinical benefit in cancer patients by two different mechanisms of action. First it may benefit patients who have a specific Wnt pathway alteration (including RNF43 mutation or RSPO fusion) and second it may act as an immune-oncology agent facilitating an immune response by converting immunogenically "cold" tumours to immunogenically "hot" tumours.

At the initiation of this study, the potential for monotherapy clinical benefit in unselected patients (patients without RNF43 LoF or RSPO fusion and cholangiocarcinoma patients) was unknown but was considered to be likely significantly less than in selected patients (RNF43 LoF or RSPO fusion patients and cholangiocarcinoma patients). In Modules 1 and 2 , patients were able to participate in an optional pre-screen, in which archival tumours could be genetically screened for upstream Wnt signalling pathway aberrations. The data from this screening could be used to retrospectively correlate presence of RNF43 LoF or RSPO fusions to response to study treatment.
One of the important emerging opportunities is the growing evidence that Wnt signalling may subvert cancer immunosurveillance, hence promoting immunoevasion and resistance to multiple immunotherapeutics, including immune checkpoint blockers.{Wang, 2018 Ref

48;Galluzzi, 2018 Ref 11;Spranger, 2015 Ref 39;Luke, 2019 Ref 25} Redx therefore believes that RXC004, used as a monotherapy or in combination with an immune checkpoint blocker, could be of benefit to a broader unselected metastatic cancer patient population through this mechanism.

In Module 1, 5/18 RECIST-evaluable patients had SD, in one case lasting for up to 26 weeks. All five of these patients had Wnt-ligand-dependent tumours . None of the patients with Wnt ligand–independent tumours had SD. Following this observation, Module 3 (intermittent monotherapy doses) was designed to enrol only patients with Wnt ligand-dependent tumours to receive RXC004 monotherapy, in order for patients to have the best chance of experiencing clinical efficacy.

Potential patients will be fully informed of the risks and requirements of the study. During the study patients will be given any new information that may affect their decision to continue participation. They will be informed that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only patients who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Please refer to IB for further information.

1.7.1.2 Potential Risks

As of 30th July 2021, 25 patients have been dosed with RXC004 in Module 1 of the current study, at doses of 0.5mg-10mg QD, in which doses of up to 2 mg QD were found to be tolerable and safe. The most frequently occurring TEAEs were fatigue (64%), nausea (56%), decreased appetite (48%), vomiting (40%), dysgeusia (40%), diarrhoea (32%), aspartate aminotransferase increased (28%), and constipation (20%).

Five patients reported ≥Grade 3 AEs that were assessed by the Investigators as possibly or probably related to RXC004: Grade 3 weight loss (1.5 mg); Grade 3 nausea/vomiting/diarrhoea (1.5 mg); Grade 3 pancreatitis (2 mg); Grade 3 enteritis and Grade 5 subdural hematoma from a fall (3 mg); Grade 3 diarrhoea/proctitis/hyponatreamia (10mg). Three DLTs have been reported in the study: Grade 3 diarrhoea in a patient at RXC004 10 mg QD (before the study was re-started at RXC004 0.5 mg), Grade 3 enteritis in a patient at RXC004 3 mg and Grade 2 colitis in patient at RXC004 3 mg.

As of 30th July 2021, a total of 16 SAEs were reported in 11 patients. Apart from diarrhoea, which occurred in two patients, and colitis/enteritis, which are similar events and occurred in two patients, no SAEs were reported in more than one patient. Nine of the 16 SAEs reported in patients who received RXC004 monotherapy were assessed by the investigator and the Sponsor as unrelated to RXC004. The other seven SAEs were assessed by the Investigator as possibly or probably related to RXC004. Six of these treatment-related SAEs occurred at RXC004 daily doses that were subsequently declared SRC to be not tolerated (RXC004 3 mg and 10 mg QD):

- Two SAEs of NCI CTCAE Grade 3/2 diarrhoea that occurred in one patient at RXC004 10 mg QD (before the study was re-started) that led to discontinuation of study drug.

- One SAE of NCI CTCAE Grade 3 diarrhoea that occurred at RXC004 1.5 mg QD and led to discontinuation of study drug. The event was also associated with a *Clostridium difficile* infection and subsequently resolved/recovered.

- One SAE of NCI CTCAE Grade 2 colitis that occurred at RXC004 3 mg QD. The event subsequently resolved and the patient continued study treatment at a lower dose (RXC004 1.5 mg).

- One SAE of NCI CTCAE Grade 3 enteritis that occurred at RXC004 3 mg QD. The event was unresolved at the time that the patient subsequently died due to a subdural hematoma following a fall (Patient 0003/019).

- One SAE of NCI CTCAE Grade 2 humerus fracture (following a fall while hospitalised for enteritis – Patient 0003/019) occurred at RXC004 3 mg QD. The event was unresolved at the time that the patient subsequently died due to a subdural hematoma (Patient 0003/019).

- One NCI CTCAE Grade 5 SAE of subdural hematoma (following a fall while hospitalised for enteritis – Patient 0003/019) occurred at RXC004 3 mg QD.

The MTD for Module 1 has been declared as RXC004 2 mg QD. At doses up to and including 2 mg QD, the most common TRAEs were fatigue (10/20 patients), nausea (7/20), anorexia (6/20), dysgeusia (6/20), and vomiting (4/20).

The principal on-target AEs of significant interest known to occur with porcupine inhibition include decreases in bone density (including bone-fragility fractures) and loss of taste (dysgeusia). Inhibiting the Wnt pathway may also predispose to inflammation in the GI tract because of the role of Wnt in the immune micro-environment.

More detailed information about the RXC004 clinical data may be found in the most recent IB and Development Safety Update Report.

1.7.1.2.1 Bone Effects

Wnt signalling is known to play a prominent role controlling many aspects of skeletal development and homeostasis. It promotes bone formation whereas its inactivation leads to more osteopenic phenotypes. It is recognised that blockade of Wnt signalling, for example through PORCN inhibition, would be expected to lead to a movement of the bone remodelling balance in a catabolic direction..{Kahn, 2014 Ref 21} Following dosing with RXC004, it is not surprising therefore that toxicology studies in both rats and dogs have identified bone as a pharmacodynamic target organ in a dose-dependent manner. These changes are considered to be a direct consequence of on-target pharmacology.

In this study, bone fractures (vertebral [T9] and clavicular in normal bone [non-metastatic]) occurred in Patient 001/001, treated with RXC004 10 mg QD, which led to a trial interruption. PK analysis indicated that RXC004 exposure levels in this patient were significantly higher than had been predicted pre-clinically due to a longer than predicted half life. As bone fractures were observed in the first patient dosed on study RXC004/0001 (10 mg) and other Phase 1 clinical trials of Wnt inhibitors, a comprehensive bone-management plan was implemented in the protocol. Patients at significant risk of bone fracture are excluded from study entry, patients are given prophylactic denosumab and bone turnover biomarkers are monitored to identify any increased risk of bone fractures. The bone management plan (Section 3.4.1) includes:

- Exclusion of patients with bone metastases
- Exclusion of patients at higher risk of bone fractures
- Monitoring of blood bone-turnover markers and BMD
- Intervention measures for patients with increased bone-fracture risk on RXC004 treatment
- Use of prophylactic denosumab (anti-RANKL monoclonal antibody) in all patients to maintain BMD from the RXC004 1.5-mg monotherapy cohort (Module 1, Cohort 3).

Importantly, the amended starting dose of RXC004 was reduced 20-fold from the original study first dose to a dose of 0.5 mg QD.

In this study, all patients from the 1.5-mg dosing group have received prophylactic denosumab (120 mg s.c. QM) from cohort 3 (1.5mg) along with vitamin D3 (cholecalciferol 800 IU QD) and calcium (1000-1500 mg QD) supplements from the time of signing the ICF and throughout the RXC004 treatment.

Since prophylactic denosumab was introduced for all patients, β-CTX levels have remained at or below the baseline levels observed and no patient has lost significant BMD (≥7% decrease

in BMD) on DEXA scanning while receiving RXC004. One patient who received a dose of 3 mg QD experienced a bone fracture after a fall. No spontaneous fractures were reported.

1.7.1.2.2 Diarrhoea and Colitis

Wnt signalling is known to play a prominent role in adult intestinal homeostasis.{Gregorieff, 2005 Ref 14} Reversible degeneration and inflammation of the GI mucosa was also observed in the pre-clinical toxicology studies conducted with RXC004. Other molecules that reduce Wnt pathway activity have previously been dosed in man and have also been associated with GI AEs.{Artem Blagodatski1†, 2014 Ref 2}

RXC004-related diarrhoea has been observed in 4 /25 patients treated with RXC004 and in two cases it was an SAE. One patient who received 10 mg (the highest RXC004 dose administered) developed an SAE of Grade 3 diarrhoea in Cycle 1, which responded to treatment with corticosteroids but recurred as Grade 2 diarrhoea three weeks after stopping treatment, possibly due to steroids being stopped. One patient who received RXC004 1.5 mg developed an SAE of Grade 3 diarrhoea on Cycle 2 Day 10, which lasted for 10 days.

Based on data up 30th July 2021, intestinal inflammation events (colitis, enteritis or enterocolitis) have been reported in four (4) patients. CTCAE Grade 3 RXC004-related colitis occurred in the patient who received 10 mg and CTCAE Grade 3 enteritis occurred in a patient who received 3 mg. CTCAE Grade 2 colitis developed in two more patients, who started treatment with RXC004 3 mg RXC004 QD. One Grade 2 event presented symptomatically in Cycle 2 and, in the fourth case, Grade 2 colitis was discovered on the RECIST staging scan in Cycle 2. Symptoms included abdominal pain, intermittent constipation, diarrhoea, nausea and/or vomiting. Blood and mucus in the stool were not apparent in the cases reported to date. Symptoms were usually accompanied by, and preceded by, a raised CRP. In two patients, the event recurred after initially responding to steroids, but responded again to further treatment.

Colitis events were not observed in any patients who commenced treatment with doses of RXC004 ≤2 mg QD and lower, and the 3 mg QD dose gave a disproportionately high exposure compared to 2 mg QD. However, events of ileitis and colitis were subsequently reported in the ongoing Phase 2 studies (RXC004/0002 and RXC004/0003), at doses of 2mg QD, so there is a potential risk for colitis in patients receiving RXC004 2mg QD as a monotherapy. It is hoped that the intermittent dosing schedules to be studies in Module 3 may reduce the risk of this event.

The RXC004/0001 study protocol excludes patients with persistent ≥Grade 2 or higher diarrhoea (any cause) that has not resolved or improved with appropriate treatment prior to study enrolment and contains guidelines for investigation and management diarrhoea/colitis (Appendix 5).

1.7.1.2.3 Dysgeusia Events

RXC004-related dysgeusia was observed in 6/20 patients who received doses of ≤ 2 mg QD, in 3/4 patients receiving 3 mg QD, and by the one patient who received 10 mg QD. An assessment for further characterisation of this event in Module 3, and guidance for the management of dysgeusia has been added to this protocol (Appendix 6)

1.7.1.2.4 Reproductive and Teratogenic Toxicity

No reproductive toxicology or teratogenic studies have been conducted with RXC004 to date, and it is unknown whether the drug is excreted in human milk. Therefore, WOCPB and men should agree to use adequate contraception prior to study entry and for the duration of study participation, and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

Please refer to the IB for further information.

1.7.2 RXC004 in Combination with Nivolumab

1.7.2.1 Potential Benefits

The Wnt pathway has been widely described as being a key pathway in immune evasion in various common tumours.{Galluzzi, 2018 Ref 11} {Spranger, 2015 Ref 39} Wnt pathway-activated tumours have been shown to be poorly infiltrated by immune cells {Grasso, 2018 #Ref 13} and pharmacological inhibition of Wnt signalling promotes cytotoxic T cell infiltration sensitising cancer cells to PD-1 inhibitors.{Feng, 2019 Ref 9;Xiao, 2018 Ref 49}

Wnt pathway activation has been linked to resistance to checkpoint inhibitors such as anti-PDL1 and anti-PD1. {Spranger, 2018 Ref 41;Wang, 2018 Ref 48;Galluzzi, 2018 Ref 11} Spranger and colleagues stratified 266 human metastatic melanoma tumour samples by cytotoxic T cell burden (CD8 +ve T cells).{Spranger, 2015 Ref 39} Wnt pathway activation (β-catenin positive cells) correlated with reduced cytotoxic CD8 +ve T cell infiltrate in melanoma patients. These initial data in melanoma linking Wnt pathway activation to exclusion of tumour fighting T cells from the microenvironment have now been extended to bladder cancer {Sweis, 2016 Ref 43} and in a recent presentation at ASCO “most solid tumours”.{Luke, 2016 Ref 25}

WNT974, a PORCN inhibitor has been combined with anti-PD1 (spartalizumab) in an ongoing Phase1 trial in 32 patients.{Janku, 2020 Ref 19} The combination was well tolerated with efficacy being observed in patients (DCR of 41%) (see section 1.2.5 for details). Durable SD was observed in patients who were refractory to prior anti-PD1 treatment.

In-house data with RXC004 in mouse syngeneic models have demonstrated that RXC004 combined with anti-PD1 results in an increase in the ratio of cytotoxic CD8 positive cells to regulatory T cells. Thus, there is a clear rationale for the combination of RXC004 with checkpoint inhibitors.

Nivolumab, is currently licensed for use as treatment for patients with the following:

- Unresectable or metastatic melanoma in monotherapy or in combination with ipilimumab (approved by EMA and FDA).
- Adjuvant treatment of melanoma with lymph node involvement or metastatic disease that has undergone complete resection (approved by EMA and FDA).
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy (approved by EMA and FDA).
- Metastatic small-cell lung cancer (SCLC) in combination with ipilimumab for first-line treatment in adults with PD-L1 and no other EGFR or ALK genomic alterations) ; it is also indicated after progression on platinum-based chemotherapy and at least one other line of therapy (approved by FDA and EMA). Patients with EGFR/ALK genomic alterations should have disease progression on FDA-approved therapy
- Advanced renal cell cancer; after prior anti-angiogenic therapy (monotherapy) or as first line treatment for intermediate/poor-risk patients (in combination with ipilimumab); or in combination with cabozantinib for first-line treatment in adults. (approved by EMA and FDA).
- Classical Hodgkin's lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin, or ≥3 lines of systemic therapy including HSCT (approved by EMA and FDA).
- Recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy (approved by EMA and FDA).
- Locally advanced unresectable or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy (approved by EMA and FDA).

- Treatment of patients with hepatocellular carcinoma who have previously received sorafenib (approved by FDA).

- Treatment of patients with metastatic, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) CRC, as single agent or in combination with

ipilimumab who have progressed after fluoropyrimidine, oxaliplatin and irinotecan (single agent approved by FDA, combination approved by EMA and FDA).

- Unresectable advance, recurrent or metastatic oesophageal squamous-cell carcinoma after prior therapy with fluoropyrimidine-and platinum-based chemotherapy (approved by EMA and FDA).
- Gastric cancer, gastroesophageal junction cancer and adenocarcinoma, in combination with fluoropyrimidine- and platinum-based chemotherapy in patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma (approved by EMA and FDA).

1.7.2.2 Potential Risks

The clinical, pre-clinical and emerging safety profile has not identified any risks that would preclude investigation of a RXC004 and nivolumab combination in an advanced cancer setting. At high exposures of RXC004 the preclinical toxicities that overlap with those commonly seen with PD-1 inhibitors are those that affect the gut mucosa.

Checkpoint inhibitors including anti PD-1, as well as antibodies directed against PDL-1 and CTLA-4, boost the endogenous immune responses directed against tumours. AEs seen with checkpoint inhibitors are frequently due to immune-mediated mechanisms and can occur in any organ system. The most commonly seen immune-mediated effects include GI effects (e.g. diarrhoea or colitis), pneumonitis, hepatic events, skin rashes and dermatitis and endocrinopathies (including hypo and hyper-thyroidism).

The safety of nivolumab administered as a single agent or in combination with ipilimumab in patients with mCRC was evaluated in the CHECKMATE-142 study (NCT02060188). For single-agent nivolumab, the most frequent SAEs reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common AEs reported in monotherapy (in ≥20% of patients) were fatigue, diarrhoea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.{Overman, 2017 Ref 34}

Immune-mediated AEs that can occur during treatment with nivolumab can be seen weeks or months after discontinuation of treatment. Symptoms of these events will be monitored throughout treatment (e.g. diarrhoea, rash, and neuropathy). Laboratory assessments will check for elevated liver enzymes, kidney and thyroid function, electrolytes, glucose and blood counts.

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the nivolumab prescribing information.

The safety profile of RXC004 in combination with nivolumab is currently being investigated in Module 2. Up to 30th July 2021, three patients had received treatment with a combination of RXC004 1 mg QD and nivolumab 480 mg i.v. Q4W. Eight SAEs were reported in these three patients, all of which were assessed as unrelated to both RXC004 and nivolumab. These were: Grade-2 left-leg weakness and two Grade 2 infections (not otherwise specified) SAEs in one patient; a Grade-3 kidney infection and Grade 3 hepatic pain in another patient; and a Grade-2 hepatic pain and two Grade 3 ascites SAEs in the third patient. One patient discontinued treatment with RXC004 due to an SAE of ascites, NCI CTCAE Grade 3, which was unrelated to RXC004 or nivolumab. No Grade 4/5 events or DLTs have been reported in Module 2 to date.

A modest and predictable safety profile was observed with another porcupine inhibitor, WNT974, in combination with the anti-PD1 agent spartalizumab (NCT01351103) in 32 patients with metastatic solid tumours. All related AEs were Grade 1-2. One Grade 3 related AE of arthralgia was reported. The study authors concluded that the safety profile was consistent with that observed during treatment with either agent as a single agent.{Janku, 2020 Ref 19}

There is the potential for synergistic effect on gut mucosal toxicity for the combination of RXC004 and nivolumab treatment; careful monitoring of GI-related AEs and their sequelae will take place in this potential study module.

1.8 Study Timetable and End of Study

The end of the study is when the last module has been completed (last patient, last visit).

The Sponsor may terminate this study at any time for reasons that include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigators to enter patients at an acceptable rate
- A decision on the part of the Sponsor to modify/suspend or discontinue development of the drug.

1.9 Study Objectives

1.9.1 Primary Objectives

The following primary objective will apply to all modules of the study:

- To assess the safety and tolerability of RXC004 when given to patients with advanced malignances alone or in combination with anti-cancer treatments, and to define the doses and schedules for further clinical evaluation.

1.9.2 Secondary Objectives

The following secondary objectives apply to all modules of the study:

- To characterise the PK profile of RXC004, following a single dose and at steady state after multiple dosing, when given orally alone or in combination with anti-cancer treatments.
- To obtain a preliminary assessment of RXC004 activity by evaluation of pharmcodynamic biomarker changes which may include, but are not limited to, Wnt pathway inhibition, gene expression signatures, and ctDNA levels.
- To obtain a preliminary assessment of the anti-tumour activity of RXC004 as a single agent or in combination with anti-cancer treatments (to include assessment of ORR, DCR, DoR and PFS).

1.9.3 Exploratory Objectives

The following exploratory objectives apply to all modules of the study:

- To obtain a preliminary assessment of RXC004 activity by evaluation of pharmacodynamic biomarkers from blood skin, and tumour, which may include, but are not limited to normal and tumour cell signalling pathway targets and modulation of gene expression, and measures of tumour infiltrating lymphocyte population.
- To explore the relationship between PK and efficacy, safety, and blood borne and tissue biomarkers.
- To collect and store pre-dose plasma and serum sample and/or analyse surplus blood or tissue including patient specific archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease and/or response to RXC004 (where response is defined broadly to include efficacy, tolerability or safety). This may include the analysis of tumour specific and circulating biomarkers, such as tumour DNA, mRNA, proteins or metabolites. In the event that additional tumour molecular profiling is required to understand further any response to RXC004, Redx may request a sample of the most recent tumour biopsy for additional research.
- To investigate predictive markers and acquired resistance to RXC004 that may be observed in tumour from patients treated with RXC004.
- To investigate the per-patient concordance between potential patient selection biomarker (and/or other molecular aberrations) and pharmacodynamic biomarkers as determined either by Redx or local test methods, in comparison to potential patient

selection biomarkers and pharmacodynamic biomarkers levels obtained by central laboratory tests.

- Characterisation in paired tumour biopsies samples of the effect of RXC004 on changes in the tumour microenvironment including but not limited to effects on immune cell subpopulations.

2 SELECTION OF STUDY POPULATION AND RESTRICTIONS

2.1 Inclusion Criteria

2.1.1 Core Inclusion Criteria

For inclusion in all modules of the study, all patients must fulfil all of the following criteria:

1. Ability to give written informed consent prior to any study-specific screening procedures, sampling and analyses; including access to all archival tumour tissue taken within the last 18 months, with the understanding that the consent may be withdrawn by the patient at any time without prejudice
2. Capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures, restrictions (Section 2.3) and has signed and dated the informed consent document
3. Aged at least 18 years at time of screening.
4. Patients must have histological or cytological confirmation of advanced malignancy not considered to be appropriate for further conventional treatment
5. Evaluable disease, either measurable on imaging, or with informative tumour marker(s), as assessed by RECIST 1.1 (Appendix 4) or other relevant response assessment criteria for tumour type. For RECIST 1.1, patients should have at least 1 lesion that qualifies as a RECIST 1.1 target lesion at baseline (within 28 days of the first dose). The use of scans obtained as part of standard clinical practice, prior to informed consent, will be accepted if they comply with RECIST 1.1 criteria and have been performed within the 28-day screening period.
6. Patients must have recovered from toxicities of prior therapies. (i.e. to CTCAE ≤ grade 2) apart from alopecia
7. Eastern Cooperative Oncology Group (ECOG) (Appendix 3) or World Health Organisation (WHO) performance status 0 or 1 with no deterioration over the previous 2 weeks and an estimated life expectancy of greater than 12 weeks
8. Organ Function Requirements - Patients must have adequate organ functions as defined below:

- AST/ALT ≤ 2X ULN (upper limit of normal) [with no underlying Liver Metastasis]
- AST/ALT ≤ 3X ULN [with underlying Liver Metastasis]
- Total Bilirubin within normal range
- Serum Creatinine ≤ 1.5X ULN
- ANC ≥ 1500/μL
- Platelets > 100,000/μL
- Hb >9g/dL

9. Females must be using adequate contraceptive measures, must not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
- Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
- Amenorrhoeic for 12 months and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma oestradiol levels in the postmenopausal range for the institution

10. Ability to swallow and retain oral medication

2.1.2 Inclusion Criteria for Genetics Research

For inclusion in the optional genetics research study patients must fulfil the following criteria:

11. Provision of optional genetics research informed consent

If a patient declines to participate in any optional component of the study, there will be no penalty or loss of benefit to the patient, and they will not be excluded from any other aspect of the main study

2.1.3 Module 3-Specific Inclusion Criteria

For inclusion in Module 3 study patients must also fulfil the following criteria:

12. Patients with Wnt ligand-dependent solid tumours, defined as:
    - Biliary tract cancers
    - Thymus cancers (thymic and thymoma WHO classification)
    - Any solid tumour with documented aberration in RNF43 and/or RSPO from central pre-screening or from a recognised panel approved by the Sponsor. See Section 5.4.2.4 and Appendix 10 for more details

Patients willing to have mandatory skin biopsies at baseline and on one occasion while on study treatment. See schedule of assessments (Appendix 9) for details.

2.2 Exclusion Criteria

2.2.1 Core Exclusion Criteria

For inclusion in all modules of the study, all patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Prior therapy with a compound of the same mechanism of action as RXC004

2. No other anti-cancer therapy, or other investigational product is permitted other than the agent(s) described in the relevant study module.
   - During the study period, patients using allowed hormonal therapy should maintain a constant dose and should not change existing regimen.
   - If a change in hormonal therapy is indicated, e.g. due to intolerable adverse effects, the regimen may be modified but change should be minimized thereafter.
3. Patients with persistent grade 2 or higher diarrhoea (any cause) that has not resolved or improved with appropriate treatment prior to study enrolment
4. Patients at higher risk of bone fractures, including;
   - Patients with bone metastases
   - Patients with β-CTX (bone turnover marker) of > 1000 pg/mL
   - Patients with Vitamin D [25(OH)D_3] deficiency defined as < 30nmol/L (<12ng/mL). [Note - Patients who fail on this criteria **alone** can be retested within the screening window (see Sec 3.4.1.2)]
   - Patients with a corrected total serum calcium level of <2 mmol/L and serum magnesium level of < 0.60 mmol/L
   - Patients with osteoporosis (as defined by a T-score of < -2.5 at L/R total hip, L/R femoral neck, or lumbar spine (L1-4) by DEXA scan) or history of fragility fractures (any fracture occurring with low-level trauma or as a result of falling < standing height and any ≥ grade 2 vertebral fracture on VFA)
   - Patients with a prior diagnosis of hyperparathyroidism, Pagets disease or Osteomalacia, considered to have no increased bone fragility risk, may be included only after consultation with the Sponsor's Medical Monitor.
   - Patients who have received treatment for type 2 Diabetes Mellitus with a Thiazolidinedione peroxisome proliferator-activated receptor gamma agonist (e.g. pioglitazone or rosiglitazone) within 4 weeks prior to study drug dosing.
   - Patients who have received oral or intravenous (i.v.) glucocorticoids for > 4weeks at daily doses equivalent to ≥7.5 mg of oral (p.o.) prednisolone within 6 weeks prior to study drug dosing
5. Patients receiving radiation to more than 30% of the bone marrow, direct radiation to their spine or pelvis, or with a wide field of radiation within 4 weeks of the first dose of study treatment.
6. Female patients who are pregnant or breast-feeding at entry
7. QTcF prolongation (> 470 msec)
8. Patients with any known uncontrolled inter-current illness including ongoing or active clinically significant infections, symptomatic congestive heart failure (with an Ejection Fraction (EF) ≤ 50% or the institutional lower limit of normal whichever is lower), hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
9. Patients with any of the following medications within 4 weeks prior to enrolment:
   - Anti-neoplastic agents

- Immunotherapy (mAbs, Interferons, Cytokines [except GCSF])
- Immunosuppressants (e.g. cyclosporin, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab, etc.).
- Another investigational drug

10. Patients with any known severe allergies (e.g. anaphylaxis) to any active or inactive ingredients in the study drugs

2.2.2 Module 2: RXC004- and Nivolumab-Specific Exclusion Criteria

In addition to the core exclusion criteria, patients must not enter Module 2 if any of the following exclusion criteria are fulfilled:

11. Patients with any contraindication to the use of Nivolumab as per approved county label (Summary of Product Characteristics or equivalent)
12. Patients with active or prior documented autoimmune disorders, drug-induced immune disorders, or inflammatory disorders within the past 5 years, including inflammatory bowel disease, rheumatoid arthritis, immune hepatitis, pneumonitis, Grave's disease, lupus and celiac disease. The following are exceptions to this criterion;
    (a) Patients with vitiligo or alopecia
    (b) Patients with type I diabetes mellitus
    (c) Patients with residual hypothyroidism due to autoimmune condition only requiring hormone replacement
    (d) Patients with psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
    (e) Patients with celiac disease controlled by diet alone
13. Patients with active infections, including tuberculosis, hepatitis B, hepatitis C or human immunodeficiency virus
14. Use of any live vaccines against infectious diseases (eg, influenza nasal formulation, varicella) within 4 weeks (28 days) of initiation of study treatment
15. Patients with body weight <40kg
16. Patients with a history of allogeneic organ transplant or active primary immunodeficiency
17. Patients with a known hypersensitivity to Nivolumab or any of the excipients of the product

2.3 Subject Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

- Patients must fast (water to drink only) from at least 2 hours prior to taking a dose to at least 1-hour post-dose for all doses

- Patients taking RXC004 are advised to avoid exposure to direct sunlight and the use of tanning equipment.

Male patients:

- Men must use a condom (with spermicide) during the study, and for 1 week after the last dose of study drug, with all sexual partners
- Where a sexual partner of a male participant is a WOCBP who is not using effective contraception, men must use a condom (with spermicide) during the study and for 6 months after the last dose of a study drug
- Must not donate sperm for 6 months after the last dose of study drug

Female patients

- Women with evidence of non-child-bearing potential at screening have no restrictions around contraception

  Women of child-bearing potential must use enhanced contraception during the study, and for 6 months after the last dose of study drug, with all male sexual partners. Highly effective methods of contraception must be used, which include having a vasectomised partner, sexual abstinence (defined as refraining from heterosexual intercourse during the study and for 5 months after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated by the Investigator, in relation to the duration of the study and the preferred/usual lifestyle of the patient) or one of the following: hormonal contraceptives which inhibit ovulation (oral, injectable, transdermal, intravaginal or implants), intrauterine device (IUD), intrauterine hormone-releasing system (IUS) (e.g., Mirena), or bilateral tubal occlusion.

2.3.1 Concomitant Treatments

All medications used during the study and taken within 30 days of the screening visit will be recorded on the CRF.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the CRF. If medically feasible, patients taking regular medication should be maintained on it throughout the study period.

Concomitant medication may be given as medically indicated within 30 days prior to administration of the study drug or within 5 half-lives of the chemical entity prior to

administration of the study drug, whichever is longer with the exception of prohibited concomitant medication (see Section Prohibited Concomitant Medication2.3.1.1)

2.3.1.1 Prohibited Concomitant Medication

The following concomitant medication is prohibited without approval from the Sponsor Physician:

- The use of any natural/herbal products or other 'folk remedies' should be discouraged; approval required by Sponsor Physician
- No growth factor support, blood products or prophylactic antibiotics are permitted during the DLT assessment periods in the study. Following this, it may be permitted following discussion with the PI and the Sponsor
- No other chemotherapy, hormonal therapy (HRT and stable treatment of > 6 months with GnRH analogues are acceptable), or other investigational product is permitted other than the combination agent(s) described in the relevant study module
- Live virus and bacterial vaccines should not be administered, e.g. yellow fever, measles, influenza nasal spray, rubella, mumps, typhoid, *Mycobacterium tuberculosis* (BCG), *Yersinia pestis* (EV series) whilst the patient is receiving study medication and during the 28-day follow-up period following IP discontinuation. An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with RXC004 are unknown. The administration of killed vaccines is allowed. Examples of killed vaccines are cholera, bubonic plague, polio, hepatitis A and rabies
- Patients must not receive any other investigational drugs while on this study, other than the combination agent(s) described in the relevant study module
- The use of some CYP3A4 inhibitors and inducers should be restricted throughout the study, as RXC004 is observed to be exclusively metabolised by CYP3A4. For a list of prohibited CYP3A4 inhibitors and inducers please refer to Appendix 7.
- For patients enrolled in Module 2, patients should not receive concurrent immunosuppressive medications. The following exceptions are allowed:
    - Use of immunosuppressive medication for the management of IP-related AEs (as per Appendix 8) or colitis events (as per Appendix 5)
    - Use of topical, inhaled or intranasal corticosteroids.
    - Systemic steroids at doses less than 10 mg/day prednisone equivalent.

2.3.1.2 Allowed medication

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- Opiates may be used for pain control and patients can receive preventive treatment for constipation
- Hormone therapies are allowed for patients who have been identified as a hormone therapy user at the start of the study
- Anticoagulant Therapy: patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.
- Diarrhoea: Diarrhoea should be promptly treated in line with the colitis management and treatment guidelines Appendix 5. Anti-diarrheal agents should not be taken prophylactically.
- Corticosteroids: Patients may receive on-study treatment oral or intravenous (i.v.) glucocorticoids for up to 4 weeks (at daily doses equivalent to ≤10 mg of oral (p.o.) prednisolone). If steroids are required for treatment of colitis (as per Appendix 5), then study treatment should be held until steroids are tapered to ≤10mg per day prednisone or equivalent. . Patients enrolled on Module 2 (RXC004 and nivolumab) may also receive treatment with steroids for immune-mediated AEs (as per Appendix 8. Steroids should be tapered to ≤10 mg/day prednisone or equivalent before re-starting nivolumab. Patients who require treatment with ≥10mg per day prednisone or equivalent for >8 weeks should permanently discontinue study treatment (RXC004 and nivolumab if applicable).
- Patients may receive immunosuppressant (e.g. infliximab for colitis or mycophenolate for hepatitis) rescue medication required for colitis (as per Appendix 5) or nivolumab related immune mediated adverse events (as per Appendix 8). Steroid refractory patients that require immunosuppressant treatment should permanently discontinue study treatment (RXC004 and nivolumab if applicable).
- Nausea/vomiting: Anti-emetic treatment can be administered if required according to the guidelines of the participating centres, except for the first dose each patient takes. Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic anti-emetic therapy.
- According to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- Anaemia: Transfusions may be used as clinically indicated for the treatment of anaemia, but should be clearly noted as concurrent medications.
- Neutropenia: Colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional Standards are allowed after the first cycle of therapy, following discussion with the PI and the Sponsor physician.

- Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study treatment is started. Prophylactic erythropoietin should not be started during the DLT period but may be started during Cycle 2 and after, following discussion with the PI and Sponsor physician.

2.3.1.3 Subsequent Therapies for Cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PORCN/Wnt pathway inhibitors or investigational drugs will be collected and included in the exploratory assessments.

2.3.1.4 COVID-19 Vaccinations

COVID-19 vaccination is permitted before or during study treatment, with the exception of live-attenuated vaccines and replication-competent vector vaccines, which are prohibited within 4 weeks of starting study treatment and whilst on study treatment.

As COVID-19 vaccines are often prioritised for cancer patients, vaccination prior to the first dose of study treatment is advisable. Where possible, COVID-19 vaccinations should be given at least 72 hours before starting study treatment and study treatment should not commence until any acute AEs from vaccination have resolved to at least Grade 1. If this is not possible, Investigators should follow their local prescribing information and policies when considering whether a patient on study treatment should receive a COVID-19 vaccination. If COVID-19 vaccination is given during the study (including the screening period), then all relevant information should be recorded in the concomitant medication CRF (i.e. vaccine name, manufacturer, date(s) given and dose).

3 STUDY TREATMENT, CONDUCT, WITHDRAWAL – CORE

3.1 Study Treatment

Module-specific study treatment details are outlined in Section 5.2 (Module 1) Section 5.3 (Module 2) and Section 5.4 (Module 3).

Additional modules may be added at a later date (following a protocol amendment) to investigate combinations with anti-cancer treatments, and to investigate the effects of dosing with and without food on RXC004 PK parameters. RXC004 will be given as a flat dose at each dose level, based on a 60 Kg patient. Eligible participants will be enrolled in sequential cohorts treated with study treatment, while being monitored for safety and DLTs.

During the dose escalation, patients will receive a single dose on the first day of doing (Cycle 0, Day 1) followed by a washout of 6-10 days for the assessment of PK, then once daily (Modules 1 and 2) or scheduled (Module 3) dosing from Cycle 1 onwards. Patients may continue to receive the study treatment until progression, unacceptable toxicity or withdrawal. Dose levels will not be weight adjusted.

3.1.1 Starting Dose (Module 1) for Study Re-start

On 29th March 2018, recruitment in clinical study RXC004/001 was temporarily halted, following clinically significant AEs observed in the first patient dosed, assessed as related to RXC004 on-target effects and Wnt pathway inhibition. Analysis of the PK data from Patient 001/001 indicated that systemic RXC004 exposure was significantly higher than that predicted from pre-clinical studies. Following manufacture of lower doses of RXC004 and inclusion of additional safety measures to the study protocol, RXC004 was restarted at 0.5 mg which was based on several considerations including:

- Clinical PK observed in Patient 001/001
- Cover required to cause tumour growth inhibition in pre-clinical cancer models
- Exposure over IC_{50} achieved by competitor PORCN inhibitors in their reported Phase1 studies

3.1.1.1 Clinical PK/Pharmacodynamics

The PK for Patient 001/001 showed that the maximum plasma concentration (C_{max}) was in line with expectations but the terminal half-life ($T_{1/2}$) was significantly longer than predicted, due to the evidence of biphasic PK resulting in a long elimination phase and a significantly higher C_{min} than expected. The calculated $T_{1/2}$ was approximately 20 h following multiple doses to steady state. This contributed to an approximately 3-fold accumulation of AUC at steady state and an approximately 50-fold increase in C_{min} compared to the prediction from modelling. The

expected $T_{1/2}$ was previously predicted using modelling in a one-compartment analysis and was calculated to be 3.5 h. Additionally, RXC004 reduced AXIN2 mRNA expression in the skin of Patient 001/001 to approximately 19% of the baseline measurement on Day 8 of Cycle 1, indicating significant Wnt pathway inhibition. The patient was not taking any concomitant medication expected to have caused a DDI with RXC004.
Emerging data show that the exposures achieved in patients dosed with 0.5–2.0 mg are broadly dose proportional and predictable from the exposure observed in the patient dosed at 10 mg in terms of half-life, Cmax, Cmin and AUC, with accumulation at steady state in line with the measured half-life (range of 8-16 h after a single dose). Pathway engagement, inhibition of AXIN2 in patient skin biopsies has also been confirmed in all dose cohorts tested.
Additional PK sample times at later time-points up to 96 h have been included in the study protocol (see Table 10) in Cycle 0, to more accurately determine the half-life of RXC004 in patients.
PK samples will be analysed for each patient before commencing continuous dosing (Cycle 1), until Redx judges that the human PK parameters for RXC004 are reliably established. In the event of the C_{min} value being outside the expected tolerated range, a different dosing schedule at the same dose (e.g. 0. 5mg QD dosing) will be considered. If the C_{min} is within the expected tolerated range and the dose is clinically tolerated, Redx will plan to initially increase the dose to 1 mg QD and be led by the emerging data and SRC for all further dose escalations.

3.1.1.2 Free-Drug Exposure Required for Efficacy in Pre-clinical Studies

The proposed new starting dose of 0.5 mg QD (or a dose and schedule that provides equivalent exposure) should provide free exposure of approximately 2 times the pharmacological IC_{50} over the dosing interval, based on the PK from Patient 001/001 and assuming dose linearity. This C_{min} cover is a similar starting point to the cover originally expected for the 10 mg dose based on original predictions from preclinical species and *in vitro* assays (Capan-2 proliferation IC_{50}).
In pre-clinical models of cancer, RXC004 has achieved significant tumour-growth inhibition with the free exposure range of 1 x IC_{50} C_{min} to 10 x IC_{50} C_{min}. The proposed starting dose should be within this range of C_{min} exposures and thus we expect to deliver potential patient benefit.

3.1.1.3 Free Exposure over IC_{50} Achieved by Competitor PORCN Inhibitors

The Novartis PORCN inhibitor WNT974 has been dosed in patients between 5 mg QD and 30 mg QD {Janku, 2020 Ref 19} These doses of WNT974 produce free exposure at C_{min} of between 3 x and 24 x the pharmacological IC_{50} of the compound and additionally a higher C_{max} and AUC than expected for RXC004 0.5 mg. WNT974 was well tolerated in this study and did not reach an MTD.
The A-Star PORCN inhibitor ETC-159 has been dosed at a range of 1–30 mg QOD in an ongoing Phase 1a/b clinical trial. Phase 1a has completed.{Ng, 2017 Ref 30} ETC-159 has

an MTD defined as 30 mg QOD (C_{min} free exposure >50 x IC_{50}), two of five patients dosed at 30 mg experienced fragility fractures while no fractures were observed at any of the lower doses. A dose of 16 mg QOD (C_{min} free exposure ~20 x IC_{50}) has been selected for evaluation in Phase 1b.
By modelling the published PK data with both ETC-159 and WNT974 we have demonstrated that RXC004 dosed at 0.5 mg, will result in significantly less exposure than both ETC159 at 16mg and WNT974 at 10 mg, both of which were tolerated doses in man.

The starting dose/schedule of further modules will be the decision of the SRC based on emerging safety and tolerability data, however, will not exceed the equivalent maximum exposure found to be tolerated in Module 1 at that point. Dose increments will be guided by safety data observed during Cycle 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and pharmacodynamic data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of treatment.

Based on emerging data, including available biomarker data and/or safety data and/or pre-clinical data, the SRC may consider alternative treatment schedules or dose intervals (for example, twice daily dosing or intermittent treatment), in consultation with the Sponsor. Please refer to the IB and relevant study protocol module for further details.

3.1.2 Dose Escalation Scheme (Modules 1 and 2)

RXC004 starting dose and dose-escalation plans for Module 1 are in Section 5.2. The details for the starting dose of RXC004 in combination with nivolumab and dose-escalation plans are in Section 5.3.
Dose, frequency and schedule in subsequent cohorts may increase or decrease in response to safety, tolerability, PK and emerging non-clinical data.
There will be no intra-patient dose escalations.

Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of study treatment. Dose escalation and de-escalation will follow a standard '3+3' scheme for Modules 1 and 2. There will be no dose escalations in Module 3. If no DLT is observed in a cohort, then dose escalation may occur.

Cohort Expansion

If one patient experiences a DLT in a group of 3 or more evaluable patients, then the cohort will be expanded to include 6 evaluable patients. Note: cohort expansion to more than 3 patients per cohort ($\geq$ 4 patients) may occur also if more than 3 patients are screened in a single cohort and are deemed eligible; in such cases dose escalation to the next higher dose will not occur until all patients (e.g. 3 or 4 patients) have completed the DLT assessment period with no DLT observed. If only one DLT is observed in the complete cohort of 6 evaluable patients, then dose escalation may occur, once all patients in the expanded cohort have completed their first cycle of treatment with RXC004. If 2 or more patients experience a DLT in a group of up

to 6 evaluable patients (including those in the dose expansion arms), irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower, intermediate dose (de-escalation) may be considered in order to better define the MTD.

The highest dose where ≤ 1 DLT is seen in 6 patients will be termed the MTD.

If a patient becomes unevaluable following dose administration they may be replaced, if required, to ensure at least 3 patients are evaluable for an assessment of safety and tolerability at that dose. There will be no minimum time period required between completion of dosing in the last evaluable patient from one cohort and the start of dosing in the subsequent cohort.

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability and pharmacokinetics of RXC004 to decide the next dose and/or schedule.

3.1.3 Definition of Maximum Tolerated Dose (Modules 1 and 2)

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD may be confirmed at the previous dose-level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated.

Definition of Evaluable Patient for Modules 1 and 2

For decisions on dose escalation, an evaluable patient is defined as a patient who has received study treatment and either:

- Has completed minimum safety evaluation requirements and has received 100% of the specified RXC004 dose in Cycle 0 and at least 66% of the intended dose of RXC004 during Cycle 1 (Patients in Module 2 must also receive 100% of the nivolumab infusion on Cycle 1 Day 1)
- Has experienced a DLT during Cycle 0 and/ or Cycle 1

Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

3.1.4 Definition of Maximum Feasible Dose (Modules 1 and 2)

A dose and schedule will be considered non-feasible and escalation will cease where PK parameters determine that a maximum absorbable dose has been reached, or where a formulation that would allow administration of RXC004 in a reasonable number of capsules of an acceptable size is not achievable.

3.1.5 Definition of MBAD (Modules 1 and 2)

- A biologically relevant PK exposure (i.e. dose predicted to sustain free plasma concentration >IC_{50}). The estimated biologically relevant PK exposure is calculated to be achieved by a dose of 0.5 mg QD;

And/or

- Biomarker (AXIN2) target engagement in either normal or tumour tissue;

And/or

- Clinical response (RECIST 1.1).

3.2 Safety Review Committee

Following the completion of each dose escalation cohort of Modules 1 and 2, the SRC will meet by telephone to evaluate the safety and tolerability and, where available, PK and pharmacodynamic of RXC004 to decide the next dose and/or schedule. Any dose interruptions and reductions will be taken into account. AEs occurring in Cycle 2 and beyond which meet the definition of a DLT or are considered clinically significant may also be considered in making dose escalation decisions (refer to RXC004 Safety Review Committee Remit, which has been provided as a separate document). Other AEs, or possible trends in AEs, during the dose escalation phase may inform dose escalation decisions.

The SRC will consist of the following:

- Principal Investigator or delegate
- IQVIA Project Manager, who will chair the committee, or delegate
- Redx Chief Medical Officer
- Redx Project Manager
- Investigator or delegate from other investigational sites

The Clinical Pharmacology Scientists, Study Statisticians, Pharmacovigilance representatives, Study Leaders and other Sponsor and non-Sponsor technical experts may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who should be present for decisions to be made. Further Sponsor or non-Sponsor experts may be consulted by the SRC as necessary.

The SRC decisions may be to:

- Proceed with dose escalation either to next defined dose escalation step or justify the rationale for reduced escalation step based on available safety, PK and pharmacodynamic data
- Expand the cohort to a maximum of 6 evaluable patients

- De-escalate the dose of RXC004 either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Stop the dose escalation part of a study module
- Adjust the dosing frequency/schedule/sequence of RXC004, with or without a concurrent change in dose
- Advise on any adjustment to study assessment time points e.g. PK sampling, based on data available during the trial and protocolled limit on blood volumes and number of samples permissible in a given period.

Following establishment of the monotherapy dose in Module 1 (MBAD/ MTD/ MFD), the SRC decisions may be to:

- Confirm the MTD, MFD, and/or MBAD
- Advise on (and approve where appropriate) required pre-medication
- Advise on any adjustment to study assessment time points e.g. PK sampling, based on data available during the trial and protocolled limit on blood volumes and number of samples permissible in a given period.

When there are other patients who are ongoing within a cohort at the time of a review, the SRC may decide to defer their decision until data from these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation. The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

3.3 Dose Modifications and Individual Stopping Criteria

The module specific dose modification guidelines and individual stopping criteria in found in Section 5.2 (Module 1) Section 5.3 (Module 2), and Section 5.4 (Module 3) respectively.

3.4 Adverse Event Management Plan

3.4.1 Bone Management plan (All Modules)

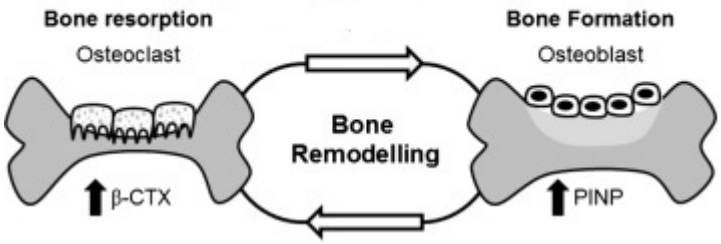
Bone Metabolism Overview

Bone is a metabolically active structure which undergoes continuous remodelling throughout life.{Crockett, 2011 Ref 5} After attaining peak bone mass, bone undergoes constant remodelling through bone resorption followed by formation sequentially by a basic multicellular unit of bone called a “bone remodelling unit”. Various biomolecules, released

into the circulation during bone resorption and formation, are called bone turnover markers (BTMs). Under optimal physiological conditions, bone resorption takes place in around 10 days.

Figure 3 Bone Remodeling Schematic

Schematic representation of the bone remodelling cycle, increased bone resorption is accompanied by an increases in β-CTX.



The BTMs are grouped into two categories based on the metabolic phase during which they are produced as:

- Bone formation markers
- Bone resorption markers

N-terminal propeptide of type 1 collagen (P1NP) is a recognised by the International Osteoporosis Foundation (IOF) as a bone formation marker, in view of its predictable response to treatment and the reliability of P1NP assays as evidenced by low intra-individual variability, smaller circadian variation, stability at room temperature, and a good assay precision. C-terminal telopeptides of type 1 collagen (CTX-1) are degradation products of Type 1 collagen of bone generated by the activity of the enzyme cathepsin K. The native CTX exists in two forms, α and β isomerised forms, with the latter being released from the resorption of mature bone.

Serum β–CTX is a well-characterised, established biochemical marker of bone resorption and is recommended in guidelines and advice from authorities such as the International Federation of Clinical Chemistry and the International Osteoporosis Foundation.{Vasikaran, 2018 Ref 46;Johansson, 2014 Ref 20;Vasikaran, 2011 Ref 44} While it is recognised that increased bone resorption is associated with increased fracture risk, the relationship in prospective studies is a relatively weak one and there is no internationally validated thresholds or criteria that identify a high risk of fracture. A number of studies have recently derived reference intervals for β–CTX and a proposed threshold of 1000 pg/ml is comparable to the upper limit in a number of

these studies.{Vasikaran, 2014 Ref 45;Michelsen, 2013 Ref 27;Gossiel, 2014 Ref 12} Currently in this study all patients are required to have a β–CTX level of <1,000 pg/mL to be eligible to receive RXC004. All eligible patients will receive prophylactic denosumab (Anti-RANKL antibody) to minimise bone mineral density loss.

The revised dose escalation range of 0.5–3.0 mg daily is expected to result in exposure levels lower than those observed at tolerated doses of WNT974 and ETC-159 (10 mg and 16 mg respectively; levels at which no fractures were reported).
To further reduce the potential for bone effects Redx will ensure that all patients receive calcium and vitamin D supplementation [vitamin D3 (cholecalciferol)]. In recognition of the fact that increased bone resorption is currently a potentially reversible effect of RXC004 at higher exposures, Redx will introduce treatment with denosumab in patients showing significant increases in β-CTX (increase of ≥350 pg/mL β-CTX from baseline or to a level above 1,000 pg/mL).

3.4.1.1 Exclusion of Patients at High Risk of Bone Fractures

The following patients are deemed to be at high risk of bone fractures and will be excluded from the study:

- Patients with bone metastases
- Patients with osteoporosis (as defined by a T-score of < -2.5 at L/R total hip, L/R femoral neck, or lumbar spine (L1-4) by DXA scan) or history of fragility fractures (any fracture occurring with low-level trauma or as a result of falling ≤ standing height)
- Patients with a β-CTX (bone turnover marker) of > 1000 pg/ml
- Patients with Vitamin D [25(OH)D_3] deficiency defined as < 30nmol/L (<12ng/mL)
- Patients with history of hyperparathyroidism, Paget's disease or Osteomalacia
- Patients with a corrected total serum calcium level of <2 mmol/L and serum magnesium level of < 0.60 mmol/L
- Patients who have received treatment for type 2 Diabetes Mellitus with a Thiazolidinedione peroxisome proliferator-activated receptor gamma agonist (e.g. pioglitazone or rosiglitazone) within 4 weeks prior to study drug dosing
- Patients who have received oral or intravenous (i.v.) glucocorticoids for ≥ 4 weeks at daily doses ≥ 7.5 mg of oral (p.o.) prednisolone (or equivalent) within 12 weeks prior to study drug dosing

3.4.1.2 Prophylactic Supplements

The following supplements should be started at screening and continue throughout the RXC004 treatment

- Vitamin D supplements 800 IU daily
- Calcium supplements 1000-1500 mg daily

Vitamin D3 (cholecalciferol) should be used as it is thought to be a more effective supplement.

Patient who fail screening due solely to 25 (OH)D3 level <12 ng/mL (30 nmol/L) should be given a single dose of oral cholecalciferol 300,000 IU and the levels rechecked approximately 3 weeks later (and within the 28-day screening window)

Those with values >12 ng/ml can then enter the study if all other entry criteria are fulfilled and will receive the long term prophylactic daily cholecalciferol 800 IU as maintenance throughout the study treatment period.

All patients will receive prophylactic denosumab (120 mg s.c. QM) along with vitamin D3 (cholecalciferol 800 IU QD) and calcium (1000-1500 mg QD) supplements from the time of signing the ICF and throughout the- RXC004 treatment.

3.4.1.3 Monitoring of Blood-Bone Turnover Markers and BMD

BMD

Osteoporosis and osteopenia are defined based on assessment of BMD using DEXA scan, with osteoporosis defined as a T-score of < 2.5 SD and osteopenia as a T-score of <- 1 and > -2.5 SD. However, BMD has low sensitivity with osteoporotic fractures occurring in both osteoporotic and osteopenic individuals.
BMD will be assessed by DEXA scan at Screening, Cycle 2, and every 3 cycles from Cycle 4 onwards i.e. Cycles 4, 7, 10 etc).

In addition to a baseline (pre-treatment) DEXA scan all patients will have a vertebral fracture assessment (VFA) scan (a lateral T & L spine assessment if a VFA cannot be performed locally) to document any asymptomatic moderate/severe vertebral fractures which occur in a significant minority of patients aged 50 years or older. .{O'Neill, 1996 Ref 33} Patients who have an asymptomatic, mild (Grade 1) vertebral fracture but who fulfil all inclusion/exclusion criteria will not be excluded from study.{Johansson, 2014 Ref 20}

Blood-bone turnover biomarkers

Blood samples for monitoring of the bone turnover markers beta C-terminal telopeptide of type 1 collagen (β-CTX) and P1NP will be routinely collected for patients.

Bone turnover biomarkers will be collected* at the timepoints detailed in the Schedule of assessments (Appendix 1 for Module 1, Appendix 2 for Module 2 and Appendix 9 for Module 3)

*note that due to circadian variations and effects of food intake on CTX measurements, β –CTX samples will be collected in the morning after an overnight fast.

The major benefit of using biochemical markers is that treatment induced changes occur much earlier than DEXA measured BMD, and the magnitude of the changes are usually much greater (i.e. a greater signal to noise ratio) than those detected by BMD. Therefore, serum β –CTX levels will be routinely monitored as a resorption marker. Samples will also be stored for subsequent measurement of other bone markers (e.g. P1NP) if indicated, during or at the end of the study.

3.4.1.4 Intervention Measures for Patients with Increased Bone-Fracture Risk on RXC004 Treatment

The interventions detailed in Table 2 should be followed for all patients on RXC004 study treatment, in the event of increased bone fracture risk.

Patients with a DEXA scan showing ≥7% worsening in BMD at lumbar spine or total hip compared to baseline will permanently discontinue study treatment. The change in BMD that can be confidently detected is termed the least significant change (LSC). A 7% decrease in BMD is approximately the 99% confidence limit for LSC and is considered as an indicator of failure to respond to treatment.{Diez-Perez, 2012 Ref 7}.

Prophylactic denosumab (XGEVA™ - 120 mg s.c. QM per approved label for prevention of skeletal-related events (SREs) in patients with bone metastases) will be administered to all patients (from the 1.5mg RXC004 monotherapy Module 1, Cohort 3). This denosumab dose and schedule is being adopted to maximise bone safety. Patients with advanced/metastatic malignancies are at potential increased risk of bone fragility if treated with a porcupine inhibitor such as RXC004. In addition, while patients with bone metastases are excluded from the protocol currently it is the intention (based on safety data and appropriate expert and regulatory review and approval) to administer RXC004 to patients with bone metastases as part of the RXC004 development programme as a significant minority of patients with metastatic disease will have bone metastases). The XGEVA™ approved dose and schedule of denosumab will be used in all patients both to maximize bone safety and allow a uniform and accurate assessment of denosumab use in combination with RXC004. Denosumab, as it is a more potent inhibitor of bone resorption compared to bisphosphonates, leads to greater increases in bone mineral density.{Miller, 2016 Ref 28}

Prophylactic use of denosumab was not adopted from start of study treatment as the significantly lower starting dose of RXC004 0.5mg (previously this was 10 mg) and the other bone protection measures reduced the potential for bone toxicity. However, as a significant number of patients (3 of 6) required denosumab treatment by the end of Cycle 1 based on reaching protocol-defined increases in β-CTX levels indicative of increasing risk of bone fragility, prophylactic denosumab is now administered to all patients (from the 1.5 mg RXC004 monotherapy cohort) based on a review of the data and advice by an independent expert in bone metabolism.

Table 2 Interventions for patients with increasing bone fracture risk

Event	Intervention
Confirmed RXC004 related fragility bone fracture	• Permanently discontinue study treatment
Patients with a DEXA scan showing ≥ 7% worsening in BMD at lumbar spine or total hip compared to baseline	• Permanently discontinue study treatment
An individual increase in β-CTX of ≥350 pg/mL from baseline (screening) and/or an individual measurement ≥1000 pg/mL β-CTX	• If serum β-CTX > 1,000 pg/mL or ≥350 pg/mL higher than the baseline level - permanently discontinue study treatment unless the patient has received clinical benefit (Investigator assessment) and continued treatment is warranted.

3.4.2 Diarrhoea/Colitis Management and Treatment Guidelines

Please refer to Appendix 5, for the treatment of diarrhoea/colitis for patients enrolled in all Modules

3.4.3 Nivolumab Toxicity Management and Dose Modification (for Module 2 patients)

Guidelines for the management of immune-mediated reactions and infusion-related reactions, for patients treated with nivolumab therapy (Module 2 – RXC004 + nivolumab combination) are provided in the Nivolumab Toxicity Management and Dose Modification guidelines (Appendix 8)

3.5 Treatment Compliance and Accountability

Study drug administration must be performed by study site staff and documented in source documents and the CRF.

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

At each visit, prior to dispensing study medication, previously dispensed study medication will be retrieved by the Investigator and compliance assessed. Subjects exhibiting poor compliance as assessed by capsule counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of RXC004 study medication during any evaluation period (visit to visit) or less than 100% of nivolumab at each infusion.

3.5.1 Treatment Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study medication supplies and packaging materials are to be inventoried and returned to IQVIA by the Investigator. The Investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by IQVIA.

3.6 Subject Withdrawal

Patients may withdraw from any aspects of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events requiring permanent discontinue as detailed in Table 4
- Severe non-compliance to this protocol as judged by the Investigator and/or Sponsor
- Confirmed disease progression
- Patients incorrectly initiated on investigational product

- Life threatening or other unacceptable toxicity
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Lack of evaluable and/or complete data
- Decision to modify the development plan of the drug
- A decision on the part of the Sponsor to suspend or discontinue development of the drug
- Extraordinary medical circumstances: Subject who, in the opinion of the Investigator should be discontinued for their well-being or if at any time the treatments prescribed by this protocol are detrimental to the subject's health, the subject may be withdrawn from the study. In this event, reasons for withdrawal should be clearly documented on the case report form (CRF).
- If subject becomes pregnant during the treatment period

Any patient who permanently discontinues investigational product should be followed up for at least 28 days and until disease progression.

Procedures for handling patients incorrectly initiated on investigational product:

Patients who do not meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the inclusion/exclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the Study Physician immediately.

Any patient who is found to have failed to comply with all the selection criteria, but has not started treatment, will be removed from the study following completion of safety follow-up activities.

Any patient started on treatment in error, as he/she has subsequently been found to have failed to comply with all the selection criteria, will undergo a risk/benefit assessment by the SRC; if the patient is judged to be receiving clinical benefit, the investigator may choose to continue to dose them with the investigational drug.

Every effort should be made to keep all patients, whether eligible or ineligible, in the study until completion of safety follow-up activities.

The Study Physician is to ensure all such contacts are appropriately documented.

4 SAFETY – CORE

4.1 Definitions of Adverse Events and Serious Adverse Events

The Investigator is responsible for recording all AEs observed during the study (from time of signed consent, washout, treatment, and follow-up) period.

Definition of AE: An AE is any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Treatment-emergent adverse events: An AE occurring after dosing and within 30 days of last dose.

Definition of Serious Adverse Event (SAE): An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death.
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospitalizations are defined as initial or prolonged admissions that include an overnight stay. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event is not an SAE. Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g. neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose. An Unexpected Adverse Drug Reaction is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Severity

The severity of the AE will be characterized as "mild, moderate or severe" according to the following definitions:

- Mild (Grade 1) events are usually transient and do not interfere with the subject's daily activities.
- Moderate (Grade 2) events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe (Grade 3) events interrupt the subject's usual daily activity.
- Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated.
- Death (Grade 5) related to AE.

Relationship

The causal relationship between the study medication and the AE has to be characterized as unrelated, unlikely, possible, probable or unknown (unable to judge).

Events can be classified as "unrelated" if there is not a reasonable possibility that the study medication caused the AE. An "unlikely" relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.

A "possible" relationship suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.

A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient, in diary or reported in response to the open-ended and non-leading verbal questioning from the study personnel (e.g., "How are you feeling?" "Have you had any health problems since the previous visit/you were last asked?"), or revealed by observation will be collected and recorded in the CRF. When collecting AEs, it is preferred to record the diagnoses (when possible) instead of recording a list of signs and

symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events Based on Examinations and Tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product unless clearly due to progression of disease under study (see Disease progression).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

COVID-19 Infections

COVID-19 infections occurring from main study ICF until 30 days after discontinuation of study treatment should be reported as adverse events. Patients who test positive for COVID-19, but do not have any symptoms should be reported as 'asymptomatic COVID-19'. If COVID-19 is suspected but not confirmed by a diagnostic test, then 'suspected COVID-19' should be reported. The AE term for the 'suspected COVID-19' should be updated when the results of the diagnostic test are known to reflect the confirmed COVID-19 or alternative diagnosis (e.g. common cold, influenza etc).

Taste Disturbances

Loss or altered taste (dysgeusia) is an on-target AE known to occur with porcupine inhibition (Ref 30, Ref 18). According to CTCAE v5, there are only two grades of dysgeusia:

Grade 1 - Altered taste but no change in diet

Grade 2 - Altered taste with change in diet (e.g. oral supplements); noxious or unpleasant taste; loss of taste.

As dysgeusia is poorly characterised by CTCAE grade alone, site research personnel will complete a taste assessment (consisting of a specific set of questions and an oral examination) at screening for each patient enrolled in Module 3, and for any patient in Module 3 who reports dysgeusia in response to the open question from the study site staff;

'Have you had any health problems since the previous visit/you were last asked?'

In such cases, the assessment will be performed at each visit until the AE has resolved. The information will be recorded and analysed as part of the overall safety objective of the study.

4.2 Reporting of Adverse Events, Serious Adverse Events and Dose Limiting Toxicities

TEAEs reported during the study will be coded using a Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidence of treatment-emergent adverse events will be summarised by disease and cohort and the following:

- System organ class and preferred term
- System organ class, preferred term and severity

These summaries will be presented for the following subsets:

- SAEs
- All AEs
- Drug-related AEs
- AEs leading to treatment discontinuation

For tables reporting AEs by severity, if a patient has multiple occurrences of an AE with the same organ class and preferred term, the most severe event will be presented.

All SAEs will be recorded on the SAE Report form, the Adverse Events form in the CRF, and source documents. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

All SAEs that are spontaneously reported within 30 days of a patient's last dose of RXC004 (for Module 1) or 90 days of a patient's last dose of nivolumab (for Module 2) are to be collected and reported as previously described.

The original CRF pages should be returned immediately to the CRF binder. The information must include at least the following:

- Name, address and telephone number of the reporting Investigator.
- Investigational product and study code.
- Patient identification number, sex and age at study entry.
- Description of the AE, measures taken and outcome.
- Preliminary classification of causal relationship by the Investigator.

The Principal Investigator (or designee) will notify IQVIA within 24 hours of identifying a DLT or SAE, whether related or unrelated to investigational drug, see Section 3.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor or IQVIA and the original placed in the SAE section of the CRF binder.

4.2.1 Reporting of SAEs and Suspected Unexpected Serious AEs to Regulatory Authorities, Ethics Committees and Investigators

In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the delegated CRO is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the regulatory authorities and Independent Ethics Committees / Institution Review Boards (IEC/ IRB) according to local laws and regulations. All investigators participating in clinical studies with the study medication will receive copies of these reports - Council for International Organisations of Medical Sciences (CIOMS) for prompt submission to their local institution / regulatory bodies. Other SAEs (i.e. expected or unrelated SAEs) should be reported per the relevant institution’s procedures. Investigators should provide written documentation of notification for each report to IQVIA.

Until such time that an AE is included in the IB reference safety information, it should be considered unexpected, regardless of whether the AE has been the subject of a previous Safety Update. All expectedness assessments will be made by the Sponsor or designee.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are required to be reported within 7 calendar days for life-threatening events and those resulting in death, or 15 calendar days for all others. These timeframes begin with the first notification of the SUSAR to IQVIA or Redx from the Investigator.

4.2.2 Follow-Up of Adverse Events

Any AEs observed from the time of consent/randomisation up to the end of the study will be followed up to resolution. Resolution means that the patient has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs that occur after the patient completed a clinical study should also be reported to IQVIA Clinical within 30 days of the last dose of study drug.

4.3 Medical Emergencies and Sponsor Contacts

4.3.1 Safety Reporting and Medical Management

Following the completion of each dose-escalation cohort of Modules 1 and 2, the SRC will meet to evaluate the safety and tolerability and, where available, PK of RXC004 to decide the next dose and/or schedule as previously discussed in SRC Section 3.2. Dose interruptions and reductions will be taken into account. AEs occurring in Cycle 2 and beyond which meet the definition of a DLT or are considered clinically significant may also be considered in making dose escalation decisions. Other AEs, or possible trends in AEs, during the dose escalation phase may inform on dose escalation.

4.3.2 Emergency Sponsor Contact

In emergency situations, the Investigator or designee should contact the Sponsor's study contact:

4.3.3 Overdose

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly. There are no data regarding RXC004 overdose in humans. An overdose and AEs should be treated per standard medical practice.

Dosing details should be captured in the CRF. If the patient receives a dose of a study drug that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as AEs in the CRF and, if serious, submitted to the Sponsor's designated safety contact on an SAE Report Form. Do not record the overdose as an AE if the patient is not symptomatic.

4.3.4 Pregnancy

A Pregnancy Report Form (or equivalent) must be completed for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) received, including any pregnancies that occur in the female partner of a male study patient. Additionally, all pregnancies should be reported that occur in a male patient's partner if the estimated date of conception occurred after the male patient's first dose of study drug. The form must be transmitted to the Drug Safety Department of IQVIA within 48 hours of becoming aware of the pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks after their delivery.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded as an AE. Abortion (whether spontaneous, therapeutic, or planned) should be reported as an SAE. Congenital anomalies or birth defects should be reported as SAEs.

5 STUDY DESIGN

5.1 Introduction

The study is a modular Phase 1, dose-escalation, open-label study to assess the safety, tolerability, PK and preliminary anti-tumour activity of RXC004 in monotherapy and in combination in patients with advanced malignancies.

The study started with the RXC004 monotherapy module (Module 1, a monotherapy dose escalation to identify the minimum biologically active dose (MBAD), maximum tolerated dose (MTD) or maximum feasible dose (MFD), in multiple patient cohorts. Module 2 was added with protocol amendment v5, a RXC004 and nivolumab combination dose escalation to identify the MTD or MFD of RXC004 in combination with nivolumab.

Module 3 will determine whether RXC004 2 mg QD monotherapy intermittent schedules are safe/tolerated. This Module will initially start with two Arms – RXC004 2 mg QD taken for 4 days, followed by 3 days off, repeated weekly for 21-day cycles (Arm 1) and RXC004 2 mg QD taken for 2 weeks, followed by 1 week off (Arm 2).The option to start further modules will be the decision of the SRC, based on emerging pre-clinical data and, safety and tolerability information from the initial module. A substantial protocol amendment with relevant preclinical and clinical data will be put in place before starting any further modules.

The dose escalation and dose escalation cohort size and the stopping criteria for Modules 1 and 2 are based upon accepted methodologies for Phase 1 oncology studies. Module 3 has a single cohort for each intermittent schedule.

5.2 Module 1 – RXC004 Monotherapy

The reason for conducting this study module is to provide the first cancer patient safety and tolerability data with RXC004.

Treatment, conduct, and withdrawal, which include starting dose and the dose escalation scheme, can be found in Section 3.1.2

Module 1 will commence by enrolling patients with advanced solid tumours into a SAD/MAD monotherapy dose-escalation arm. Eligible participants will be enrolled in sequential cohorts treated with RXC004 given as an oral capsule dose while being monitored for safety and DLTs.

Dose levels will not be weight-adjusted and the starting dose for the study will be RXC004 0.5 mg QD on Days 1-21 inclusive (for Cycle 1 and subsequent cycles). Dose increments will be guided by safety data observed during Cycle 1, as well as on-going assessment of safety beyond

Cycle 1 in earlier cohorts, plus PK and pharmacodynamic data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 or Cycle 1 of treatment. Patients will receive a single dose of RXC004 (Cycle 0) followed by a washout period (6-10 days) before receiving 21 continuous days dosing of RXC004 capsules (refer to Figure 4).

Module 1 will evaluate the safety and tolerability of RXC004 as monotherapy to provide dose(s) and schedules(s) for further modules, each evaluating the safety and tolerability of a specific combination agent. Module 1 will also provide preliminary efficacy readouts.

5.2.1 Module 1: Study Objectives

The study objectives are detailed in Section 1.9

5.2.2 Module 1 Eligibility Criteria

5.2.2.1 Module 1-Specific Inclusion Criteria

There are no Module 1-specific inclusion criteria. Patients must fulfill all of the core inclusion criteria in order to be eligible to receive study treatment in Module 1. The core inclusion criteria are detailed in Section 2.1.1

5.2.2.2 Module 1-Specific Exclusion Criteria

There are no Module 1-specific exclusion criteria. Patients must not meet any of the core exclusion criteria in order to be eligible to receive study treatment in Module 1. The core exclusion criteria are detailed in Section 2.

5.2.2.3 Restrictions

Study restrictions are explained in Section 2.3 and prohibited concomitant treatments are explained in Section 2.3.1.

5.2.3 Ascending Monotherapy SAD/MAD

Module 1 will commence with an accelerated dose-escalation schedule and enrol three patients into a cohort with follow-up for AEs and DLT.

Patients will receive a single dose of RXC004 on Day 1 followed by a 6-10 days' washout period (Cycle 0) [this washout period may change based upon emerging data]. Cycles of 21

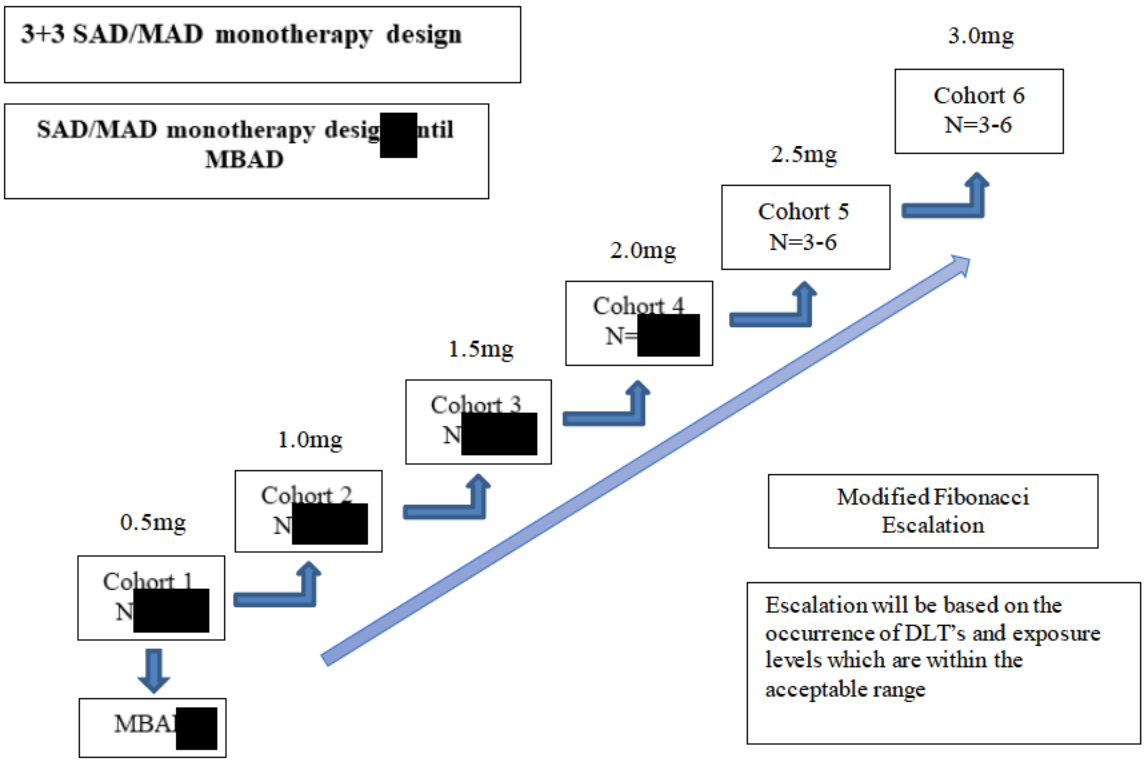
days of multiple dosing will then begin until the patient is withdrawn from the study (Cycle 1 onwards).

Dose escalation will continue in a 3+3 design until MBAD (as defined in Section 3.1.5) has been found to be tolerated. Subsequent dose escalation will continue in a 3+3 design until MTD/MFD has been reached.

The decision to dose escalate will be made upon the assessment of the safety and tolerability data collected up until the time of study drug administration on Cycle 2, Day 1. This DLT assessment period was selected as any acute toxicities leading to cessation of dose escalation in this study are anticipated to present within this duration. Doses and/or schedules of RXC004 will be defined by the SRC.

Optional skin-punch biopsies will be taken from all patients in Module 1 at baseline and while receiving treatment for analysis of pharmacodynamic markers of Wnt pathway inhibition (see Schedule of Assessments in Appendix 1).

Figure 4 Module 1 RXC004 monotherapy SAD/MAD



- SRC approval for next cohort escalation or expansion required.
- In this example schematic diagram MBAD is achieved following the completion of Cohort 1
- Single dose of RXC004 following by a washout period of 6-10 days (Cycle 0) then 21 days' continuous dosing (Cycle 1 onwards) until withdrawal.

In Module 1, MBAD will be defined using either PK or pharmacodynamic data.

5.2.4 Selection of Doses

In Module 1, the starting dose of RXC004 will be 0.5 mg given once daily on Days 1–21 inclusive.

The study will start with Module 1 (monotherapy), in which the selected RXC004 starting dose of 0.5 mg QD (for the multiple dosing schedule) will be used, based on the clinical PK observed in Patient 001/001, the cover required for tumour efficacy in pre-clinical studies and the exposure over IC_{50} achieved by competitor PORCN inhibitors in their reported Phase1 studies (see Section 3.1.1). Eligible participants will be enrolled in sequential cohorts treated with RXC004, given as an oral capsule dose while being monitored for safety and DLTs.

5.2.5 Selection and Timing of Dose for Each Patient

The doses and duration of treatment for Module 1 is detailed in Section 5.2.3. The exact times the study drug was administered and comments are to be recorded directly on the appropriate page of the CRF.

5.2.5.1 Dose Regimen

The pre-clinical toxicology data support continuous dosing of RXC004 in humans, and Module 1 will start with this schedule. However, based on emerging data, the SRC may decide to propose the exploration of intermittent schedules in some modules.

5.2.5.2 Dose-Escalation Plan

A general description of the study dose-escalation scheme can be found in Section 3.1

The dose-escalation scheme will not exceed doubling of the dose, in principle. However, up to a quadrupling of the dose may be permitted in the first two escalations only, if the drug concentrations of the first or second level are immeasurable or below the predicted target drug exposure for biological effect (for example more than 2-fold) and there have been no significant safety or tolerability issues. This will ensure that the fewest possible cohorts are exposed to RXC004 below the presumed therapeutic dose. The planned dose escalation scheme has the flexibility to be amended in light of emerging data.

Redx will interpret the single dose PK data before continuous dosing commences. If exposure levels indicate that a continuous schedule is not appropriate the patient may be discontinued or referred to the SRC to whether an alternative dosing schedule should be considered.

Table 3 shows an indicative dose escalation scheme for Module 1. All dose levels beyond Cohort 1 may change in light of emerging safety, tolerability, and PK data, and also evolving relevant pre-clinical data.

Table 3: Indicative Dose-Escalation Scheme for Module 1

Planned Dose levels	**Dose**
1	0.5 mg QD
2	1.0 mg QD
3	1.5 mg QD
4	2.0 mg QD
5	2.5 mg QD
6	3.0 mg QD

Note: This indicative dose and schedule optimisation scheme subject to SRC recommendation.

The pre-clinical toxicology data support continuous dosing of RXC004 in humans, and Module 1 will start with this schedule. However, based on emerging data, the SRC may decide to propose the exploration of intermittent schedules in some modules.
Please see IB for further details.

5.2.6 Dose-Limiting Toxicity for Module 1 (RXC004 Monotherapy)

The DLT assessment period runs from the start of dosing with RXC004 (Cycle 0 Day 1) up to Cycle 1 Day 21 for patients enrolled in Module 1.

A DLT is defined as an AE or abnormal laboratory value that occurs from the first dose of study treatment up to Cycle 1 Day 21, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that despite optimal therapeutic intervention meets any of the following criteria:

1. Haematological toxicity that is:
    - CTCAE ≥Grade 4 present for more than 4 consecutive days
    - Grade 3 neutropenia (ANC ≥ 500 to < 1000 cells/mm^3) of any duration accompanied by fever (≥ 38.5°C) and/or systemic infection
    - Grade 3 thrombocytopaenia (25,000 to < 50,000/mm^3) with clinical evidence of bleeding
2. Any other confirmed haematological toxicity CTCAE ≥Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)
3. Non-haematological toxicity CTCAE ≥Grade 3 including:

- Laboratory abnormalities that are considered clinically significant by the investigator (with or without clinical symptoms or signs)
- QTc prolongation (> 500 msec or 60 msec above baseline)

4. Any other toxicity that:
    - Is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC
    - Is a protocol defined stopping criterion and is suspected to be RXC004 related
    - Results in an interruption of dosing schedule of more than 14 days

A DLT excludes:

1. Inadequately treated ≤Grade 3 nausea and/or vomiting and ≤Grade 3 diarrhoea
2. Any toxicity clearly unrelated to RXC004 e.g. solely related to the disease or disease-related process under investigation
3. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

The incidence and type of DLT-type toxicity emerging from treatment beyond Cycle 1 Day 21 will be taken into account by the SRC in determining dose-escalation steps.

5.2.7 RXC004 Monotherapy: Dose Modifications

If a patient experiences a clinically significant and/or unacceptable event including a DLT not attributable to the disease or disease-related processes under investigation, RXC004 dosing may be interrupted or the dose reduced and supportive therapy administered as required.

If the event resolves or reverts to ≤ CTCAE grade 2, treatment with RXC004 may be restarted using the rules below for dose modifications, only following agreement with the Sponsor Physician. Patients who are at the lowest possible dose, i.e., in Cohort 1 or who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

For all other events, if the event does not resolve to ≤ CTCAE grade 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the event.

Maximum tolerated dose will be defined in the presence of optimal supportive care for the event in question.

5.2.8 Study Treatment Discontinuation Criteria

RXC004 dose interruption and stopping criteria are detailed in Table 4

Table 4 Module 1 Dose Interruption and Stopping Criteria

Event	Action
Diarrhoea	Treat as per Diarrhoea/Colitis Management and Treatment Guidelines
1st incidence of diarrhoea ≥ grade 2 (suspected RXC004 related):	Please refer to Appendix 5 Temporarily interrupt RXC004 for up to 14 days*. Consider restarting at lower dose if resolved to < grade 1
2nd occurrence of ≥ grade 2 diarrhoea	Temporarily interrupt RXC004 for up to 14 days*. Consider restarting at lower dose if resolved to < grade 1
3rd occurrence of ≥ grade 2 diarrhoea	Permanently discontinue study treatment
Bone events	
Confirmed RXC004 related fragility bone fracture (excluding grade 1 vertebral deformities)	Permanently discontinue study treatment
Patients with a DXA scan showing ≥ 7% worsening in BMD at lumbar spine or total hip compared to baseline	Permanently discontinue study treatment
An individual increase in β-CTX of ≥350pg/ml from the baseline (screening) value **or** in individual measurement of ≥1000pg/ml	Permanently discontinue study treatment unless the patient has received clinical benefit (investigator assessment) and continued treatment is warranted.
Hepatic events	
Grade 3 increases in ALT or AST or ALP (> 5 x ULN if baseline normal, >5 x baseline, if baseline abnormal)	Permanently discontinue study treatment
Grade 2 increases in ALT or AST or ALP (> 3 x ULN if baseline normal, >3 x baseline, if baseline abnormal) with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)	Permanently discontinue study treatment

Event	Action
Grade 2 increases in ALT or AST (> 3 x ULN if baseline normal, >3 x baseline, if baseline abnormal) and total bilirubin > 2 x ULN or INR* > 1.5 or other evidence of impairment to the synthesis function of the liver]	Permanently discontinue study treatment
*Unless patient is receiving warfarin	
Other adverse events	
Grade 3-4 toxicity (1st event^)	Interrupt RXC004 (max. 14 days*), resume at the next lowest dose level when resolved (grade ≤ 2 or returns to baseline).
Grade 3-4 toxicity (subsequent events^)	Permanently discontinue study treatment
Grade < 3 toxicity (all events^)	Decision to interrupt RXC004 (max. 14 days*) is at the Investigator's discretion. Resume at same dose prior to interruption.
^ Excluding diarrhoea	
Surgery	Interrupt RXC004 (max. 14 days*), resume at full dose. RXC004 should be stopped 3 days prior to surgery and resumed approx. 10 days later. If the wound has not healed a further 7 days are permitted prior to re-starting RXC004 at the discretion of the Investigator and with approval of Sponsor Physician. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after RXC004 is swallowed, the dose may be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 4 hours after the scheduled dose time. If greater than 4 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.

Event	Action
Corticosteroid use	Patients receiving corticosteroids for treatment of diarrhoea should hold RXC004 (for max. 14 days*) as per Diarrhoea/Colitis Management and Treatment Guidelines (please refer to Appendix 5)
	Patients receiving corticosteroids for any indication other than diarrhoea, should continue RXC004 at current dose level.
	Patients who require on-study oral or intravenous (i.v.) glucocorticoids for > 4weeks at daily doses equivalent to ≥7.5 mg of oral (p.o.) prednisolone (for any indication other than diarrhoea) should temporarily interrupt RXC004 (for a maximum of 14 days*) if receiving clinical benefit (in the opinion of the investigator) and resume at full RXC004 dose once the daily corticosteroid dose equivalent falls to <7.5 mg PO prednisolone.
	RXC004 should be permanently discontinued for patients who require on-study oral or intravenous (i.v.) glucocorticoids for > 4weeks at daily doses equivalent to ≥7.5 mg of oral (p.o.) prednisolone and are not receiving clinical benefit from RXC004 (in the opinion of the investigator)

* RXC004 interruptions of greater than 14 days may be allowed for patients judged by investigator to be clinically benefiting from study treatment, and only after consultation with Sponsor

The dose of RXC004 must not be adjusted under any other circumstances unless prior agreement is given by the Sponsor. All dose modification and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the CRF.

5.2.9 Biomarker Samples

An archival or a newly acquired tumour biopsy will be requested from every patient enrolled in the study. Archived/newly acquired biopsies are optional (but encouraged) in the Module 1 dose escalation.

Optional Skin biopsies to assess downstream markers of Wnt expression may be taken from all consenting patients in Module 1. (see Appendix 1 Schedule of Assessments).

In all patients participating in the study, the taking of non-mandatory tumour biopsies will be encouraged and can be taken from each patient at up to 3 time points during the study;

1. At baseline (prior to first dose of RXC004)
2. During RXC004 dosing (see SoA for biopsy timings)

At the time of tumour biopsy, blood samples for assessment of PK and blood borne biomarkers will be taken; Analysis of these samples will include, but not be restricted to, PORCN/Wnt status and functional PORCN/Wnt inhibition, e.g. phosphorylation and/or expression of downstream markers.

5.2.10 Exploratory Assessments

Plasma and PBMC pharmacodynamic samples (all sites) will be obtained at C0D1 (prior to first dose) and at C1D8, C1D15, Day 1 of each cycle thereafter and treatment discontinuation. These samples may be used to examine gene and protein expression changes, including measurement of inflammatory markers. Fresh whole blood (from selected sites of close proximity) will be obtained at C0D1 (prior to first dose), and pre-dose at C1D8, C1D15 and C2D1. Fresh whole blood may be stained for cell surface markers to identify immune cell populations present in the circulation before and after treatment. Circulating tumour DNA (ctDNA) will be collected pre-dose at C0D1 and post-dose on C2D1, C4D1 and at treatment discontinuation. Analysis of total amounts and/or tumour mutations (including Wnt pathway aberrations) in ctDNA samples may be evaluated and correlated to patient response.

5.3 Module 2 – RXC004 and Nivolumab Combination

Based on the safety profile observed to date, a decision has been made by Redx and the SRC to start Module 2.

The reason for conducting this study module is to provide the first cancer patient safety and tolerability data with RXC004 in combination with nivolumab.

Module 2 will commence by enrolling patients with advanced solid tumours into a SAD/MAD monotherapy dose escalation arm. Eligible participants will be enrolled in dose-escalation cohorts treated with RXC004 given as an oral capsule dose in combination with a PD1 infusion. The dose of nivolumab will be a fixed dose of (480 mg every 4 weeks, and will remain at this dose level throughout the study. The dose of RXC004 will be escalated. The RXC004 starting dose for combination with nivolumab will be a lower dose than the highest confirmed safe and tolerated dose from the monotherapy study (Module 1). The RXC004 dose will be dose-escalated to the MTD in combination in as few dose-cohorts as possible. The RXC004 dose

used in Module 2 will not be escalated to exceed the MTD for RXC004 in monotherapy (2mg RXC004 QD).

Patients will take a single dose of RXC004 to evaluate single dose PK, then start on continuous RXC004 dosing up 3-7 days later in combination with nivolumab every 28 days (Cycle 1).

Each cycle will be 28 days from Cycle 1, Day 1.

Dose increments will be guided by safety data observed during Cycle 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and pharmacodynamic data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 0 or Cycle 1 of treatment. (Figure 5)

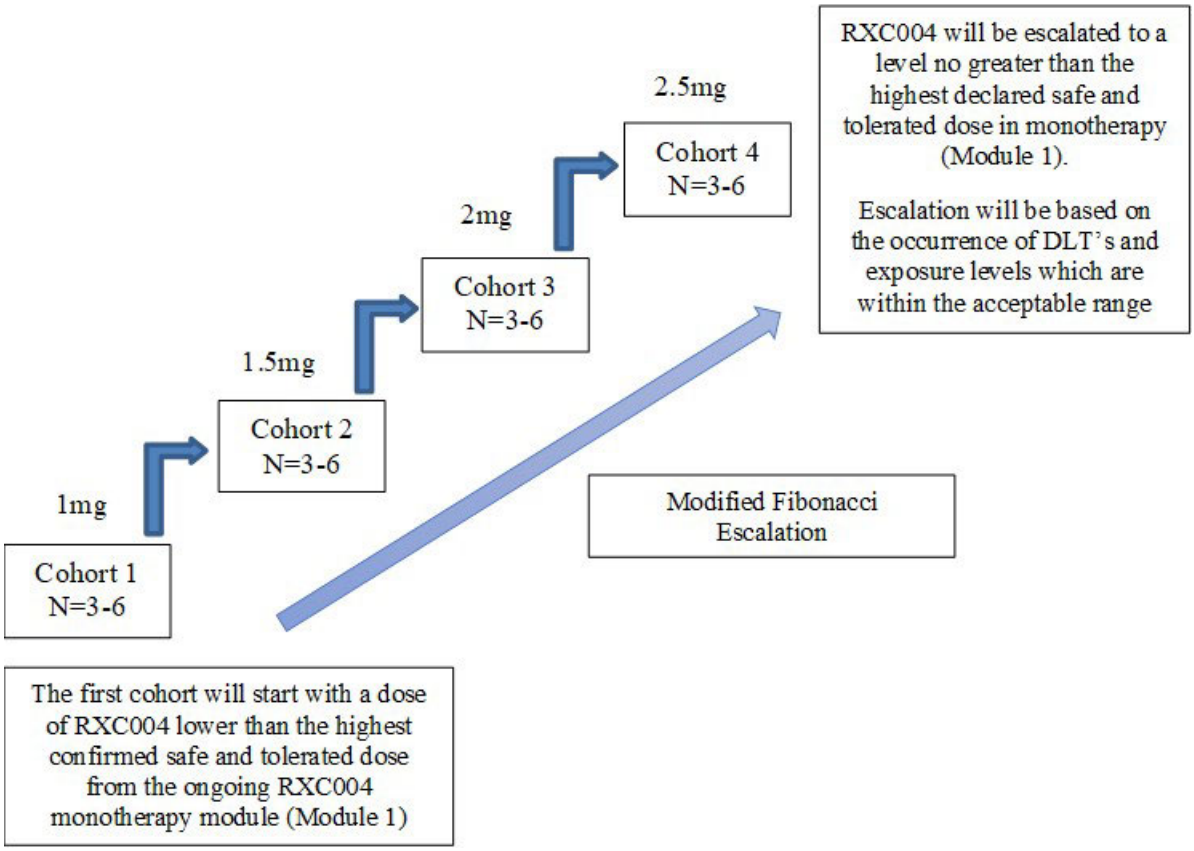
Patients will have the option to have their tumour tissue (primarily from an archival source) tested for genetic aberrations (including upstream Wnt pathway aberrations such as RNF43 mutations and RSPO-fusion) by next generation sequencing (NGS) or MassArray technologies.

RXC004 will be administered orally in combination with anti PD1 infusion in patients with advanced solid malignancies. There will be escalation of the RXC004 dose in each cohort with intensive safety monitoring to ensure the safety of the patients. The design of this Module 2 also allows the RXC004 & anti-PD1 combination tolerability and PK to be characterised in an unselected population of patients.

Figure 5 Module 2 dose escalation

3+3 SAD/MAD design

Escalation of RXC004 with fixed dose of Nivolumab (480mg)



5.3.1 Module 2 Objectives

The objectives are detailed in Section 1.9

5.3.2 Module 2 Eligibility Criteria

5.3.2.1 Module 2 Specific Inclusion Criteria

The core inclusion are detailed in Section 2.1.1. There are no Module 2 specific inclusion criteria. Patients must fulfill all of the core inclusion criteria in order to be eligible to receive study treatment in Module 2.

5.3.2.2 Module 2 Specific Exclusion Criteria

The core and Module 2 specific exclusion are detailed in Sections 2.2.1 and 2.2.2 respectively. Patients must not receive study treatment in Module 2 if any of the Core or Module 2 specific exclusion criteria are fulfilled.

5.3.2.3 Restrictions

Study restrictions are explained in Section 2.3 and prohibited concomitant treatments are explained in Section 2.3.1.

5.3.3 Module 2: Ascending Combination MAD

Module 2 will enroll three patients into a cohort with follow up for AEs and DLT.

Patients will start with a single dose of RXC004 followed by a washout of 3-7 days (Cycle 0). RXC004 and nivolumab will commence at Cycle 1. The first cohort will be daily RXC004 and 480 mg nivolumab every 4 weeks (28 days).

The DLT period will be until the end of Cycle 1. Dose escalation will continue in a 3+3 design until MTD/MFD has been reached in the combination. Decisions on doses and/or schedules of RXC004 in combination will be made in discussion with the SRC.

5.3.4 Selection of Doses for Module 2

In Module 2, the starting dose of RXC004 will be at a lower dose than the highest confirmed safe and tolerated dose from the ongoing monotherapy study (Module 1). The RXC004 dose used in Module 2 will not be escalated to exceed the MTD for RXC004 in monotherapy (2mg RXC004 QD).

Nivolumab will be administered at 480mg q4w, which is an approved dose and regimen from the nivolumab prescribing information. The dose of nivolumab will not be modified in this module.

5.3.5 Selection and Timing of Dose for Each Subject

The doses and duration of treatment for Module 2, is detailed below. The exact times the study drug was administered and comments are to be recorded directly on the appropriate page of the CRF.

5.3.5.1 Dose Regimen

Module 2 will start with a continuous dose of RXC004 that is lower than the highest confirmed safe and tolerated dose from the ongoing monotherapy study (Module 1).

All patients will start with a single RXC004 dose in Cycle 0, followed by a 3-7 day washout. Nivolumab will commence on Cycle 1, Day 1 concurrently with daily RXC004. Cycle 1 onwards will be 28 days in length.

The RXC004 and nivolumab combination dose escalation will start with continuous dosing of RXC004, but based on emerging data the SRC may decide to propose the exploration of intermittent combination schedules.

5.3.5.2 The nivolumab dose and regimen selected for this study are based on the approved prescribing information for nivolumab. The recommended dosage for nivolumab is 240 mg Q2W or 480 mg Q4W. 480 mg Q4W has been selected to complement a 28-day cycle of RXC004 and reduce the number of patient visits required. If a patient continues in the study on nivolumab alone, this treatment may be continued for a maximum of 12 months in total.Dose-Escalation Plan

The dose-escalation scheme will not exceed doubling of the dose.

Dose, frequency and schedule in subsequent cohorts may increase or decrease in response to safety, tolerability, pharmacokinetic and emerging non-clinical data. The RXC004 dose used in Module 2 will not be escalated to exceed the MTD for RXC004 in monotherapy (2mg RXC004 QD).

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability and pharmacokinetics of RXC004 in combination with nivolumab to decide the next dose and/or schedule.

Table 5 shows an indicative dose escalation scheme for Module 2. All dose levels beyond cohort 1 may change in light of emerging safety, tolerability, and pharmacokinetic data, and also evolving relevant pre-clinical data.

Table 5 Indicative Dose Escalation Scheme for Module 2

Planned Dose levels	RXC004 Dose (Starting Cycle 0)	Nivolumab Dose/Regimen (Starting Cycle 1)
1	1 mg QD	480mg q4w
2	1.5 mg QD	480mg q4w
3	2 mg QD	480mg q4w

Note: This indicative dose and schedule optimisation scheme is subject to SRC recommendation.

The pre-clinical toxicology data supports continuous dosing of RXC004 in humans, and Module 2 will start with this schedule. However, based on emerging data the SRC may decide to propose the exploration of intermittent RXC004 in combination with nivolumab schedules. The nivolumab dose and regimen will not be adjusted in this module.
Please see RXC004 IB and nivolumab prescribing information for further details.

5.3.6 Dose-Limiting Toxicity for RXC004 + Nivolumab Combination (Module 2)

The DLT assessment period runs from the start of dosing with RXC004 and nivolumab (Cycle 1 Day 1) up to Cycle 1 Day 28 where nivolumab treatment is administered every 28 days starting on C1D1.

A DLT is defined as an AE or abnormal laboratory value that occurs from cycle 1 day 1 up to Cycle 1 Day 28, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and is possibly related to RXC004, nivolumab or both agents and that despite optimal therapeutic intervention meets any of the following criteria;

1. Haematological toxicity that is:
   - ≥ CTCAE grade 4 neutropenia present for more than 4 consecutive days
   - Grade 3 neutropenia (ANC ≥ 500 to < 1000 cells/mm^3) of any duration accompanied by fever ≥ 38.5°C and/or systemic infection
   - Grade 3 thrombocytopenia (25,000 to < 50,000/mm^3) with clinical evidence of bleeding
2. Any other confirmed haematological toxicity ≥ CTCAEv4 grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)
3. Non-haematological toxicity ≥ CTCAE grade 3 including:

- Laboratory abnormalities that are considered clinically significant by the investigator (with or without clinical symptoms or signs)
- QTc prolongation (> 500 msec or 60 msec above baseline)

4. Any other toxicity that:
   - Is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC
   - Is a protocol defined stopping criteria and is suspected to be RXC004 or Nivolumab related
5. Any grade 3 or higher immune-related adverse events

A DLT excludes:

1. Inadequately treated grade ≤3 nausea and/or vomiting and grade ≤3 diarrhoea
2. Any toxicity clearly unrelated to RXC004 and/or Nivolumab e.g. solely related to the disease or disease-related process under investigation.
3. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

5.3.7 Dose Modifications

RXC004 dose reduction and interruption are permitted. Nivolumab dose reduction is not permitted but dose interruption/delay is permitted.

RXC004 may be dose interrupted (withheld) for up to 14 days until a clinically significant (any grade) and/or a grade ≥ 3 related adverse event resolves to baseline or ≤ grade 1. Patients that experience a RXC004 related adverse events that do not resolve to baseline or ≤ grade 1 after 14 days of dose interruption/delay despite appropriate treatment must be discussed with Sponsor, before re-starting RXC004.

Adverse events that are assessed as being causally related nivolumab should be managed as per the Nivolumab Toxicity Management and Dose Modification Guidelines (Appendix 8). If either agent alone is interrupted or discontinued for a related-AE the other agent (nivolumab or RXC004) may be continued if the patient is judged (by the investigator) to be receiving clinical benefit. If a patient continues in the study on nivolumab alone, this treatment may be continued for a maximum of 12 months in total.

5.3.8 Study Treatment discontinuation Criteria

RXC004 and nivolumab dose interruption and stopping criteria are detailed for in Table 6

Table 6 Module 2 Dose Interruption and Stopping Criteria

Event	Action
Colitis events (e,g. Colitis, ileitis, enterocolitis etc)	
Grade 1	If receiving RXC004, either as monotherapy or in combination with nivolumab; Reduce RXC004 to a lower dose and manage as per Appendix 5 (and Appendix 8 if applicable)
Grade 2	If receiving RXC004, either as monotherapy or in combination with nivolumab Interrupt RXC004. Manage as per Appendix 5 and Appendix 8 if applicable. When event has resolved to Grade ≤1[a] and steroids tapered to ≤10 mg of prednisone per day (or equivalent), resume RXC004 at a lower dose and nivolumab (if applicable) at 480 mg once every month. If event re-occurs after re-starting study treatment, then RXC004 and nivolumab (if applicable) should be permanently discontinued.
Grade 3	If receiving RXC004 monotherapy; Interrupt RXC004. Manage as per Appendix 5 When event has resolved to Grade ≤1[a] and steroids tapered to ≤10 mg of prednisone per day (or equivalent), resume RXC004 at a lower dose. If event re-occurs after re-starting study treatment, then RXC004 should be permanently discontinued. If receiving RXC004 in combination with nivolumab; **permanently discontinue both agents** and manage as per Appendix 5 and Appendix 8.

Event	Action
Grade 4	If receiving RXC004, either as monotherapy or in combination with nivolumab; **Permanently discontinue study treatment (both agents if applicable)**. Mange as per Appendix 5 and Appendix 8
Dysgeusia events	
Grade 1 or 2	RXC004 related; Consider dose reduction, depending on clinical symptoms Manage as per Appendix 6 Interrupt RXC004 treatment if dysgeusia is associated with >5kg weight loss from baseline
Grade 2 associated with a 10-20% decrease in body weight	RXC004 related; Manage as per Appendix 6 Reduce RXC004 to a lower dose.
Grade 2 associated with a >20% decrease in body weight	RXC004 related; Manage as per Appendix 6 Permanently discontinue RXC004. Nivolumab can continue if clinical benefit is judged by investigator for a maximum of 12 months total treatment.
Other adverse events	
Any event that meets discontinuation criteria for nivolumab (see Appendix 8)	Permanently discontinue nivolumab. RXC004 can continue, if clinical benefit is judged by investigator.

Event	Action
Any event that meets nivolumab treatment hold (see Appendix 8)	Interrupt nivolumab and manage as per Appendix 8. Nivolumab can be re-started when event is resolved to ≤Grade 1 and any steroid taper completed (to 10mg prednisone equivalent). RXC004 can continue whilst nivolumab is held, if the patient is judged (by the investigator) to be receiving clinical benefit.
Grade 3-4 toxicity (1st event)	RXC004 related; Interrupt RXC004 and provide supportive care, resume at the next lowest dose level when resolved (grade ≤ 2 or returns to baseline). Interruptions >14 days should be discussed with Sponsor before re-starting. Nivolumab related; See guidelines in Appendix 8
Grade 3-4 toxicity (subsequent recurrence of a previously experienced event)	RXC004 and/or nivolumab related; Permanently discontinue study treatment
All Grade events	Study treatment can be discontinued for any clinically significant AEs that in the investigator's opinion warrants treatment discontinuation.

Event	Action
Bone events	
Confirmed RXC004 related fragility bone fracture (excluding grade 1 vertebral deformities)	Permanently discontinue RXC004. Nivolumab can continue, if clinical benefit is judged by investigator for a maximum of 12 months total treatment.
Patients with a DXA scan showing ≥ 7% worsening in BMD at lumbar spine or total hip compared to baseline	Permanently discontinue RXC004. Nivolumab can continue, if clinical benefit is judged by investigator for a maximum of 12 months total treatment.
An individual increase in β-CTX of ≥350pg/ml from the baseline (screening) value **or** in individual measurement of ≥1000pg/ml	Permanently discontinue study treatment unless the patient has received clinical benefit (investigator assessment) and continued treatment is warranted.
COVID-19 infection	
Positive COVID-19 test	Interrupt RXC004, until acute symptoms have resolved. Interruptions >14 days should be discussed with Sponsor before re-starting.
Surgery	Interrupt RXC004 (max. 14 days[b]), resume at full dose. RXC004 should be stopped 3 days prior to surgery and resumed approx. 10 days later. If the wound has not healed a further 7 days are permitted prior to re-starting RXC004 at the discretion of the Investigator and with approval of Sponsor Physician. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after RXC004 is swallowed, the dose may be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed RXC004 dose	Allowed to take the scheduled dose up to 4 hours after the scheduled dose time. If greater than 4 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.

a. Attempts should be made to confirm that the colitis has resolved to Grade ≤ 1 (e.g. normalised CRP or fecal calprotectin if raised during event; GI appearance normalised on X-ray/CT or endoscopy) before restarting RXC004.

b. RXC004 interruptions of greater than 14 days may be allowed for patients judged by investigator to be clinically benefiting from study treatment, and only after consultation with Sponsor

5.3.9 Biomarker Samples

An archival or a newly acquired tumour biopsy will be requested from every patient enrolled in the study. Archived/newly acquired biopsies are optional (but encouraged) in the Module 2 dose escalation.
In all patients participating in the study, the taking of non-mandatory tumour biopsies will be encouraged and can be taken from each patient at up to 3 time points during the study;

1. At baseline (prior to first dose of study treatment)
2. During study treatment dosing (see SoA for biopsy timings)

At the time of tumour biopsy, blood samples for assessment of PK and blood borne biomarkers will be taken; Analysis of these samples will include, but not be restricted to, functional Wnt pathway inhibition, immune gene signature and immune cell infiltration.

5.3.10 Exploratory Assessments

The circulating soluble factors and PBMC pharmacodynamic samples (all sites) will be obtained at C0D1 (prior to first dose) and on C1D15 and Day 1 of each cycle thereafter. These samples may be used to examine gene and protein expression changes, including measurement of inflammatory markers. Fresh whole blood (from selected sites of close proximity) will be obtained at C0D1 (prior to first dose), and pre-dose at C1D15 and C2D1. Fresh whole blood may be stained for cell surface markers to identify immune cell populations present in the circulation before and after treatment. Circulating tumour DNA (ctDNA) and RNA (ctRNA) will be collected pre-dose at C0D1, post-dose on C1D15 and Day 1 of each subsequent cycle and at treatment discontinuation. Analysis of total amounts and/or tumour mutations (including Wnt pathway aberrations) in ctDNA samples may be evaluated and correlated to patient response.

5.4 Module 3

Module 3 will investigate the PK, Wnt pathway inhibition, incidence/severity of Wnt pathway related adverse events and anti-tumour activity of RXC004 when given at 2 different intermittent dosing schedules, in a selected group of patients with Wnt ligand dependent advanced solid tumours.

Following the completion of Module 1, the 2mg QD dose was selected as the recommended starting dose for Phase 2 studies, with options of interruptions and dose reductions to manage potential toxicities. The most frequently occurring treatment related AEs in module 1 (all doses) were fatigue (52%), nausea (44%), decreased appetite (40%), dysgeusia (40) and

vomiting (24%). The median RXC004 exposure in Module 1 was approximately 7 weeks so these adverse events were generally observed during the first two treatment cycles. Of the observed adverse events, only dysgeusia, a known on-target toxicity of Wnt pathway inhibitors, was observed to be dose-related and 4 out of 6 patients in the 2mg cohort reported dysgeusia within the first 2 treatment cycles. Module 3 will explore whether intermittent dosing schedules have the potential to deliver clinical anti-tumour activity in selected patients with Wnt ligand dependent tumours and whether intermittent dosing, giving short treatment breaks, has the potential to reduce incidence of treatment related toxicities such as dysgeusia. If so, an intermittent dosing schedule could be a future alternative to dose reduction in the management of treatment related adverse events.

5.4.1 Module 3: Study Objectives

The study objectives are detailed in Section 1.9

5.4.2 Module 3 Eligibility Criteria

5.4.2.1 Module 3 Specific Inclusion Criteria

Module 3 specific inclusion criteria can be found in Section 2.1.3. Patients must fulfill all of the core and Module 3 specific inclusion criteria in order to be eligible to receive study treatment in Module 3. The core inclusion criteria are detailed in Section 2.1.1

5.4.2.2 Module 3 Specific Exclusion Criteria

There are no Module 3 specific exclusion criteria. Patients must not meet any of the core exclusion criteria in order to be eligible to receive study treatment in Module 3. The core exclusion criteria are detailed in Section 2.

5.4.2.3 Restrictions

Study restrictions are explained in Section 2.3 and prohibited concomitant treatments are explained in Section 2.3.1.

5.4.2.4 Pre-screening for tumours with RNF43 mutations and RSPO fusions

All patients enrolled into Module 3 must have Wnt dependent solid tumours, defined as;

- Any solid tumour with a predicted loss of function RNF43 mutation (see Appendix 10 for details).
- Any solid tumour with a RSPO fusion (see Appendix 10 for details)
- Biliary tract cancer

- Thymus cancers (thymic and thymoma WHO Classification)

Eligible patients with RNF43 mutations or RSPO fusions, detected either in a tumour sample or in circulating tumour DNA (CTDNA), will be identified by either a central genetics screening approach or local laboratory assessments. Patients with colorectal, pancreatic, gastric, prostate or squamous non-small cell lung cancers may submit archival tumour samples to the central genetic screening (study pre-screening).

Diagnostic/archival tumour FFPE samples may be sent to Northern Genetics Service for central genetic screening for RNF43 mutations and RSPO fusions. This is an ISO 15189 accredited NHS laboratory and part of the Newcastle NHS Trust, UK. During analytical validation, the RNF43 iPLEX assay, that detects 33 known RNF43 loss-of-function variants, performed at 100% for Analytical Sensitivity / Positive agreement (PPA) and 100% for Analytical Specificity/ Negative agreement (NPA). During analytical validation, the RSPO iPLEX assay, that detects 7 known RSPO gene fusions, performed at 100% for Analytical Sensitivity / PPA and 100% for Analytical Specificity / NPA. See Appendix 10 for a list of the mutations and fusions covered by these iPLEX tests. In addition, patient diagnostic/archival tumour biopsy samples will also be tested in a mini-panel DNAseq for the following genes: RNF43, APC, CTNNB1, AXIN1, AXIN2, BRAF, MLH1 and KRAS. During analytical validation the custom 8 gene DNAseq panel, analyzed on an Illumina MiSeq platform and processed through a SOPHiA DDM pipeline (CCCP_A_QIA_v1), performed with an Analytical Sensitivity / PPA of 99.03%, and an Analytical Specificity / NPA of 100%. RNF43 predicted loss-of-function mutations detected in this DNAseq assay will also be eligible, and could include mutations or aberrations in RNF43 beyond those listed in Appendix 10. As RNF43 is a tumour suppressor gene in context of the Wnt pathway, further screening is likely to identify previously unseen RNF43 loss-of-function mutations. The remaining 7 genes on the DNAseq panel will be used to retrospectively investigate whether aberrations in these genes correlate with response to therapy (exploratory analysis).

Data from central genetic screening will be shared with investigators to aid future treatment decisions.

Patients with any solid tumours with predicted loss of function RNF43 mutations or RSPO fusions from other local testing of blood or tumour will also be eligible to enter the study, provided that the assay used for testing has adequate analytical validation for this purpose (i.e. fully CE-marked for the purpose of investigating RNF43 mutations or RSPO fusions; partially CE-marked for their analytical performance or having achieved a minimum

validation specification of >90% for Analytical Sensitivity / PPA and >95% for Analytical Specificity / NPA for the detection of the aberrations in the genes of interest and performed in an ISO accredited, CLIA or CAP accredited lab). If aberrations are detected by local tests that are not included in the list in Appendix 10, these may be included in the study on discussion with the Sponsor.

5.4.3 Dose Rationale

In Module 3, intermittent schedules of RXC004 will be investigated. The intermittent schedules will use 2mg QD RXC004, which has already shown to be safe and tolerated when used continuously in Module 1 of this study. This dose delivers Cmin values > 3-fold IC50 in patients, which is expected to lead to >50% Wnt pathway inhibition, while also being safe and tolerable.

Module 1 opened in 2018 with a RXC004 dose of 10mg once daily, but the dose was not tolerated in the first patient and the Module 1 dose escalation was restarted on 18th March, 2019 with 0.5mg RXC004. As of the 30th July, 25 patients have been dosed with RXC004 monotherapy in Module 1 of the study at doses of 0.5mg (4), 1mg (3), 1.5mg (7), 2mg (6), 3mg (4) and 10mg (1)

At doses up to and including 2 mg QD, the most common treatment related AEs were fatigue (10/20 patients), nausea (7/20), decreased appetite (6/20), dysgeusia (6/20), and vomiting (4/20). Of these, only dysgeusia appeared to be dose related. No Grade 4/5 treatment related AEs or bone fragility events were reported at any of these dose levels of RXC004.

A detailed description of the RXC004 risks is provided in Section 1.7.1. Details of the pharmacology, efficacy, and safety of RXC004 is also provided in the RXC004 Investigator's Brochure.

5.4.4 RXC004 Intermittent Schedules

Module 3 will enroll 6 evaluable patients per Arm, with follow up for PK, pharmcodynamics and AEs.

An evaluable patient in Module 3 is defined as a patient that has received study treatment and either:

- Has completed minimum safety evaluation requirements and has received 100% of the specified RXC004 dose in Cycle 0 and at least 80% of the intended dose of RXC004 during Cycles 1 and 2.

- Has permanently discontinued study treatment due to a related adverse event

Subjects will start with a single dose of RXC004 followed by a washout of 3-7 days (Cycle 0). RXC004 schedules will commence on Cycle 1, Day 1. Each treatment cycle will be 21 days. Study treatment will continue until disease progression, intolerable toxicity or withdrawal of consent. Module 3 will start with two treatment Arms of intermittent RXC004 schedules;

- Arm 1 – 2mg QD RXC004 for 4 days, followed by 3 days off, repeated weekly for 21 day treatment cycles
- Arm 2 – 2mg QD RXC004 for 2 weeks, followed by 1 week off (21 day treatment cycles)

Patient enrolment into Arms 1 and 2 will run concurrently.

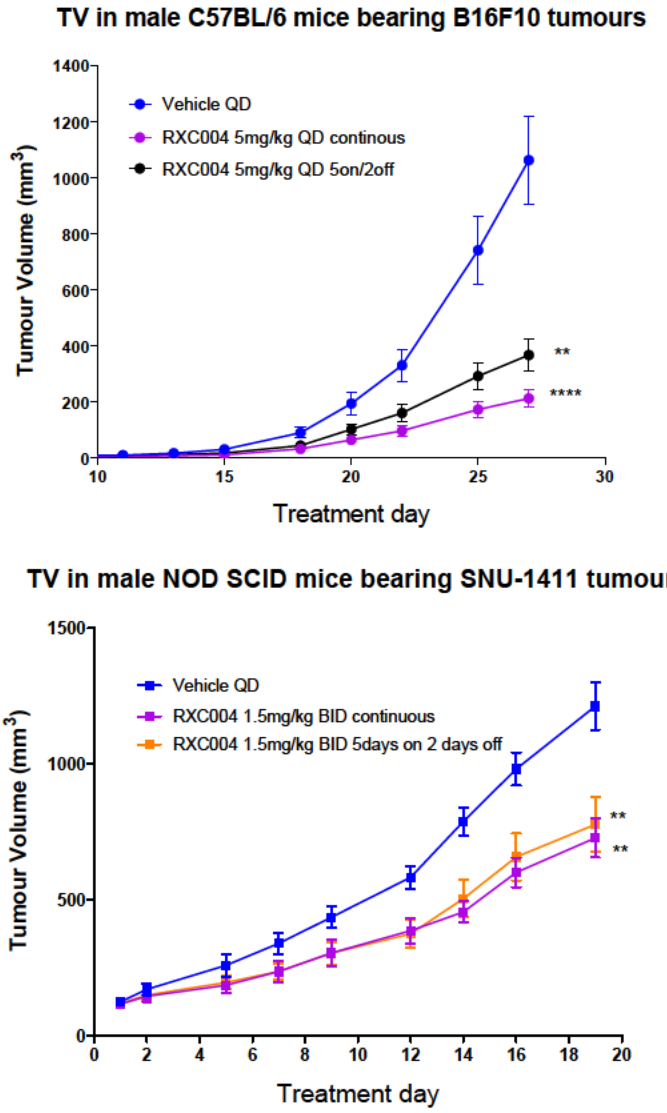
Further RXC004 monotherapy arms may be opened after review of safety and tolerability information from Arms 1 and 2, relevant data from Modules 1 and 2 and any emerging preclinical data.

Mandatory skin punch biopsies will be taken from all patients in Module 3 at baseline and while receiving treatment for analysis of pharmacodynamic markers of Wnt pathway inhibition, alongside PK sampling (see Schedule of Assessments in Appendix 9).

5.4.5 Intermittent Schedule Rationale

Redx have previously demonstrated that RXC004 is efficacious when delivered on a 5 days on/2 days off schedule in multiple mouse oncology models (see Figure 6 below). Due to differences in half-life between mouse and human, with RXC004 having a significantly longer half-life in man (11 to 13 h compared to 2.4 to 3.4 h in mice) this pre-clinical schedule is most closely matched by the 4 days on/3 days off schedule in man.

Figure 6 Dose-dependent effects of RXC004 in B16F10/C27BL/6 syngeneic model and the SNU-1411 xenograft model.



Time course of RXC004 effects on tumour size in in two models with two dosing schedules QD: once daily, 5 on/2 off: five days dosing with 2 days non-dosing. Statistical comparisons by ANOVA. P <0.05 denoted by "*", P <0.01 denoted by "**", P <0.001 denoted by "***" and P <0.0001 as "****".

The two schedules were selected following compartmental modelling of plasma PK data from all dose cohorts in Module 1, in which a naïve pooled approach was employed. Model estimates were used to simulate the exposure of four different dose sequential regimens: 5 days on/2 days off; 4 days on/3 days off; 2 weeks on/1 week off and 2 weeks on/2 weeks off. Of these four potential intermittent treatment regimens the 4 days on/3 days off and 2 weeks on/1 week off regimens were selected to be studied in Module 3 because over a 21-day

treatment cycle these respectively give 14% and 24% of time below the IC_{50} for Wnt pathway inhibition and at least 72 % of time above the target C_{min} of >3-fold IC_{50} in patients.

5.4.6 RXC004 Dose Modifications

If a patient experiences a clinically significant and/or unacceptable event not attributable to the disease or disease-related processes under investigation, RXC004 dosing may be interrupted, the dose reduced and supportive therapy administered as required.

If the event resolves or reverts to CTCAE ≤Grade 2, treatment with RXC004 may be restarted using the rules below for dose modifications, only following agreement with the Sponsor physician.

If the event does not resolve to CTCAE ≤Grade 2, or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the event.

5.4.7 Study Treatment Discontinuation Criteria

RXC004 dose-interruption and stopping criteria are detailed in Table 7

Table 7 Module 3 Dose-Interruption and Stopping Criteria

Event	Action
Colitis events (e,g. Colitis, ileitis, enterocolitis etc.)	
Grade 1	Reduce RXC004 to a lower dose and manage per Appendix 5
Grade 2	Interrupt RXC004. Manage per Appendix 5. When event has resolved to Grade ≤1[a] and steroids tapered to ≤10 mg of prednisone per day (or equivalent), resume RXC004 at a lower dose. If event recurs after re-starting study treatment, then RXC004 should be permanently discontinued.

Event	Action
Grade 3	Interrupt RXC004. Manage per Appendix 5. When event has resolved to Grade ≤1[a] and steroids tapered to ≤10 mg of prednisone per day (or equivalent), resume RXC004 at a lower dose. If event recurs after re-starting study treatment, then RXC004 should be permanently discontinued.
Grade 4	**Permanently discontinue RXC004.** Manage per Appendix 5
Dysgeusia events	
Grade 1/2	RXC004 related; Consider dose reduction, depending in clinical symptoms Manage per Appendix 6 Interrupt RXC004 treatment if dysgeusia is associated with >5kg weight loss from baseline
Grade 2 associated with a 10-20% decrease in body weight	RXC004 related; Manage per Appendix 6 Reduce RXC004 to a lower dose.
Grade 2 associated with a >20% decrease in body weight	RXC004 related; Manage per Appendix 6 Permanently discontinue RXC004.
Bone events	
Confirmed RXC004-related fragility bone fracture (excluding Grade 1 vertebral deformities)	Permanently discontinue study treatment
Patients with a DEXA scan showing ≥ 7% worsening in BMD at lumbar spine or total hip compared to baseline	Permanently discontinue study treatment

Event	Action
An individual increase in β-CTX of ≥350 pg/mL from the baseline (screening) value **or** in individual measurement of ≥1000 pg/mL	Permanently discontinue study treatment unless the patient has received clinical benefit (Investigator assessment) and continued treatment is warranted.
Other adverse events	
Grade 3-4 toxicity (1st event)	RXC004 related: Interrupt RXC004 (max. 14 days[b]), resume at the next lowest dose level when resolved (≤Grade 2 or returns to baseline).
Grade 3-4 toxicity (subsequent recurrence of a previously experienced event)	RXC004 related; Permanently discontinue study treatment
All grade events	Study treatment can be interrupted or discontinued for any clinically significant AEs that in the Investigator's opinion warrants treatment interrupted or discontinuation.
COVID-19 infection	
Positive COVID-19 test	Interrupt RXC004, until acute symptoms have resolved. Interruptions >14 days should be discussed with Sponsor before re-starting.
Surgery	Interrupt RXC004 (max. 14 days[b]), resume at full dose. RXC004 should be stopped 3 days prior to surgery and resumed approx. 10 days later. If the wound has not healed a further 7 days are permitted prior to re-starting RXC004 at the discretion of the Investigator and with approval of Sponsor Physician. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after RXC004 is swallowed, the dose may be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 4 hours after the scheduled dose time. If greater than 4 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.

a. Attempts should be made to confirm that the colitis has resolved to Grade ≤ 1 (e.g. normalised CRP or fecal calprotectin if raised during event; GI appearance normalised on X-ray/CT or endoscopy) before restarting RXC004.

b. RXC004 interruptions of greater than 14 days may be allowed for patients judged by investigator to be clinically benefiting from study treatment, and only after consultation with Sponsor

AE, adverse event; BMD, bone mineral density; COVID-19, Coronavirus disease 2019

The dose of RXC004 must not be adjusted under any other circumstances unless prior agreement is given by the Sponsor. All dose/schedule modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the CRF.

5.4.8 Biomarker Samples

An archival or a newly acquired tumour biopsy will be requested from every patient enrolled in the study. Archived/newly acquired biopsies are optional (but encouraged) in the Module 3 In all patients participating in the study, the taking of non-mandatory tumour biopsies will be encouraged and can be taken from each patient at up to 2 time points during the study;

- At baseline (prior to first dose of RXC004)
- During RXC004 dosing (see SoA for biopsy timings)

Two mandatory skin biopsies to assess downstream markers of Wnt expression will also be taken from all patients in Module 3 (see Appendix 9 Schedule of Assessments for timing).

At the time of tumour and skin biopsies, blood samples for assessment of PK and blood borne biomarkers will also be taken; Analysis of these samples will include, but not be restricted to, genetic screening for tumour samples only, RXC004 plasma concentrations, Wnt pathway activation status and functional PORCN/Wnt inhibition, e.g. phosphorylation and/or expression of downstream markers.

5.4.9 Exploratory Assessments

Plasma and PBMC pharmacodynamic samples (all sites) will be obtained at C0D1 (prior to first dose) and during treatment (see Appendix 9 specific tumour mutations (including Wnt pathway aberrations) in samples may be evaluated and correlated to patient response.

6 STUDY TREATMENT

Detailed information describing the preparation, administration, and storage of RXC004 is located in the Pharmacy Manual.

Detailed information describing the preparation, administration, and storage of Nivolumab is located in the Nivolumab Prescribing Information

6.1 Method of Assigning Subjects to Treatment

Upon approval of subject registration, the sponsor or designee will assign each subject to a Module, Arm and dose cohort. The cohort assignment decisions will be documented in the clinical trial master file.

6.2 Identity of Investigational Product(s)

6.2.1 RXC004

RXC004 drug product is provided in 0.5 and 1.0mg. A complete description of the chemistry and formulation may be found in the Investigational Medicinal Product Dossier. The Quality Control Standards and requirements for RXC004 study medication are described in separate release protocols/ Certificate of Analysis.

RXC004 is formulated as two dosage strengths capsules (0.5mg & 1.0mg), manufactured by Quay Pharma, Deeside Industrial Park, CH5 2NS, United Kingdom. The RXC004 capsules strengths are 0.5, 1.0mg for oral administration.

Stability testing of RXC004 is ongoing. Please refer to the current IMP label for the Expiry Date associated with the current shelf-life of the product.

Reformulation to the lower doses required for the clinical study is currently underway. When the development is complete the IMPD will be updated accordingly and submitted to the relevant regulatory authority.

6.2.2 Nivolumab

Nivolumab will be supplied as 240mg or 480mg vial solutions for infusion after dilution.
480mg of nivolumab will be used per administration (one 480mg vial or two 240mg vials)

Preparation and administration of nivolumab;

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colourless to pale-yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains extraneous

particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.

- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL For patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.

- Mix diluted solution by gentle inversion. Do not shake

- The dose of nivolumab for administration must be prepared by the Investigator's or site's designed IP manager using aseptic technique. Total time from needle puncture of the vial to the end of administration should not exceed;

    - 8 hours at room temperature

    - 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F)

- The infusion should be administered over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

- Do not co-administer other drugs through the same intravenous line

- The intravenous line should be flushed at the end of the infusion.

6.3 Packaging, Labelling and Storage

6.3.1 RXC004

The capsules will be supplied in white 50 mL HDPE Duma bottles, 24 capsules per bottle, which are labelled appropriately as required by regulatory bodies and should be stored in the site pharmacy at ambient temperature, 20°±5°C. Full details of daily dispensing will be captured in the Pharmacy manual.

6.3.2 Nivolumab

Nivolumab will be centrally supplied by RedX as two 240mg/24mL vial solutions for infusion after dilution.

Storage;

- Unopened vials must be stored in a refrigerator (2°C to 8°C). The vials must be kept in the original package in order to protect from light. Vials should not be frozen. The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

- Infusion must be completed within 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions (2°C-8°C) and protected from light for up to 24 hours [a maximum of 8 hours of the total 24 hours can be at room temperature (20°C-25°C) and room light].

- Do not use after the expiry date which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

- Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.4 Selection of Doses in the Study

The starting dose for Modules are described in sections 5.2, 5.3, and 5.4 for Module 1, 2 and 3, respectively.

The starting dose/schedule of further modules will be the decision of the SRC based on emerging safety and tolerability data, however will not exceed the equivalent maximum exposure found to be tolerated in Module 1 at that point.

6.5 Selection and Timing of Dose for Each Subject

The doses and duration of treatment for each Module are detailed in the appropriate Module specific study design section. The doses and duration of treatment for Module 1, 2 and 3 are detailed in Section 5.2.5, Section 5.3.5 and Section 5.4.3., respectively. The exact date and times the study drug was administered and comments are to be recorded directly on the appropriate page of the eCRF.

7 STUDY ENDPOINTS

7.1 Efficacy

The preliminary assessment of efficacy is a secondary objective of the study. The efficacy measures for this study include objective response rate, duration of response disease control rate and PFS based on the RECIST version 1.1 guidelines.

Tumour Assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix 4 of this Clinical Study Protocol.

Baseline scans for RECIST should be performed within 28 days of first dose (the use of scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period should be detailed in the consent form). Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment.

Tumour assessments will be performed using full body (chest, abdomen and pelvis) CT/ MRI for soft-tissue lesion only and bone scan (with additional confirmatory imaging – plain x-ray, CT/ MRI) for bone metastasis (in patients who develop bone metastasis after study start). The methods of assessment used at baseline should be used at each subsequent follow-up assessment.

Scans will take place at timepoints detailed in the Schedule of assessments (Appendix 1, Appendix 20 and Appendix 9). Scans may be performed at other times, as clinically indicated.

Imaging tumour assessments will cease at objective progression. In the event of a patient discontinuing treatment for reasons other than progression they should continue to be followed for progression unless there is withdrawal of consent. Progression criteria for imaging tumour assessment will be determined by the following assessments:

- RECIST criteria for soft-tissue lesions only (lymph nodes, visceral metastasis, prostate)
- Bone Scans will be conducted at screening/baseline to rule out bone metastasis and during treatment if investigator suspects disease progression/development of bone metastasis

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should

be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). In order for a patient to be considered in disease control the patient must have at least stable disease for the first 2 scheduled scans (12 weeks for Module 1 or 16 weeks for Module 2). In addition the disease control rate at 18 or 24 weeks will be presented (for patients who have at least stable disease for the first 3 scheduled scans on Module 1 or 2 respectively).

For patients who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response for NTLs: CR, PD and Non CR/Non PD.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan and Schedule of Assessments (Appendix 1 for Module 1, Appendix 2 for Module 2, 0 for Module 3)

Calculation or Derivation of Tumour Response Variables

At each tumour assessment response will be based on RECIST 1.1 criteria RECIST 1.1 based on the status of their disease compared with baseline and previous visit assessments.

Progression of target lesions (TLs) will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study, including baseline). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the nadir sizes, including baseline) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)
- If > 1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by > 20% or more compared to the smallest sum of diameters on study), PD takes precedence over NE
- A visit response of CR will not be allowed if any of the TL data is missing

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be < 10mm to be considered non-pathological) and no new lesions have developed since baseline.

A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

To be considered a PR or CR in the clinical trial report, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 35 days.

When the Investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

For further details see Appendix 4

7.2 Safety

Safety assessments will include physical examination, vital signs, biochemistry and haematology, laboratory screens (including bone turnover markers) (see Schedule of Study Assessments in Appendix 1). Adverse events will also be noted at every clinical visit and recorded at least every week. For all administrations in hospital, the patients must wait for at least 60 minutes from the time of the RXC004 administration for observation and repeat vital

signs. Performance status will be measured weekly in Cycle 1, thereafter at the beginning of each cycle.

7.2.1 Adverse Events

Investigator and study personnel will report all AEs and SAEs elicited during subject questioning; discovered during physical examination; revealed by diagnostic or laboratory testing; or found by other means. These events must be recorded on the CRF and/or SAE form, as appropriate.

Use open-ended or non-directed method of questioning at each study visit to elicit the reporting of AEs.

Use the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 to grade adverse event severity. These criteria are provided in the study manual. When CTCAE criteria cannot be used, the event should be graded as mild, moderate, severe or fatal.

7.2.2 Clinical Laboratory Evaluations

The Investigator, IQVIA Clinical Medical Monitor, and Redx Chief Medical Officer (CMO) will review clinical laboratory tests for results of potential clinical significance at all the time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

Table 8 includes a list of analytes to be collected during the study.

Table 8: Laboratory Test: Required Analytes

Serum Chemistry	Haematology	Other
Albumin Amylase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Iron Lactate dehydrogenase Lipase Phosphorus Potassium Serum lipase Sodium Magnesium Total protein Uric acid IgG[a]	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • Reticulocyte count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	**Pregnancy test:** Female patients of childbearing potential only require a serum test at screening. Pregnancy tests (serum or urine) should be repeated if required by local regulations. **Urinalysis** Color and appearance pH Bilirubin Glucose Ketones Nitrite Occult blood Protein Urobilinogen CA 125 testing (patients with ovarian cancer only) **Thyroid Function Monitoring (Module 2 only)** TSH Free T3 (reflex)[c] Free T4 (reflex)[c]
Lipid Panel	**Standard LFT Monitoring**	**Bone Monitoring**
Total cholesterol Triglycerides LDL HDL CRP	Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin (If total bilirubin is elevated above ULN)	β-CTX Vitamin D[b] P1NP

aTotal IgG is obtained by an automated assay such as rate nephelometry. As long as the IgG is measured and not total immunoglobulin, institutional normal method of assessment is acceptable.

bAt screening only

c Free T3 or T4 only need to be measured if TSH is abnormal or if Investigator judges that there may be an AE related to the endocrine system

Bone monitoring: Blood samples (fasted) at time points detailed in the Schedule of Assessments (Appendix 1**Error! Reference source not found.** for Module 1, Appendix 2 for Module 2 and 0 for Module 3) and serum harvested for analysis.

7.2.3 Vital Signs, Physical Findings and Other Safety Assessments

Safety assessments will include physical examination, vital signs, biochemistry, haematology and urinalysis laboratory screens (see Schedule of Study Assessments, Appendix 1 for Module 1, Appendix 2 for Module 2 and Appendix 9 for Module 3). Measurements of heart rate, body temperature, blood pressure and respiratory rate will be made after the patient has been resting supine for a minimum of 5 minutes. Adverse events will also be noted at every clinical visit and recorded at least every week. For all administrations in hospital, the patients must wait for at least 60 minutes from the time of the RXC004 administration for observation and repeat vital signs. Performance status will be measured weekly in cycle 1, thereafter at the beginning of each cycle.

7.3 Pharmacokinetics and Pharmacodynamics

7.3.1 Pharmacokinetic Endpoints

RXC004 PK data will be summarised using descriptive statistics (N, mean, SD, median, min, max for all parameters, also geometric mean for C_{max} and AUC) to determine the pharmacokinetic behaviour of RXC004 on multiple dosing and to confirm relevant exposure to RXC004. This may also permit investigation of any significant metabolites. Venous blood samples (2 mL) for determination of concentrations of RXC004 in plasma will be taken at the times presented in Table 10**.** The date and time of collection of each sample will be recorded. Samples will be split, one for RXC004 and one for the metabolite identification work.

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. After 2 or more cohorts have been completed the timing of later PK samples will be re-assessed based on emerging PK data and the desire to characterise 80% of the AUC in all patients. The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Table 10.

If a patient misses any doses of RXC004 within 3 days of PK sampling, please contact the IQVIA representative as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to baseline assessments.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterisation of metabolites, if consent for this exploratory research has been obtained.

7.3.2 Determination of Drug Concentration in Pharmacokinetic Samples

Samples for determination of RXC004 concentrations in plasma will be analysed using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses in order to investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

PK parameters will be estimated for each patient using WinNonlin® (Phoenix 64 Build 8.0.0.3176) or suitable alternative. The following parameters will be derived, where appropriate, from the individual plasma concentration versus time profiles of RXC004.

Table 9: Definition of PK Parameters

PARAMETER	DEFINITION
C_{max}	The maximum observed concentration.
t_{max}	The time at which C_{max} was apparent.
AUC_{0-t}	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at t_{last} (the time of the last quantifiable concentration) calculated by the linear trapezoidal rule.
λ_z	The apparent terminal rate constant, estimated using the negative slope of the least square regression analysis of the log concentration versus time data for the terminal linear portion of the curve.
$t_{½}$	The apparent terminal half-life, calculated from $Log_e 2 / \lambda_z$.
$AUC_{0-\infty}$	The area under the concentration-time curve estimated from time zero to infinity as the sum of the two areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z.
CL	The systemic clearance calculated as: Dose/ $AUC_{0-\infty}$.
V_{ss}	The apparent volume of distribution at steady state calculated as: Dose/AUC x (AUMC/ $AUC_{0-\infty}$ - T/2) where T is the duration of intravenous injection.

Where appropriate the following pharmacokinetic parameters will be estimated

Single dose:

Plasma

- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Concentration at 24 hours (C24) (and concentration at 12 hours (C12) if start with twice daily dosing)
- Terminal rate constant (λz)
- Terminal half-life ($T_{½}$)
- Area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24}), from zero to the time of the last measurable concentration (AUC_{0-t}) and from zero to infinity (AUC)
- Plasma clearance (CL/F)
- Apparent volume of distribution (Vz/F)
- Mean residence time (MRT)

Multiple dose:

Plasma:

- Maximum plasma concentration at steady-state ($C_{ss,max}$)
- Time to $C_{ss,max}$ ($t_{ss,max}$)
- Minimum concentration at steady-state (Css, min)
- Area under the plasma concentration-time curve in the dosing interval (AUCtau)
- Plasma clearance at steady-state (CLss/F)
- Mean residence time at steady-state (MRTss)
- Swing

PK Analysis for Day 1 and Cycle 2 Day 1 (pre-dose):

- Dose proportionality
-
- Accumulation Ratio (Rac)
- Dose normalised Cmax
- Dose normalised AUCs
-

Plasma and pharmacodynamic samples will be collected according to the schedule in Table 10. These samples will be collected from the following patients:

Table 10: PK Plasma Sampling Schedule

Study Visit		Timing of Sample Relative to RXC004 Administration											
	Pre-dose	0.5 h (± 10 min)	1 h (± 10 min)	2 h (± 30 min)	4 h (± 30 min)	6 h (± 30 min)	8 h (± 30 min)	10 h (± 30 min)	12 h (± 30 min)	24 h (± 1h)	48 h (± 2h)	72 h* (± 2h)	96 hr* (± 2h)
C0D1	X	X	X	X	X	X	X	X	X	X	X	X	X
C1D1	X												
C1D15#	X	X	X	X	X	X	X	X	X	X			
C2D1	X												
C3D1to C6D1	X												

*72hr and 96hr PK will be completed in the first cohort of module 1 (RXC004 monotherapy), but may be stopped for subsequent cohorts if the terminal elimination phase indicates that this is not required. 72hr and 96hr PK is not required for Module 2 (RXC004 and nivolumab combination) and Module 3 (intermitent RXC004 schedules)

For Module 3 the 'on treatment' PK full time course will take place on C1D11 (see Schedule of Assessments - Appendix 9, for more details)

7.3.3 Pharmacodynamic Endpoints

7.3.3.1 Module 1

Skin, blood and tumour Sample Collection

Skin punch biopsy samples will be collected, where possible and where consent has been given, from any suitable patient enrolled into Module 1, according to the schedule of assessments. These samples will be collected at baseline and on treatment.

PBMC, plasma and ctDNA samples for pharmacodynamic analysis will be collected from all patients at baseline and on treatment, according to the schedule of assessments.

Fresh whole blood will be collected from a subset of patients at baseline and on treatment, according to the table of scheduled assessments (depending on proximity of site for analysis of this fresh sample).

Optional paired tumour biopsies will be also collected, where possible, from any suitable patient enrolled into module 1.

As pharmacodynamic data become available, the timing of pharmacodynamic sampling may be adjusted, but the frequency of blood samples obtained will not increase.

Table 11: Module 1 : Pharmacodynamic samples / Tumour Collection Schedule

	Tissue samples		**Blood samples**			
Study Visit	**Skin punch biopsy**	**Tumour Collection (optional)**	**PBMC**	**Plasma**	**ctDNA**	**Fresh whole blood[a]**
C0D1	Pre-dose[b]	Pre-dose[b]	Pre-dose	Pre-dose	Pre-dose	Pre-dose
C1D8	N/A	N/A	Approx. 4-6hr post dose	Approx 4-6hrs post dose	N/A	Pre-dose
C1D15	Approx. 4-6hr post dose	N/A	Approx. 4-6hr post dose	Approx 4-6hrs post dose	N/A	pre-dose
C2D1	N/A	Post dose[e]	Approx. 4-6hr post dose	Approx 4-6hrs post dose	Approx 4-6hrs post dose	Pre-dose
CXD1[c]	N/A	Cy4 (+/- 1 Cy)[e]	Approx. 4-6hr post dose	Approx. 4-6hr post dose	Cycle 4 Day 1 only. Approx. 4-6hr post dose	N/A
End of treatment/disease progression[d]	N/A	Post dose	Post dose	Post dose	Post dose	N/A

a Whole blood samples will be collected from sites of close proximity to Redx laboratory only

b Baseline tissue samples can be taken at any time after initial consent up to the first dosing. Investigator discretion should be used on likelihood of a patient being eligible

c CXD1 is Day 1 of each subsequent cycle

d Samples should be taken at the Final Study Visit, which should be performed as soon as practically possible after discontinuation of study drug (ideally within 7 days)

e Between 4-12 hours post dose

7.3.3.1.1 Exploratory endpoints from pharmacodynamic samples

Skin punch biopsies will be collected in Module 1. These samples may be analysed for gene and protein expression to determine target engagement of the Wnt pathway.

PBMC pharmacodynamic samples will be collected for all patients. These samples may be analysed for the effect of drug administration on induced PORCN/Wnt or related pathway activity.

Plasma samples may be used to analyse circulating soluble factors, such as relevant tumour markers and markers of immune function, in baseline and on-treatment samples. These may be analysed by enzyme linked immunosorbent assay (ELISA), or other relevant methods.

ctDNA samples may be used to analyse circulating tumour DNA/RNA (ctDNA/RNA). Total amounts and/or analysis of mutations/genetic alterations in ctDNA/RNA may be analysed and associated with response to treatment.

Fresh whole blood pharmacodynamic samples may be analysed by flow cytometry for changes in markers of immune cell populations, including, but not limited to, markers for immune cell subsets. In addition, assays of immune function such as stimulated cell activation (assessed by marker expression, cytokine secretion, proliferation, etc.) may be conducted using whole blood samples.

Paired tumour biopsies may be monitored for gene/protein changes. This data may be used to examine changes in Wnt pathway activation and/or immune cell changes in the tumour microenvironment.

Additional pharmacodynamic markers, (e.g., monitoring other inflammatory markers, measuring specific cell populations, RNA profiles of specific cell populations, or measuring cell surface markers that can be measured by flow cytometry, Western blot, or ELISA) may be evaluated at the discretion of the sponsor using excess pharmacodynamic or PK samples.

Tumour Samples

An archival or a newly acquired biopsy will be requested from every patient enrolled in the study. These archived/newly acquired biopsies are optional (but encouraged) in the study.
Candidate biomarkers, e.g. upstream Wnt pathway aberrations (RNF43 mutation, RSPO fusion) will be analysed in archived/newly acquired tumour samples to investigate the relationship between these biomarkers and efficacy outcomes following treatment.
Paired tumour biopsy samples, where available, will be analysed for exploratory pharmacodynamic endpoint measurements as described in Section 7.3.3.1.1

7.3.3.2 Module 2

Blood and tumour Sample Collection

PBMC, circulating soluble factors, ctDNA and ctRNA samples for pharmacodynamic analysis will be collected from all patients at baseline and on treatment, according to the table of scheduled assessments.

Fresh whole blood will be collected from a subset of patients at baseline and on treatment, according to the table of scheduled assessments (depending on proximity of site for analysis of this fresh sample).

Optional paired tumour biopsies will be also collected, where possible, from any suitable patient enrolled into module 2.

As pharmacodynamic data become available, the timing of pharmacodynamic sampling may be adjusted, but the frequency of blood samples obtained will not increase.

Table 12: Module 2: Pharmacodynamic samples / Tumour Collection Schedule

	Tumour Samples	**Blood Samples**				
Study Visit	**Paired tumour biopsies[f]**	**PBMC**	**Circulating soluble factors**	**ctDNA**	**ctRNA**	**Fresh whole blood[a]**
C0D1	(Optional) predose[b]	predose	predose	predose	predose	predose
C1D15	(Optional) post dose	Approx. 4-6hr post dose	Approx 4-6hrs post dose	Approx 4-6hrs post dose	Approx 4-6hrs post dose	predose
C2D1	N/A	Approx. 4-6hr post dose	Approx 4-6hrs post dose	Approx 4-6hrs post dose	Approx 4-6hrs post dose	Predose
CXD1[c]	(Optional) During Cycle 3 of treatment	Approx. 4-6hr post dose	Approx. 4-6hr post dose	Approx. 4-6hr post dose	Approx. 4-6hr post dose	N/A

End of treatment/disease progression[d]	N/A	N/A	N/A	Post final dose	Post final dose	N/A

a Whole blood samples will be collected from sites of close proximity to Redx laboratory only

b Baseline tumour samples can be taken at any time after initial consent up to the first dosing. Investigator discretion should be used on likelihood of a patient being eligible

c CXD1 is Day 1 of each subsequent cycle

d Samples should be taken at the IP discontinuation visit

7.3.3.2.1 Exploratory endpoints from pharmacodynamic samples

PBMC pharmacodynamic samples will be collected for all patients. These samples may be analysed for the effect of drug administration on induced PORCN/Wnt or related pathway activity.

Plasma samples may be used to analyse circulating soluble factors, such as relevant tumour markers and markers of immune function, in baseline and on-treatment samples. These may be analysed by enzyme linked immunosorbent assay (ELISA), or other relevant methods.

ctDNA and ctRNA samples may be used to analyse circulating tumour DNA/RNA (ctDNA/RNA). Total amounts and/or analysis of mutations/genetic alterations in ctDNA/RNA may be analysed and associated with response to treatment.

Fresh whole blood pharmacodynamic samples may be analysed by flow cytometry for changes in markers of immune cell populations, including, but not limited to, markers for immune cell subsets. In addition, assays of immune function such as stimulated cell activation (assessed by marker expression, cytokine secretion, proliferation, etc.) may be conducted using whole blood samples.

Paired tumour biopsies may be monitored for gene/protein changes. This data may be used to examine changes in Wnt pathway activation and/or immune cell changes in the tumour microenvironment.

Additional pharmacodynamic markers, (e.g., monitoring other inflammatory markers, measuring specific cell populations, RNA profiles of specific cell populations, or measuring cell surface markers that can be measured by flow cytometry, Western blot, or ELISA) may be evaluated at the discretion of the sponsor using excess pharmacodynamic or PK samples.

7.3.3.2.2 Tumour Samples

An archival or a newly acquired biopsy will be requested from every patient enrolled in the study. These archived/newly acquired biopsies are optional (but encouraged) in the study.

Candidate biomarkers, e.g. upstream Wnt pathway aberrations (RNF43 mutation, RSPO fusion) will be analysed in archived/newly acquired tumour samples to investigate the relationship between these biomarkers and efficacy outcomes following treatment.

Paired tumour biopsy samples, where available, will be analysed for exploratory pharmacodynamic endpoint measurements as described in Section 7.3.3.2.1

7.3.3.3 Module 3

Skin punch biopsy samples will be collected in Module 3, at baseline and on treatment according to the schedule of assessments (Appendix 9). Skin punch biopsies are mandatory in Module 3.

PBMC, circulating soluble factors, ctDNA and ctRNA samples for pharmacodynamic analysis will be collected from all patients at baseline and on treatment, according to the table of scheduled assessments (Appendix 9).

Fresh whole blood will be collected from patients from UK sites at baseline and on treatment, according to the table of scheduled assessments (Appendix 9)

Optional paired tumour biopsies will be also collected, where possible, from any suitable patient enrolled into module 3.

As pharmacodynamic data become available, the timing of pharmacodynamic sampling may be adjusted, but the frequency of blood samples obtained will not increase.

7.3.3.3.1 Exploratory endpoints from pharmacodynamic samples

PBMC pharmacodynamic samples will be collected for all patients. These samples may be analysed for the effect of drug administration on immune cell composition, PORCN/Wnt or related pathway activity.

Plasma samples may be used to analyse circulating soluble factors, such as relevant tumour markers and markers of immune function, in baseline and on-treatment samples. These may be analysed by enzyme linked immunosorbent assay (ELISA), or other relevant methods.

ctDNA and ctRNA samples may be used to analyse circulating tumour DNA/RNA (ctDNA/RNA). Total amounts and/or analysis of mutations/genetic alterations in ctDNA/RNA may be analysed and associated with response to treatment.

Fresh whole blood pharmacodynamic samples may be analysed by flow cytometry for changes in markers of immune cell populations, including, but not limited to, markers for immune cell subsets. In addition, assays of immune function such as stimulated cell activation (assessed by marker expression, cytokine secretion, proliferation, etc.) may be conducted using whole blood samples.

Paired skin punch biopsies may be monitored for Wnt pathway activity through gene or protein expression changes.

Paired tumour biopsies may be monitored for gene/protein changes. This data may be used for example, to examine changes in Wnt pathway activation and/or immune cell changes in the tumour microenvironment.

Additional pharmacodynamic markers, (e.g., monitoring other inflammatory markers, measuring specific cell populations, RNA profiles of specific cell populations, or measuring cell surface markers that can be measured by flow cytometry, Western blot, or ELISA) may be evaluated at the discretion of the sponsor using excess pharmacodynamic or PK samples.

7.3.3.3.2 Tumour Samples

An archival or a newly acquired biopsy will be requested from every patient enrolled in the study. These archived/newly acquired biopsies are optional (but encouraged) in the study. These archival samples may be collected at screening and may be sent for central genetic screening as described in Section 5.4.2 and/or analysed for exploratory endpoint measurements as described in Section 7.3.3.3.1.

Candidate biomarkers may also be analysed in archived/newly acquired tumour samples to investigate the relationship between these biomarkers and efficacy outcomes following treatment.
Paired tumour biopsy samples, where available, will be analysed for exploratory pharmacodynamic endpoint measurements as described in Section 7.3.3.3.1

7.4 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. Adverse events and, when applicable, clinical laboratory data will be graded using NCI CTCAE, version 5.0.

Response will be assessed according to RECIST v1.1 (Appendix 4) which includes standard criteria for evaluating response in solid tumours. Prostate cancer responses will be assessed via PCWG3 criteria, which are standard accepted modifications of RECIST. The intervals of evaluation in this protocol are appropriate for disease management.

8 QUALITY CONTROL AND QUALITY ASSURANCE – CORE

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following QC checkpoints will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s).
- Central laboratories for biomarker analysis.
- Local laboratories for clinical laboratory parameters and ECGs.
- Centre Initiation visit.
- Early centre visits post-enrollment.
- Routine centre monitoring.
- Ongoing centre communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, Sponsor and/or IQVIA Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study centre visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

8.1.1 Monitoring

The Sponsor has engaged the services of a contract research organization (CRO), IQVIA, to perform all monitoring functions within this clinical study. IQVIA's clinical monitors will work in accordance with SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study centre, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly and that

data are recorded correctly and completely. Monitors will also compare entries in eCRFs with corresponding source data prior to data cleaning by IQVIA Data Management and inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study centre. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each centre while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For the following items, this check will be 100%:

- Subject identification number.
- Subject consent obtained.
- Subject eligibility criteria (inclusion and exclusion criteria).
- Efficacy variables.
- Medical record of AE.

For all other items, 100% of the data will be checked.

8.1.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of IQVIA. Single data entry with source data verification (SDV) will be performed for EDC.
A validated and 21 CFR Part 11 compliant Electronic Data Capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study centre. Data collection will be completed by authorized study centre staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study centre staff prior to the study being initiated and any data being entered into the system for any study patients.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study centre staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, subject files, etc.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

8.1.3 Quality Assurance

Study centres, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or IQVIA on behalf of Redx. In addition, inspections may be conducted by regulatory bodies at their discretion.

All required data will be entered into the clinical and/or safety database in accordance with Code of Federal Regulations (CFR) 21 Part 11 compliance. The database will include an audit

trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password protected environment. All missing data will be explained.

Data entered in the system must be verifiable against source documents and will be reviewed manually for validity and completeness against the source documents by a clinical monitor from Redx or its designee. If necessary, the study site will be contacted for corrections or clarifications.

9 STATISTICS

9.1 Determination of Sample Size

The sample size for Module 1 is not based on a formal sample size calculation, as no formal statistical hypothesis is being tested. The estimated maximum number of patients (n=30) has been based on the expected number of cohorts and the desire to obtain adequate tolerability, safety, pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the IMP and procedures. The total number of patients required will depend upon the toxicities encountered and the number of dose cohorts required.

For Module 2, there will approximately 18 patients.

Module 3 will recruit 6 patients who are evaluable for DLT assessment per cohort.

9.2 Statistical Methods

All analyses, summaries, and listings will be performed using SAS® software (version 9.3 or higher). Modules will be summarized separately.

A baseline assessment will be defined as the last assessment performed prior to the first dose of study treatment. While many of these assessments will be performed on the day of the first dose, others will be performed during screening. If a patient is missing an assessment typically performed on the day of the first dose, screening values may be substituted as baseline.

Patient disposition, demographics, and baseline characteristics will be summarised using descriptive statistics.

In general, all efficacy, safety, and PK variables will be summarised using descriptive statistics. Continuous variables will be summarised by descriptive statistics (sample size [n], mean, standard deviation [SD], median, minimum and maximum). Categorical variables will be summarised in frequency tables (n, frequencies, and percentages). Individual subject data will be presented in listings. Missing data will not be imputed unless otherwise stated

The study data from each module will be analyzed and reported based on all patient data up to the time when all module patients have completed at least 6 cycles of treatment or have discontinued study treatment. Data will be listed, summarized, and analyzed by dose level and overall.

Analysis Populations
Four analysis populations will be defined for use with various analyses.

- The Safety Population will consist of all patients who enrolled and receive at least one dose of study drug.
- The PK Evaluable Population will consist of those patients deemed by the sponsor or pharmacokineticist to have sufficient PK concentration data to be meaningfully included in the PK analysis summaries.
- The PD Evaluable Population will consist of those patients deemed by the sponsor or translational scientist to have sufficient PD assessment data to be meaningfully included in the PD analysis summaries.
- The Efficacy Evaluable Population will include patients who receive a radiographic assessment at baseline, received at least one dose of study treatment, and at least one post-dose radiographic tumour assessment, or progressed ahead of the first scan.

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or greater. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug: March 2017 or later version).

9.2.1 Efficacy Analyses

Overall Response Rate (ORR) (CR+PR), Duration of Response (DoR), Disease Control Rate (DCR) (CR+PR+SD) will be calculated for the efficacy evaluable population based on modified RECIST guidelines (Appendix 4).
At each tumour assessment visit patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD or NE depending on the status of their disease compared with baseline and previous visit assessments.

Progression of target lesions (TLs) will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study, including baseline). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

The best overall response will be determined programmatically for each patient as CR, PR, SD, PD or NE, based on the best response recorded from start of study treatment to end of treatment, including any assessments for confirmation after the end of treatment.

Objective Response Rate

Objective response rate is defined as the number of patients who have at least one response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1) that is confirmed at least 4 weeks later divided by the number of response evaluable patients.

Disease Control rate

Disease control rate is defined as the proportion of all patients dosed that have a visit response of at least SD, PR or CR at the second schedule scan post baseline, scheduled at week 12 for module 1 or week 16 for module 2. Therefore, earlier visit responses of CR, PR that become PD at the second post baseline scan or NE responses at the second post baseline scan do not constitute disease control. A time window of 1 week around the visit will be applied and it is recommended that any visits occurring within 1 week of the scheduled time will be acceptable; however, if an earlier visit is defined as PD then the visit response at the second post baseline scan would also be defined as PD. If the second post baseline scan is missing or NE, but the next evaluable response is SD or better, then the patient will be defined as having non-progressive disease at the second post baseline scan visit. Disease control rate will also be assessed for patients who have at least SD for the first 3 scheduled post baseline scans (ie 18 weeks for module 1 and 24 weeks for module 2.

Percentage Change in Tumour Size

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change from baseline in the sum of the diameters of TLs.

The best percentage change in tumour size will be the patient's value representing the largest decrease (or smallest increase for those patients whose tumour target lesions do not show a decrease) from baseline in tumour size.

Duration of response

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

Progression Free Survival

Progression-free survival (PFS) will also be assessed. Analyses will be done at the RP2D and pooled for all patients in a module.
Progression free survival (PFS) is defined as the time from start of treatment (first dose of RXC004, or combination agent if relevant, whichever is first) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a subject for PFS the subject will be censored at the latest of the dates contributing to a particular overall visit assessment

9.2.2 Safety Analyses

The Safety Population will be used to summarize the safety endpoints for this study. Safety and tolerability will be assessed by:

- physical examination (including BP, Pulse, skin assessment),
- evaluation of laboratory parameters - clinical chemistry, haematology and urinalysis (including urea creatinine and specific gravity)
- ECG
- number of withdrawals, discontinuations and dose reductions
- number of DLTs
- assessment of AEs (graded by CTCAE): adverse events will be summarized by MedDRA system organ class and preferred term based on the worst grade observed for each patient. If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences
- SAEs

9.2.3 Data to be Analysed

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by IQVIA and approved by the Sponsor prior to database lock.

9.2.4 Missing Data

Missing data will not be imputed unless otherwise stated.

9.3 Subject Disposition

The disposition summary will include all dosed patients.

9.4 Subject Characteristics

Patient characteristics will be obtained at screening and will be summarised for all patients administered RXC004. Summaries will include descriptive statistics for continuous variables (sample size, mean, standard deviation, median, minimum, and maximum) and for categorical variables (sample size, frequency and percent). Subject characteristics may include, but are not limited to: age, gender, race/ethnicity, height, weight, and body mass index (BMI).

Subject characteristics will be summarised using the Safety Population.

9.5 Efficacy Analyses

Objective response rate and disease control rate will be summarized per dose level and pooled by module.

Duration of response will only be evaluated for the subgroup of patients with an ORR using the Kaplan-Meier method, provided there are sufficient response to make it meaningful.

Best change in tumor size whilst on treatment (ie greatest decrease or smallest increase for subjects whose tumors do not show a decrease) will be presented in the form of waterfall plots, with the bars being colour coded by dose level.

Changes in tumor size for individual patients across time will also be presented by spider plots.

PFS will be analyzed using the method of Kaplan-Meier, for patients who receive the recommended Phase 2 dose, and also pooling together all doses within a module.

9.6 Safety

9.6.1 Adverse Events

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of the study drug and within 30 days of last dose of RXC004 in the case of module 1 and within 90 days of last dose of nivolumab for module 2. Adverse event summaries will include incidence of treatment-emergent AEs by MedDRA preferred term and system organ class, SAEs including deaths, AEs that led to study drug discontinuation, AEs leading to death, treatment related AEs and AEs by maximum severity..

9.6.2 Clinical Laboratory Evaluations

Shift tables to characterize changes from baseline will be presented for graded haematology, clinical chemistry, and coagulation parameters. All data will be presented in listings. Other summaries will be presented on a data-driven basis.

9.6.3 Vital Signs Measurements, Physical Exams, ECG and Other Safety Evaluations

All data will be presented in listings. Shift tables for change from baseline for ECG parameters and vital signs measurements based on ranges specified in the SAP will be provided

9.7 Health Outcomes Analyses

No health outcomes analyses will be conducted in this study.

9.8 Pharmacokinetic and Pharmacogenetic Analyses

Blood samples will be collected and stored to assess any potential differences in PK or toxicity that may be reflected in host genetics. The results of the PK and pharmacogenetic analyses may be presented in reports separate to the CSR.

9.9 Interim Analyses

No formal interim analysis is planned.

10 ETHICS

10.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the Informed Consent Form (ICF) and any other written information and/or materials to be provided to the patients. The Investigator will provide the Redx or IQVIA with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study centre(s). The Investigator should submit the written approval to Redx via IQVIA before enrolment of any subject into the study.

Redx and IQVIA should approve any modifications to the ICF that are needed to meet local requirements. The Investigator will supply documentation to Redx via IQVIAas required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.
The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

Redx via IQVIA will provide Regulatory Authorities, Ethics Committees and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki, the principles of Good Clinical Practice (current ICH guidelines) and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human

patients. The study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety and well-being of the participating study patients are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated consent form.

10.4 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Redx or their representative(s) will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a Redx or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

11 STUDY ADMINISTRATION – CORE

11.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

11.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, IQVIA, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

11.3 Investigator Information

11.3.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

11.3.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Section 14). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements. The study will not be able to start at any centre where the Investigator has not signed the protocol.

11.3.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study centre will be set forth in the Clinical Trial Agreement.

11.4 Financing and Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

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13 APPENDICES

Appendix 1 Schedule of Assessments - Module 1

	Prescreen	Screening	Cycle 0 6-10 days++	Cycle 1			C2	C3	C4	C5	C6 onwards	Final study visit[10]	30-day follow-up	PFS follow-up
Cycle Day		-28 to 0	1	1	8	15	1	1	1	1	1		+/- 3 days	
Informed consent	x	x												
Pharmacogenetics (optional consent)		x												
Demography & baseline assessments		x												
Smoking status & alcohol consumption		x												
Medical & surgical history		x												
Inclusion/exclusion criteria**		x	x											
Bone Scan		x	As clinically indicated											
Physical exam (including height) & weight [1]		x	x	x	x		x	x	x	x	x	x		
Performance status (ECOG)		x	x	x	x	X	x	x	x	x	x	x	x	
Vital signs [2]		x	x	x	x	X	x	x	x	x	x	x		
ECG [3]		x	x	x	x		x	x	x	x	x			
DXA Scan (Including VFA at baseline)		x					x		x		Cycle 7 and every 3 cycles thereafter			
Clinical chemistry/ haematology*		x		x	x	x	x	x	x	x	x	x		
Urinalysis*		x	x	x	x		x	x	x	x	x			
Bone Markers (β-CTX^^^ & P1NP)		x			x	X	x[14]	x[14]	x	x	x	x		
Pharmacokinetics [9]			x	x		X	x	x	x	x	Cycle 6 only			
Tumour biopsy (archive or newly acquired)[5]	x	x					x	A single optional additional biopsy at Cy4 (+/- 1 Cy)				x		
PD PBMC sample [6]			x		x	X	x	x	x	x	x	x		
PD plasma sample[6]			x		x	X	x	x	x	x	x	x		
PD ctDNA sample			x				x		x			x		
Fresh blood for PD analysis[12]			x		x	X	x							
Tumour assessment (RECIST 1.1 CT or MRI)[4]		x		Every 6 weeks +/- 1 week from Cycle 1 Day 1 until RECIST1.1 defined progression										
Biomarker (germ line DNA) testing [8]		x												
Skin biopsy (target engagement) [7]		x				x								
Denosumab dosing			120 mg sc Denosumab once every month from C0D1 until IP discontinuation											
Vitamin D and Calcium supplements[11]		From consent until end of study drug treatment												

	Prescreen	Screening	Cycle 0 6-10 days++	Cycle 1			C2	C3	C4	C5	C6 onwards	Final study visit[10]	30-day follow-up	PFS follow-up
RXC004 Dose administration			x	Multiple dosing at specified schedule										
Concurrent medications		x	x	x								x		
Adverse events		x	x	x								x	x	
Patient diary card review				x	x	X	x	x	x	x	x	x	x	
Subsequent anti-cancer therapy												x	x	x

Footnotes - General

Assessments made on Day 1 of each cycle are to be conducted prior to RXC004 administration, unless specified otherwise.
Additional assessments may be conducted as clinically indicated.
A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.
* Female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle.
**Eligibility criteria to be re-checked at Cycle 0 prior to dose administration.
^^^ Morning after an overnight fast
++The PK from Cy0D1 will be analysed with fast turnaround, sites will be informed if the exposure level is deemed inappropriate to start continuous treatment

Assessment Specific

1. Patient's height will be recorded at Screening. A full physical examination is required at Screening and prior to Day 1 of each cycle and Day 8 of Cycle 1; Symptom-directed physical examination is acceptable at other time-points. Weight will be recorded at Screening and on Day 1 of each cycle.
2. On each hospital administration day, vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the RXC004 administration. Patient status will be monitored during RXC004 administration and repeat vital signs will be taken if needed.
3. On Cycle 0, Day 1 and Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and 30 mins (+/- 15 mins) after RXC004 administration. On Day 1 of all other cycles, a resting 12-lead ECG will be conducted pre-dose only.
4. CT or MRI performed at Screening and up to 7 days prior to end of Cycles 2, 4, 6 & 8. Bone scans may be included if relevant for patients with bone metastases that develop after study start.

Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.

5. Patients with suitable archived biopsy samples should be encouraged to consent to provide these for biomarker/PD evaluation. The study will encourage taking newly acquired biopsies for biomarker/PD evaluation at screening (in the absence of suitable archival material), 4-12 hours post-dose during treatment (Cycle 2, at Cycle 4 (+/- 1 Cycle) and/or at the point of disease progression. Although optional, every effort should be made to collect newly acquired pre and post-dose biopsy samples from patients and imaging techniques may be used to facilitate this process.
6. Blood samples will be taken to obtain PBMC or plasma, pre-dose at /C0D1 visit, approx. 4-6hrs post dose at C1D8, C1D15 and day 1 of each subsequent Cycle (CXD1) visits and at disease progression/discontinuation of study treatment
7. Skin biopsies will be taken at predose (preferably at screening) and on PK profile day Cycle 1, Day 15, approximately 4-6h post-dose. Exact time of dose administration and biopsy sampling must be recorded.
8. Consenting patients will have a 10 mL blood sample taken for preparation of a germ-line DNA sample at Screening (recommended time-point only).
9. Patients will have PK blood sampling conducted at the following sample times

Cycle 0: Day 1 - Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 48 h, 72 h and 96h post-dose.
Cycle 1, Day 15: Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h & 24 h
Cycle X, Day 1 - A single pre-dose sample will also be taken on Cycles 1-6 on Day 1.

Each schedule will not exceed 12 samples taken out to 96 hours post RXC004 administration. The SRC may advise on adjusted time-points. The actual time for each blood draw must be accurately recorded.

10. The Final Study Visit should be performed as soon as practically possible after discontinuation of study drug (ideally within 7 days)

11. Vitamin D (800 IU OD) and calcium (1000 to 1500 mg OD) supplementation should commence at screening and continue throughout the treatment period

12. Fresh blood may be requested from investigator sites in close proximity to RedX laboratories. All samples should be taken predose

13. Blood samples will be taken to obtain ctDNA, pre-dose at C0D1 visit, approx. 4-6hrs post dose at C2D1 and C4D1 visits, and at disease progression/discontinuation of study treatment

14. Day 1 and Day 15 bone markers will be assessed on Cycle 2 and Cycle 3 for the first 3 cohorts only (0.5mg, 1mg and 1.5mg RXC004). All subsequent cohorts will have bone markers assessed on Day 1 only of Cycle 2 and Cycle 3

Appendix 2 Schedule of Assessments - Module 2

	Module 2 (RXC004 + Nivolumab) Schedule of Assessments									
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (28 day cycle)**		**Cycle X Day 1 (28 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**90 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 +/- 1d**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**+/- 3d**	
Pre-Screening informed consent (optional)	X									
Diagnostic / Archival tumour tissue (optional)	X									
Genetic screening for RNF43/RSPO aberrations (optional)	X									
Informed consent		X								
Pharmacogenetics (optional consent and blood sample)[i]		X								
Demography & baseline characteristics		X								
Smoking status & alcohol consumption		X								
Medical/surgical history		X								
Inclusion/exclusion criteria**		X								
Bone Scan		X	As clinically indicated							

	Module 2 (RXC004 + Nivolumab) Schedule of Assessments									
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (28 day cycle)**		**Cycle X Day 1 (28 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**90 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 +/- 1d**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**+/- 3d**	
HepB, HepC and HIV testing		X								
Physical examination[a]		X	X	X		X	X			
ECOG/WHO performance status		X	X	X		X	X			
Pregnancy test (WOCBP only)		(X)	(X)	(X)		(X)				
Vital signs (including height and weight)[b]		X	X	X	X	X	X	X		
Clinical chemistry / Haematology		X	X	X	X	X	X	X	X	
TSH (reflex T3/T4)[m]		X		X	X	X	X	X	X	
Urinalysis*		X	X	X	X	X				
ECG		X	X	X	X	X[h]	X			
DXA scan (including VFA*** at baseline)		X				Cycle 2, 4 and 7, and every third cycle thereafter				
Tumour biopsy (optional - archive or newly acquired)		X			X[g]	X[g]				
Blood samples for bone turnover biomarkers		X			X	X	X			
Blood sample for circulating soluble factors[c]			X		X	X				

	Module 2 (RXC004 + Nivolumab) Schedule of Assessments									
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (28 day cycle)**		**Cycle X Day 1 (28 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**90 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 +/- 1d**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**+/- 3d**	
Blood sample for PBMC (viable cells)[c]			X		X	X				
Fresh blood for PD analysis[d]			X		X	Cycle 2 Day 1 only				
Blood sample ctDNA analysis[e]			X		X	X	X			
Blood sample ctRNA analysis[e]			X^n		X^n	X^n	X^n			
RECIST 1.1 assessments (by CT/MRI)[j]		X	Every 8 weeks +/- 1 week from Cycle 1 Day 1 until RECIST1.1 defined disease progression							
Vitamin D3 and Calcium supplements		Patients should commence 800 IU vitamin D3 (Cholecalciferol) QD and 1000-1500 mg calcium QD supplements from ICF signature until RXC004 discontinuation								
Denosumab dosing[o]			120 mg sc Denosumab once every month from C0D1 until RXC004 discontinuation							
RXC004 dosing			X	Multiple dosing at cohort specified schedule						
Nivolumab dosing[k]				X		X				
RXC004 PK[f]			X	X	X	X	X			
Concomitant medication		X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	
Patient diary card review				X	X	X	X			

	Module 2 (RXC004 + Nivolumab) Schedule of Assessments									
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (28 day cycle)**		**Cycle X Day 1 (28 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**90 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 +/- 1d**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**+/- 3d**	
Subsequent anti-cancer therapy							X	X	X	X

Footnotes - General

Assessments made on Day 1 of each cycle are to be conducted prior to RXC004 administration, unless specified otherwise.
Additional assessments may be conducted as clinically indicated.
A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.
* Female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle
**Eligibility criteria to be re-checked at Cycle 1 prior to dose administration.
***A lateral T & L spine assessment if a Vertebral Fracture Assessment (VFA) cannot be completed locally

a A full physical examination is required at Screening and prior to Day 1 of each cycle ; Symptom-directed physical examination is acceptable at other time-points
b Vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the RXC004 administration. Patient status will be monitored during RXC004 administration and repeat vital signs will be taken if needed. Height is required at screening only. Weight will be recorded at Screening and on Day 1 of each cycle.
c Pre-first dose on Cycle 0 Day 1 and 4-6hrs post dose on Cycle 1 Day 15 and Day 1 of each subsequent cycle
d Fresh blood samples to be collected from selected sites only (in close proximity to RedX laboratory). All samples should be collected pre-dosing.
e Pre-first dose on Cycle 0 Day 1 and 4-6hrs post dose on Day 1 of each subsequent cycle and at progression/discontinuation
f Patients will have PK blood sampling conducted at the following sample times

Cycle 0: Day 1 - Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, and 48 h post-dose.
Cycle 1, Day 15: Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h & 24 h
Cycle X, Day 1 - A single pre-dose sample will also be taken on subsequent samples on Day 1.

The SRC may advise on adjusted time-points. The actual time for each blood draw must be accurately recorded.

g An optional 'on treatment' biopsy at C1D15 and during Cycle 3 of treatment, preferably from the same site as the baseline biopsy sample
h On Cycle 0, Day 1 and Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and 30 mins (+/- 15 mins) after RXC004 administration. On Day 1 of all other cycles, a resting 12-lead ECG will be conducted pre-dose only.
i Consenting patients will have a 10 mL blood sample taken for preparation of a germ-line DNA sample at Screening (recommended time-point only).
j CT (preferred) or MRI, each preferably with IV contrast. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging time points per patient. Note that where there is a rationale for assessment of bone lesions that develop after study start, these assessments will be performed as part of the CT or MRI assessment and will not require additional radiological bone scan assessment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.
k 480mg IV infusion over 60 minutes, q4w +/- 3 days, unless an infusion needs to held due to an adverse event. Results for chemistry, haematology and thyroid function labs must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing. If a patient continues in the study on nivolumab alone, this treatment may be continued for a maximum of 12 months in total.
l Follow up assessments should be performed 30 days after discontinuation of IP and 90 days after last dose of nivolumab
m T3 and T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system
n For patients with Wnt ligand dependent tumours only (RNF43/RSPO aberrations or biliary/thymus cancers).

- All patients must receive denosumab before first dose of RXC004. 120 mg sc denosumab should be administered approximately once every month from C0D1 until RXC004 discontinuation. Investigators may delay subsequent denosumab doses until the next scheduled visit providing that there is no significant increase in β-CTX compared to baseline, according to Investigator judgement

Appendix 3 Performance Status Scale

ECOG	
Score	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4 Response Evaluation Criteria for Solid Tumours (RECIST)

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
New measureable lesions[1]	Always represents progressive disease (PD)
New nonmeasureable lesions	Always represents progressive disease (PD)
Non-index lesions	Changes contribute to defining best overall response of CR, PR, SD, and PD

From RECIST v1.1

1) Measureable lesion must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm)

Appendix 5 Colitis Management and Treatment Guidelines

Events of colitis or enteritis were reported in four patients who commenced treatment at doses of 3 mg QD or 10 mg QD. Events of ileitis and colitis were subsequently reported in the ongoing Phase 2 studies (RXC004/0002 and RXC004/0003), at doses of 2mg QD, so there is a potential risk for colitis in patients receiving RXC004 2mg QD as a monotherapy.

RXC004-related diarrhoea/colitis may present as abdominal pain with other symptoms including intermittent constipation, diarrhoea, nausea and/or vomiting. In some cases, symptoms may be minimal. Blood and mucus in the stool may not be apparent.

Symptoms may be preceded by or accompanied by a raised CRP and neutrophil count.

If lower GI tract inflammation is suspected, infectious and other causes should be excluded, including CMV and *C .difficile*. Attempts should be made to definitively diagnose the condition with a CT scan, and colonoscopy/sigmoidoscopy with biopsy, if clinically safe to do so.

Nivolumab is known to cause colitis (See Appendix 8) so patients receiving the combination of RXC004 and nivolumab may be at higher risk of this event. These guidelines are consistent with guidance for nivolumab-related colitis. However, for patients who are receiving RXC004 plus nivolumab, please also refer to the most current version of the nivolumab SPC/USPI.

Management:

Monitoring of CRP or fecal calprotectin levels may help to monitor the response to treatment.

Grade	**Management**
Grade 1 colitis (asymptomatic but evidence on CT scan)	Continue RXC004 at a lower dose and repeat the CT scan within 4 weeks. No action is needed for nivolumab. No additional treatment is indicated. If the Grade 1 colitis is evident on the second scan despite the lower dose of RXC004, it should be managed as Grade 2 colitis and the scan should be repeated within 4 weeks

Grade	**Management**
Grade 2 colitis (abdominal pain, mucus or blood in stool)	Pause RXC004 (and nivolumab if applicable) Manage with corticosteroids at a dose of 0.5mg/kg methylprednisolone equivalent. When symptoms have resolved, taper over 2-4 weeks. If symptoms recur during tapering, the steroid dose may need to be increased again. If no improvement in 72 hrs despite treatment, treat as Grade 3 RXC004 can be restarted at a lower dose after colitis has resolved to Grade ≤ 1* and steroids tapered to physiological levels (<10mg prednisone per day equivalent dose) over at least 1 month. If steroids cannot be tapered to physiological levels within 12 weeks of commencing steroid treatment, then RXC004 (and nivolumab if applicable) should be permanently discontinued.
Grade 3 colitis(severe or persistent abdominal pain, fever, ileus; peritoneal signs)	Pause RXC004 (and nivolumab if applicable) Seek specialist advice Manage with corticosteroids at a dose of 1mg/kg methylprednisolone equivalent. When symptoms improve, taper steroids to physiological levels over 4-8 weeks and consider use of prophylactic antibiotics and anti-fungals If the patient is receiving RXC004 as a monotherapy, RXC004 can be restarted at a lower dose after colitis has resolved to Grade ≤ 1* and steroids tapered to

Grade	**Management**
	physiological levels (<10mg prednisolone equivalent dose) over at least 1 month.. **If the patient is receiving RXC004 in combination with nivolumab, both agents should be permanently discontinued** If steroids cannot be tapered to physiological levels within 12 weeks of commencing steroid treatment, then RXC004 (and nivolumab if applicable) should be permanently discontinued. Additional anti-inflammatory medications (e.g infliximab) may be indicated if no improvement in 48-72 hrs. **It is important to rule out bowel perforation and refer to infliximab SMPC/USPI for general guidance before using infliximab** If anti-inflammatories are required, RXC004 (and nivolumab if applicable) should be permanently discontinued.
Grade 4 colitis (life-threatening consequences)	Manage per Grade 3 Colitis. **RXC004 and nivolumab (if applicable) should be permanently discontinued.**

*Attempts should be made to confirm that the colitis has resolved to Grade ≤ 1 (e.g normalised CRP or fecal calprotectin if raised during event; GI appearance normalised on X ray/ CT or endoscopy) before restarting RXC004.

If there is any recurrence of colitis ≥ Grade 2 after recommencing RXC004, **RXC004 and nivolumab (if applicable) should be permanently discontinued.**

Appendix 6 Dysgeusia treatment guidelines

As there are no recognised standard international guidelines for the management of this multifactorial event, investigators are advised to consult their local practice guidelines for the management of dysgeusia. Please refer to Table 7 for instructions on dose reductions and interruptions for dysgeusia.

Some interventions may be effective in treating dysgeusia:

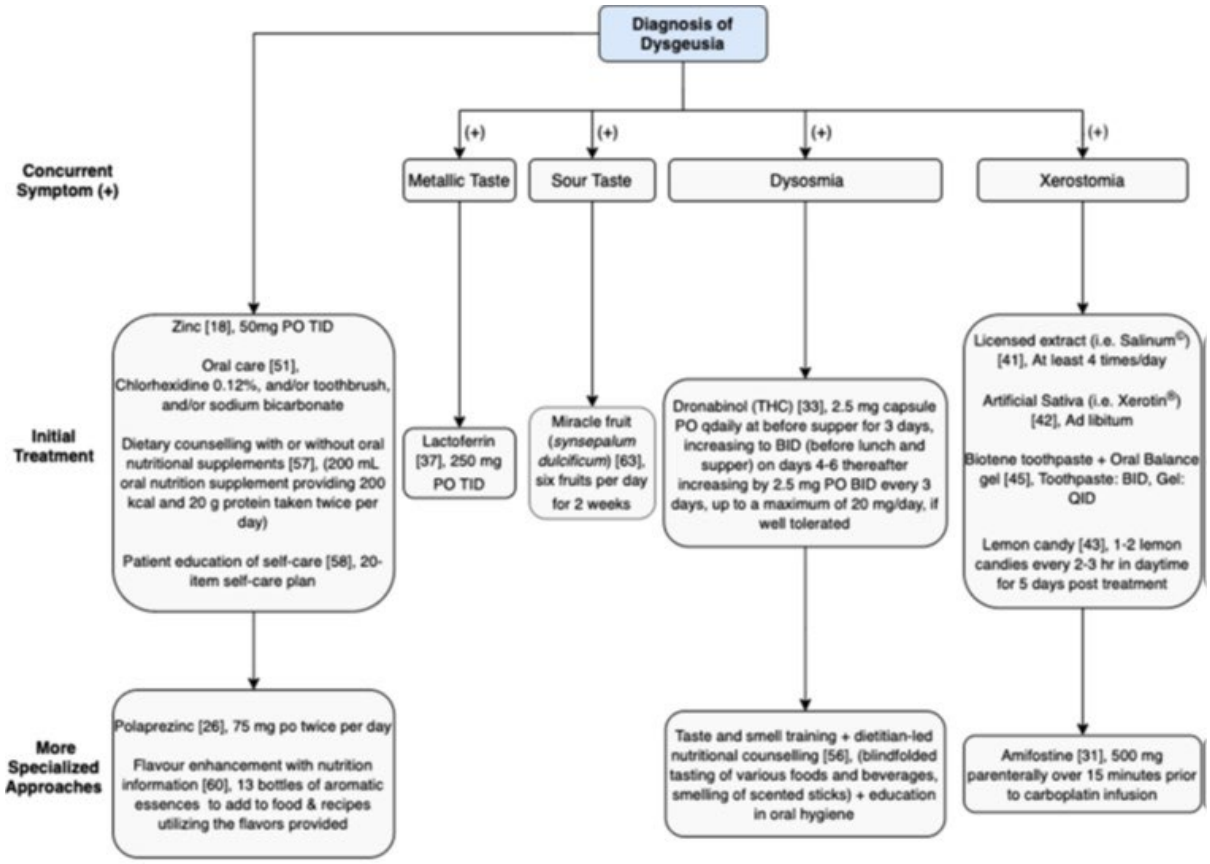
- Treatment with oral pilocarpine and artificial saliva may help in cases where there is also dry mouth
- Zinc supplements may help in cases where there is evidence of zinc deficiency
- Alpha lipoic acid is an antioxidant capsule supplement which may improve flavour sensation
- Good oral hygiene and chlorhexidine (or similar) mouthwashes

Patients may be advised of some ways that they can manage dysgeusia, for example:

- Cooking or eating food in non-metallic cookware
- Avoiding foods that taste bitter or metallic
- Flavoring foods with seasonings and spices
- Eating food cold may help to reduce unpleasant flavor sensations
- Frequently brushing teeth
- Rinsing with mouth wash regularly
- Using chewing gum. Lozenges or mints to stimulate saliva production

A dysgeusia treatment algorithm has been developed by Sevryugin et al.{Sevryugin, 2021 Ref 36} based on their review of published studies of dysgeusia interventions and is included to assist Investigators with the management of dysgeusia that occurs during treatment with RXC004. However, it is acknowledged that not all of the management suggestions may be readily available or applicable to patients in this study.

Figure from {Sevryugin, 2021 Ref 36}



Legend:
PO: by mouth; TID: three times a day; BID: twice a day; QID: four times a day

Appendix 7 Prohibited CYP3A4 Inhibitors and Inducers

CYP 3A4 Inhibitors	**CYP 3A4 Inducers**
Strong CYP 3A4 Inhibitors *Concomitant use of these drugs has the potential to increase the exposure of RXC004 over 5-fold* *These agents must not be given within 14 days of first dose of study treatment* boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir,	**Strong CYP 3A4 Inducers** *Concomitant use of these drugs has the potential to decrease the exposure of RXC004 by over 80%* *These agents must not be given within 14 days of first dose of study treatment* aptalutimide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Moderate CYP3A4 Inhibitors *Concomitant use of these drugs has the potential to increase the exposure of RXC004 by 2-5-fold* *A washout period of 14 days is recommended and a minimum washout period of 5 half-lives (See SMPC or USPI) is required before first dose of study treatment.* aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil lansoprazole	**Moderate CYP 3A4 Inducers** *Concomitant use of these drugs has the potential to decrease the exposure of RXC004 by 60-80%* *A washout period of 14 days is recommended and a minimum washout period of 5 half-lives (See SMPC or USPI) is required before first dose of study treatment.* bosentan, efavirenz, etravirine, phenobarbital, primidone
Weak CYP3A4 Inhibitors *These are not prohibited but should be used with caution as they may increase the exposure of RXC004 by 1.25 -2- fold* chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor, omeprazole	**Weak CYP3A4 Inducers** *These drugs are not prohibited- they have the potential to decrease the exposure of RXC004 by 20-50% which is within the scope of the dose reduction allowances* armodafinil, modafinil, rufinamide

For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Appendix 8 Nivolumab Toxicity Management and Dose Modification Guidelines (Patients enrolled onto Module 2 only)

Recommendations for nivolumab modifications are provided in the dose-modification section of the nivolumab Prescribing Information and summarised here.

Nivolumab toxicity management and dose modifications

Adverse Event	Severity	Investigations, Treatment and Dose modification
Colitis	Grade 1 diarrhoea or colitis	Investigations: FBC, UEC, LFTs, CRP, TFTs. Stool microscopy for leucocytes/ova/parasites, culture, viral PCR, C. diff. toxin and cryptosporidia Treat with oral fluids and loperamide. Avoid high fibre/lactose diet. If Grade 1 symptoms persist for >14 days treat as per Grade 2 Continue treatment
	Grade 2 diarrhoea or colitis	Investigations as per Grade 1. Exclude steatorrhea Consider abdominal X-ray and sigmoidoscopy/colonoscopy for signs of Colitis. Start prednisolone 0.5-1mg/kg or consider oral budesonide 9mg od if no bloody diarrhoea. Once recovered to Grade 1, wean steroids over 2-4 weeks. If no improvement in 72hrs, treat as per Grade 3. Withhold dose[a]
	Grade 3 diarrhoea or colitis	Investigations as per Grade 2 with daily FBC, UEC, LFTs and CRP Conduct Sigmoidoscopy/colonoscopy and consider biopsy. Early surgical review if bleeding, pain or distension. Review diet (e.g nil by mouth, clear fluids, TPN) Treat with IV (methyl)prednisolone 1-2 mg/kg. Wean steroids over 4-8 weeks. If no improvement in 72 hours start Infliximab 5mg/kg (if no perforation/sepsis/TB/hepatitis/congestive heart failure – Must have had flexsigmoidoscopy/colonoscopy prior)[b] Withhold dose[a]

Adverse Event	Severity	Investigations, Treatment and Dose modification
	Grade 4 diarrhoea or colitis	Investigations and treatment as per Grade 3 Permanently discontinue
Pneumonitis	Grade 1	Bloods (FBC/UEC/LFTs/Ca/ESR/CRP). Consider sputum sample screening for viral/bacterial infection. Chest X-ray Continue treatment
	Grade 2	Investigations as per Grade 1. Monitor symptoms daily Start antibiotics if suspicion of infection. If no evidence of infection or no improvement with antibiotics after 48hrs add in prednisolone 1mg/kg/day orally. Once improved to baseline, wean steroids over at least 6 weeks. If no improvement after 48hrs, manage as per Grade 3 Consider Pneumocystis prophylaxis depending on the clinical context High resolution CT +/- bronchoscopy and BAL pending appearances Withhold dose[a]
	Grade 3 or 4	Admit patient and perform investigations as per Grade 2. Treat with (methyl)prednisolone IV 2-4 mg/kg/day and cover with empiric antibiotics. Once improved to baseline wean steroids over at least 8 weeks. If no improvement after 48hrs add infliximab 5mg/kg (or MMF if concurrent hepatic toxicity). High resolution CT +/- bronchoscopy and BAL pending appearances Permanently discontinue
Hepatitis (non-HCC)	Grade 1: ALT or AST >ULN-3XULN	If > ULN-3XULN repeat in 1 week Continue treatment

Adverse Event	Severity	Investigations, Treatment and Dose modification
	Grade 2: ALT or AST 3-5XULN	Re-check LFTs/INR/albumin every 3 days. Review medications, e.g. statins, antibiotics and alcohol history. Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies If rising ALT/AST when re-checked start oral prednisolone 1 mg/kg. Once resolved to Grade 1, wean steroids over 2 weeks. Re-escalate if worsening; Nivolumab treatment may be resumed once prednisolone ≤ 10 mg Consider imaging for metastases/clot Withhold dose[a]
	Grade 3:AST or ALT 5-20XULN	Re-check LFTs/INR/albumin every day. Other investigation as per Grade 2. If ALT/AST < 400 and normal bilirubin/INR/albumin treat with oral prednisolone 1 mg/kg. If ALT/AST > 400 or raised bilirubin/INR/low albumin treat with i.v. (methyl)prednisolone 2 mg/kg. Once improved to G2, can change to oral prednisolone and wean over 4 weeks Perform US with Doppler. Low threshold to admit if clinical concern Permanently discontinue
	Grade 4: ALT or AST >20xULN	Investigations as per Grade 3 Treat with i.v. (methyl)prednisolone 2 mg/kg. If condition worsens despite steroids, add mycophenolate mofetil (MMF) 500-1000 mg bd. If worse on MMF, consider addition of tacrolimus. Hepatology consult and consider liver biopsy Permanently discontinue
Hepatitis (HCC)	ALT/AST within normal limits at baseline and increases to >3-5XULN Or	Re-check LFTs/INR/albumin every 1-3 days If rising ALT/AST when re-checked start oral prednisolone 1 mg/kg. If no improvement within 3-5 days on oral prednisolone 1 mg/kg, consider additional workup (liver biopsy, liver US) and

Adverse Event	Severity	Investigations, Treatment and Dose modification
	AST/ALT is more than 1-3XULN at baseline and increases to 5-10XULN	treatment with methylprednisolone 2-4mg/kg/day. Immunosuppressives (e.g.MMF) should be considered if no improvement on steroids. If toxicity resolves to Grade ≤1 or baseline, wean steroids over 2 weeks. Re-escalate if worsening; nivolumab treatment may be resumed once prednisolone ≤ 10 mg. Consider hepatologist consult and US with Doppler Withhold dose[a]
	AST/ALT increased to >10XULN or total bilirubin increases to >3XULN	Investigations and treatment as above. Permanently discontinue
Hypophysitis	Grade 2	Pituitary axis assessment, MRI pituitary protocol (also exclude brain metastases), visual field assessment. Monitor TFTs. Start oral prednisolone 0.5-1 mg/kg od after pituitary axis assessment. If no improvement in 48h, treat as severe with i.v. (methyl)prednisolone. Wean steroids based on symptoms over 2-4 weeks to 5 mg prednisolone. Do not stop steroids Refer to or consult endocrinologist Withhold dose[a]
	Grade 3	Investigations as per Grade 2 Initiate i.v. (methyl)prednisolone 1 mg/kg after sending bloods for pituitary axis assessment. Analgesia as needed for headache. Aim convert to prednisolone and wean as symptoms allow over 4 weeks to 5 mg Refer to or consult endocrinologist Withhold dose[a]
	Grade 4	Investigations as per Grade 1 Treatment as per Grade 3 Refer to or consult endocrinologist

Adverse Event	Severity	Investigations, Treatment and Dose modification
		Permanently discontinue
Adrenal Insufficiency	Grade 2	Withhold dose[a]
	Grade 3 or 4	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Admit to hospital immediately and start treatment of newly onset type I DM. Withhold dose[a]
	Grade 4 hyperglycemia	Treat as per Grade 3 Permanently discontinue
Nephritis and Renal Dysfunction	Grade 1 (creatinine 1.5 x baseline or > ULN-1.5x ULN)	Review hydration status, medications, urine test/culture if urinary tract infection symptoms Dipstick urine and send for protein assessment UPCR. Repeat creatinine weekly. If worsens, manage as per Grade 2 If obstruction suspected: renal ultrasound +/- doppler to exclude obstruction/clot Continue treatment
	Grade 2: creatinine > 1.5-3x baseline or > 1.5-3x ULN	Investigation as per Grade 1 and review creatinine/K+ in 48h-72h; if not improving discuss with nephrologist and need for biopsy and if attributed to irAE, If proteinuria: for 24 h collection or UPCR If blood: phase contrast microscopy and GN screen* if nephrologist recommends Initiate steroids (oral prednisolone 0.5-1 mg/kg) Renal ultrasound +/- doppler to exclude obstruction/clot Withhold dose[a] - Repeat creatinine/K+ every 48h If returns to Grade 1/baseline – recommence treatment (if on steroids, only once < 10 mg prednisolone) If not attributed to irAE - may continue treatment
	Grade 3: creatinine > 3x baseline or > 3-6x ULN Serum creatinine more than 1.5 and up to 6 times the ULN	Investigation per Grade 2, plus admit patient for monitoring and fluid balance; repeat creatinine every 24 h; early discussion with nephrologist and need for biopsy; if worsening, initiate (methyl)prednisolone 1-2 mg/kg i.v.

Adverse Event	Severity	Investigations, Treatment and Dose modification
		Withhold dose[a]
	Serum creatinine >6 x ULN	Investigations per Grade 3, plus patient should be managed in hospital where renal replacement therapy is available initiate i.v.(methyl)prednisolone 1-2 mg/kg Permanently discontinue
Skin	Grade 1 (skin rash with or without symptoms, <10% BSA)	Physical examination. Exclude other causes e.g. viral illness, infection, other drug rash etc. Topical steroids (mild strength) +/- oral or topical anti-histamines may be administered Continue treatment
	Grade 2 (10-30% BSA)	Investigations as per Grade 1 Topical steroids (moderate strength) +/- oral or topical anti-histamines may be administered Consider dermatology referral and skin biopsy Continue treatment
	Grade 3 rash (>30% BSA, or 10-30% BSA with substantial symptoms) or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Investigations as per Grade 1 Topical treatments as above (potent). Initiate steroids: if mild to moderate 0.5-1 mg/kg prednisolone od for 3 days then wean over 1-2 weeks; or if severe i.v. (methyl)prednisolone 0.5 -1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks Dermatology referral and skin biopsy Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Investigations as per Grade 1 i.v. (methyl)prednisolone 1-2 mg/kg Seek urgent dermatology review Permanently discontinue

Adverse Event	Severity	Investigations, Treatment and Dose modification
Peripheral neurological toxicity (For specific recommendations for Myasthenia Gravis and Guillain-Barré syndrome, see 'other')	Grade 1	Comprehensive neurological examination Diabetic screen, B12/folate, HIV, TSH, consider vasculitic & autoimmune screen, review alcohol history & other medications Consider need for MRI/MRA brain or spine (exclude CVA, structural cause) Continue treatment
	Grade 2	Investigations as per Grade 1, plus consider NCS/EMG for lower motor neurone motor and/or sensory change Consider pulmonary function/sniff/diaphragmatic function tests and neurological consultation Initial observation reasonable or initiate prednisolone 0.5-1 mg/kg (if progressing, e.g. from mild) and/or pregabalin or duloxetine for pain. Taper steroids over 4-8 weeks. If worsening, treat as per Grade 3 Withhold dose[a]
	Grade 3	Admit patient. Involve neurologist in care. Daily neurological review +/- daily vital capacity MRI brain/spine advised NCS/EMG. Lumbar puncture. Pulmonary function assessment Initiate (methyl)prednisolone 2 mg/kg i.v. Taper steroids over 4-8 weeks. Withhold dose[a]
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Lumbar puncture, PCR for HSV, cytology and consider viral culture Oral prednisolone 0.5-1 mg/kg or i.v. (methyl)prednisolone 1-2 mg/kg if very unwell (Exclude bacterial and ideally viral infections prior to high-dose steroids). Consider concurrent empiric antiviral (i.v. acyclovir) and antibacterial therapy CNS imaging and consider neurological consultation

Adverse Event	Severity	Investigations, Treatment and Dose modification
		Withhold dose[a]
	Immune-mediated encephalitis	Lumbar puncture, PCR for HSV, cytology and consider viral culture Oral prednisolone 0.5-1 mg/kg or i.v. (methyl)prednisolone 1-2 mg/kg if very unwell (Exclude bacterial and ideally viral infections prior to high-dose steroids). Consider concurrent empiric antiviral (i.v. acyclovir) and antibacterial therapy CNS imaging Permanently discontinue
Thyroid function	Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4	Thyroxine 0.5-1.5 µg/kg (start low in elderly, if cardiac history) Continue treatment
	Thyrotoxicosis (DDx thyroiditis, Grave's disease)	Investigations: Anti-TSH Receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan Propranolol or atenonol for symptoms; consider carbimazole if anti-TSH Receptor Ab positive Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper if unwell, Withhold dose[a]
Infusion reactions	Grade 1 or 2	Interrupt or slow rate of infusion
	Grade 3 or 4	Permanently discontinue
Other	Other Grade 3AEs - First occurrence - Recurrence of same Grade 3 adverse events	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	If myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) Permanently discontinue
	Guillain-Barré syndrome (GBS)	Nerve conduction studies (acute polyneuropathy) Lumbar puncture (elevated protein with normal WBC count). Pulmonary function tests with vital

Adverse Event	Severity	Investigations, Treatment and Dose modification
		capacity and maximum inspiratory/expiratory pressures. Antibody testing for GBS variants, e.g. GQ1b in Miller Fisher variant Use of steroids not recommended in idiopathic GBS If no improvement or worsening, plasmapheresis or intravenous immunoglobulin indicated. Neurological consultation. Consider location of care where ventilatory support available (required in 15%-30% idiopathic cases) Permanently discontinue
	Myasthenia Gravis	Check for ocular muscle and proximal muscle fatigability. AChR and anti-MuSK antibodies Bedside tests, e.g. Tensilon test or ice pack test with neurological input. Repetitive nerve stimulation and single fibre EMG Steroids indicated (oral or i.v. depending on symptoms). Pyridostigmine initial dose 30 mg tds. If no improvement or worsening, plasmapheresis or IVIG may be considered Additional immunosuppressants azathioprine, cyclosporine, mycophenolate Avoid certain medications, e.g. ciprofloxacin, beta-blockers, that may precipitate cholinergic crisis Neurological consultation Permanently discontinue
	Requirement for 10mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse event lasting 12 weeks or longer	Permanently discontinue

Appendix 9 Module 3 Schedule of Assessments

	Module 3 (RXC004 monotherapy intermittent schedules) Schedule of Assessments								
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21 day cycle)**		**Cycle X Day 1 (21 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D11(-1d)**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**q6w (+/- 1 week)**
Pre-Screening informed consent (optional)	X								
Diagnostic / Archival tumour tissue	X	X (optional)							
Genetic screening for RNF43/RSPO aberrations (optional)	X								
Informed consent		X							
Pharmacogenetics (optional consent and blood sample)[i]		X							
Demography & baseline characteristics		X							
Smoking status & alcohol consumption		X							
Medical/surgical history		X							
Inclusion/exclusion criteria**		X							
Bone Scan		X	As clinically indicated						
Physical examination[a]		X	X	X		X	X		

	Module 3 (RXC004 monotherapy intermittent schedules) Schedule of Assessments								
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21 day cycle)**		**Cycle X Day 1 (21 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D11(-1d)**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**q6w (+/- 1 week)**
ECOG/WHO performance status		X	X	X		X	X		
Pregnancy test (WOCBP only)		(X)	(X)	(X)		(X)			
Vital signs (including height and weight)[b]		X	X	X	X	X	X	X	
Clinical chemistry / Haematology		X	X	X	X	X	X	X	
Urinalysis*		X	X	X	X	X			
ECG		X	X	X	X	X[h]	X		
DXA scan (including VFA*** at baseline)		X				Cycle 2, 4 and 7, and every third cycle thereafter			
Skin punch biopsy (mandatory)			X[m]		X[m]	X[m]			
Newly acquired tumour biopsy (optional)		X			X[g]				
Blood samples for bone turnover biomarkers		X			X	X	X		
Blood sample for circulating soluble factors[c]			X		X	X			
Blood sample for PBMC (viable cells)[c]			X		X	X			

	Module 3 (RXC004 monotherapy intermittent schedules) Schedule of Assessments								
	Pre-Screening	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21 day cycle)**		**Cycle X Day 1 (21 day cycles)**	**IP Discontinuation**	**30 day Safety Follow-up[l]**	**PFS Follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D11(-1d)**	**+/- 3d**	**Within 7 days of discontinuation**	**+/- 3d**	**q6w (+/- 1 week)**
Fresh blood for PD analysis[d]			X		X	Cycle 2 Day 1 only			
Blood sample ctDNA analysis[e]			X		X	X	X		
Blood sample ctRNA analysis[e]			X		X	X	X		
RECIST 1.1 assessments (by CT/MRI)[j]		X	Every 6 weeks +/- 1 week from Cycle 1 Day 1 until RECIST1.1 defined disease progression						
Vitamin D3 and Calcium supplements		Patients should commence vitamin D3 (cholecalciferol 800IU QD) and calcium 1000-1500 mg QD supplements from ICF signature until RXC004 discontinuation							
Denosumab dosing[o]			120 mg sc. denosumab QM from C0D1 until RXC004 discontinuation						
RXC004 dosing			X	2 mg QD intermittent schedule[k]					
RXC004 PK[f]			X	X	X	X	X		
Concomitant medication		X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	
Taste Assessment[n]		X	At each visit – only if patient reports a taste disturbance						
Patient diary card review				X	X	X	X		
Subsequent anti-cancer therapy							X	X	X

Footnotes - General

Assessments made on Day 1 of each cycle are to be conducted prior to RXC004 administration, unless specified otherwise.
Additional assessments may be conducted as clinically indicated.
A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.
* Female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle
**Eligibility criteria to be re-checked at Cycle 1 prior to dose administration.
***A lateral T & L spine assessment if a Vertebral Fracture Assessment (VFA) cannot be completed locally

a A full physical examination is required at Screening and prior to Day 1 of each cycle ; Symptom-directed physical examination is acceptable at other time-points

b Vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the RXC004 administration. Patient status will be monitored during RXC004 administration and repeat vital signs will be taken if needed. Height is required at screening only. Weight will be recorded at Screening and on Day 1 of each cycle.

c All samples should be collected pre-dose

d Fresh blood samples to be collected from UK sites only. All samples should be collected pre-dosing.

e Samples should be collected pre-dose for all samples.

f Patients will have PK blood sampling conducted at the following sample times

Cycle 0: Day 1 - Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, and 48 h post-dose.
C1D11: Predose, then 30 mins, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h & 24 h
Cycle X, Day 1 - A single pre-dose sample will also be taken on subsequent samples on Day 1.

The SRC may advise on adjusted time-points. The actual time for each blood draw must be accurately recorded.

g An optional 'on treatment' biopsy during Cycle 1 Day 11 treatment visit, preferably 4-6hrs post dose and from the same site as the baseline biopsy sample. The actual time of collection should be accurately recorded.

h Triplicate ECGs should be collected as follows;
Cycle 0: Day 1 – Pre-dose (within 30 mins of first dose), then 1 h ± 10 mins and 12 h ± 30 mins post-dose
Cycle 1, Day 11- Predose (within 30 mins of dose), then 1 h ± 10 mins and 12 h ± 30 mins post-dose
Cycle X, Day 1 - Pre-dose (within 30 mins of dose)

i Consenting patients will have a 10 mL blood sample taken for preparation of a germ-line DNA sample at Screening (recommended time-point only).

j CT (preferred) or MRI, each preferably with IV contrast. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging time points per patient. Note that where there is a rationale for assessment of bone lesions that develop after study start, these assessments will be performed as part of the CT or MRI assessment and will not require additional radiological bone scan assessment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.

k Arm 1 treatment schedule is 2mg QD RXC004 for 4 days, followed by 3 days off, repeated for 21 days per cycle of treatment. Arm 2 treatment schedule is 2mg QD RXC004 for 2 weeks, followed by 1 week off. Further arms investigating other intermittent schedules may be added after review by SRC. Results for chemistry and haematology labs must be available before starting a new treatment cycle (within 3 days) and reviewed by the treating physician or Investigator prior to dosing

l Follow up assessments should be performed 30 days after last dose of RXC004

m Mandatory skin punch biopsies will be collected from all patients. All patients should consent to two skin punch biopsies – pre-dose on C0D1 (baseline) and one 'on study treatment' biopsy on either C1D11 or C2D1. The first 3 patients in a given Arm will also have a skin punch biopsy on C1D11 (RXC004 dosing day sample) and the last 3 patients will have a skin punch biopsy pre-dose on C2D1 (off RXC004 sample). Patients will have skin punch biopsies conducted at the following sample times (the actual time of collection should be accurately recorded);

- All patients - C0D1 - Predose
- Patients 1 to 3 within an Arm - C1D11 - 4-6 hrs post dose
- Patients 4 to 6 within an Arm - C2D1 - Predose

n A taste assessment (consisting of a specific set of questions) will be performed at screening and at each study visit when patient reports a taste disturbance. Please see Section 4.2 for more details

o All patients must receive denosumab before first dose of RXC004. 120 mg sc denosumab should be administered approximately once every month from C0D1 until RXC004 discontinuation. Investigators may delay subsequent denosumab doses until the next scheduled visit providing that there is no significant increase in β-CTX compared to baseline, according to Investigator judgement

Appendix 10 RNF43/RSPO aberrations

In Module 3 of the study patients must have a Wnt dependent tumour, defined as:

- Any solid tumour with a predicted loss of function RNF43 mutation
- Any solid tumour with a RSPO fusion
- Biliary tract cancer
- Thymus cancers

Patients with the following RNF43 mutations are eligible for the study:

Nucleotide	Protein
c.64C>T	p.(Gln22Ter)
c.85G>T	p.(Gly29Ter)
c.122C>G	p.(Ser41Ter)
c.122C>A	p.(Ser41Ter)
c.137C>T	p.(Ala46Val)
c.207delT	p.(Phe69LeufsTer7)
c.245T>C	p.(Leu82Ser)
c.337C>T	p.(Arg113Ter)
c.349_350insC	p.(Arg117ProfsTer8)
c.349delC	p.(Arg117AlafsTer41)
c.394C>T	p.(Arg132Ter)
c.433C>T	p.(Arg145Ter)
c.454C>T	p.(Arg152Ter)
c.457C>T	p.(Gln153Ter)
c.461C>T	p.(Pro154Leu)
c.476G>A	p.(Trp159Ter)
c.477G>A	p.(Trp159Ter)
c.484G>A	p.(Val162Met)
c.505G>A	p.(Ala169Thr)
c.557T>C	p.(Ile186Thr)
c.599_600insC	p.(Trp200SerfsTer60)
c.599G>A	p.(Trp200Ter)
c.600G>A	p.(Trp200Ter)
c.647C>A	p.(Ser216Ter)
c.673delC	p.Arg225AlafsTer194)
c.776G>A	p.(Trp259Ter)

c.777G>A	p.(Trp259Ter)
c.931delC	p.(LeuL311SerfsTer108)
c.988C>T	p.(Arg330Ter)
c.1009C>T	p.(Arg337Ter)
c.1111C>T	p.(Arg371Ter)

Patients with documented LoF RNF43 mutations other than those listed above may be allowed after consultation with Sponsor.

Patients with the following RSPO fusions are eligible for the study:
PTPRK (NM_001291981.1) exon 1 :: RSPO3 (NM_032784.4) exon 2
PTPRK (NM_001291981.1) exon 2 :: RSPO3 (NM_032784.4) exon 2
PTPRK (NM_001291981.1) exon 7 :: RSPO3 (NM_032784.4) exon 2
PTPRK (NM_001291981.1) exon 13 :: RSPO3 (NM_032784.4) exon 2
EIF3F (NM_001568.2) exon 1 :: RSPO2 (NM_178565.4) exon 1
EIF3F (NM_001568.2) exon 1 :: RSPO2 (NM_178565.4) exon 2
NRIP1 (NM_003489.3) 5’ UTR :: RSPO2 (NM_178565.4) exon 1
HNF4G (NM_001330561.1) 5’ UTR :: RSPO2 (NM_178565.4) exon 1
PVT1 (NR_00367.3) exon 1 :: RSPO2 (NM_178565.4) exon 1
PVT1 (NR_00367.3) exon 1 :: RSPO2 (NM_178565.4) exon 2

Exon numbering based on the stated reference sequences using sequential numbering where the first coding exon is defined as exon 1.

Patients with documented RSPO fusions other than those listed above may be allowed after consultation with Sponsor.

14 SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Modular, Multi-Arm Phase 1, Adaptive Design Study To Evaluate The Safety And Tolerability Of RXC004, Alone And In Combination With Anti-Cancer Treatments, In Patients With Advanced Malignancies

PROTOCOL NO: RXC004/0001

This protocol is a confidential communication of Redx Pharma, plc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Redx Pharma , plc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the centre in which the study will be conducted. Return the signed copy to CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

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