Trinity Delta

Redx Pharma

Update

New data draws attention to promising fibrosis assets

7 October 2022

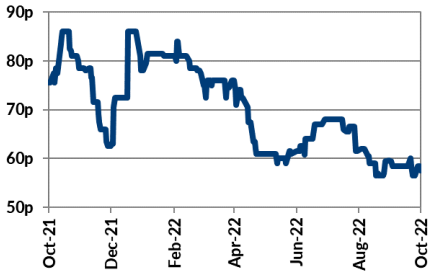
Redx Pharma has a proven track record of creating innovative and commercially relevant small molecule drugs, with five current in-house and partnered assets in clinical development. The lead in-house programmes, RXC004, a porcupine inhibitor for Wnt-ligand dependent solid tumours, and RXC007, a ROCK2 inhibitor for broad fibrosis indications, are advancing through Phase II trials. Recently presented preclinical data suggest RXC007 can materially inhibit fibrosis in a range of lung fibrosis models. The earlier stage RXC008, a promising preclinical GI targeted ROCK inhibitor for Crohn's related strictures, expands the fibrosis franchise further. Cash resources, coupled with June's £34.3m equity raise, provide funding into CY2024. Clinical data from the two lead programmes are expected throughout the coming year. Our rNPV-based valuation remains £458m (vs £434m), or 138p/share.

Year-end: September 30	2020	2021	2022E	2023E
Revenues (£m)	5.7	10.0	19.2	4.0
Adj. PBT (£m)	(8.8)	(15.0)	(21.0)	(44.7)
Net Income (£m)	(9.2)	(21.6)	(21.4)	(45.0)
Adj.EPS (p)	(5.2)	(5.9)	(6.8)	(12.9)
Cash (£m)	27.5	29.6	43.6	31.0*
EBITDA (£m)	(7.5)	(19.1)	(19.9)	(44.3)

Source: Trinity Delta Note: Adjusted numbers exclude share-based payments and exceptionals. * Our cash forecast assumes receipt of £25m in additional funding in FY23

- **ROCK inhibitors could have significant potential in fibrosis** ROCK inhibition brings the opportunity to alter the outcomes of many fibrotic diseases. RXC007, a ROCK2 inhibitor, will undertake a Phase II trial in idiopathic pulmonary fibrosis (IPF), with plans to expand future development to interstitial lung diseases (ILD). This is based on impressive preclinical data in various lung fibrosis and relevant models that demonstrated marked reductions in collagen deposition and fibrosis. The clean toxicity profile suggests the ability to combine RXC007 with existing treatments. RXC008, a locally acting pan-ROCK inhibitor for fibrostenotic Crohn's disease, is completing IND/CTA preparations.
- **IPF alone could be a blockbuster opportunity** IPF is a chronic lung disease which is often fatal. The two available treatment options together generated >$4bn in 2021 sales. They only slow disease progression, are poorly tolerated, and discontinuation is high. Hence, there is large unmet need for novel IPF therapies. IPF represents only around 20-50% of ILDs, hence there is much broader potential for successful development in ILD. RXC007 is one of only three ROCK2 inhibitors in clinical trials.
- **Clinical data expected during 2023** We expect a stream of clinical results over the coming 12-24 months. The first are Phase II data for RXC004 as monotherapy from H123, albeit key insights into the value of RXC004 in Wnt-ligand dependent cancers will be combination data in H223. H223 will also see RXC007 Phase IIa IPF data and RXC008 IND/CTA submissions.
- **rNPV valuation remains £458m or 138p/share** Our risk-adjusted pipeline NPV model ascribes a valuation, based on conservative assumptions, of £458m or $596m (equivalent to 138p/share).

Price	57.5p
Market Cap	£192.57m
Enterprise Value	£132.87m
Shares in issue	334.9m
12 month range	54.0-90.0p
Free float	13.6%
Primary exchange	AIM London
Other exchanges	N/A
Sector	Healthcare
Company Code	REDX
Corporate client	Yes



Company description

Redx Pharma specialises in the discovery and development of small molecule therapeutics, with an emphasis on oncology and fibrotic diseases. It aims to initially progress them through proof-of-concept studies, before evaluating options for further development and value creation.

Analysts

Lala Gregorek
lgregorek@trinitydelta.org
+44 (0) 20 3637 5043

Philippa Gardner
pgardner@trinitydelta.org
+44 (0) 20 3637 5042

Redx Pharma: Fibrosis could prove transformative

Redx Pharma's medicinal chemistry expertise has been proven by its consistent track record, with five programmes now in the clinic. The strategy is to partner certain assets, sometimes as early as preclinical, and develop selected in-house programmes to key value-inflection points. The proprietary assets focus on selected oncology indications and broader fibrosis diseases. The lead compounds are progressing through clinical trials, with data due to be released throughout the coming 12-24 months. We have covered other aspects of the investment case in previous notes, with this note focusing on the developments in the fibrosis programmes. Multiple lines of evidence show ROCK inhibition has great potential to be a powerful therapeutic tool in the treatment of fibrosis, both in the lung and beyond. RXC007 is a selective ROCK2 inhibitor in Phase IIa for idiopathic pulmonary fibrosis (IPF) and RXC008 is an innovative pan-ROCK inhibitor completing IND/CTA preparation for Crohn's disease. Our rNPV based valuation remains £458m ($595m) or 138p/share.

Proven track record of creating innovative small molecules

Redx Pharma has a demonstrable track record, with its medicinal chemistry expertise proven to solve complex targeting issues. This has resulted in five innovative, and highly differentiated, compounds now in the clinic. Active risk management has resulted in a well-balanced pipeline, with a mix of in-house and partnered programmes, that should provide a stream of news flow over the next 12-24 months. RXC004, an innovative porcupine inhibitor for Wnt-ligand dependent cancers, is in Phase II trials, with monotherapy arms expected to deliver top line data from H123 and checkpoint inhibitor (CPI) combination arms due to report H223. Phase IIa data for RXC007, a ROCK2 inhibitor for various fibrosis indications, in IPF is expected to report H223. Partnered assets, with AstraZeneca and Jazz Pharmaceuticals, are also advancing.

Investment case is detailed in previous notes…

Redx Pharma's investment case was explored in our extensive February 2022 Outlook, which also covered the key in-house programmes and the expected progress with partnered projects. The Outlook report illustrated how Redx Pharma is differentiated from its peers, the rationale underpinning the strategy pursued, and the importance of managing development risks. In this, and prior notes, we discussed the relevance of the Wnt pathways in selected oncology indications and the design of the RXC004 Phase II proof-of-concept clinical programme, highlighting the major opportunities, especially as combination (CPI) treatments, for Wnt driven tumours such as genetically selected MSS mCRC (microsatellite stable metastatic colorectal cancer) and metastatic pancreatic cancer, and biliary cancer.

…with this note focused on the opportunities in fibrosis

This Update focuses on Redx Pharma's fibrosis programmes, reflecting the greater understanding of the role of ROCK2 inhibition in various fibrosis indications, how the forthcoming RXC007 Phase II trials should provide valuable insights into its eventual clinical positioning, and, importantly, the high clinical need and resultant commercial opportunities that an effective and well-tolerated anti-fibrotic could help address. An additional pan-ROCK inhibitor, RXC008, targeting fibrostenotic Crohn's disease through localised activity in the gut is preparing for clinical trials. The relatively early stages of these programmes mean they are ascribed little value within our rNPV model; however, if the preclinical promise is replicated in clinical trials, they could be transformative for Redx Pharma.

RXC007: a leading ROCK inhibitor for fibrosis

The ROCK pathways are well characterised but chemically difficult to address

RXC007 is a novel and highly specific small molecule that targets the ROCK2 (Rho Associated Coiled-Coil Containing Protein Kinase 2) receptor. The ROCK pathways are a biologically and clinically validated target that sit at a nodal point in a cell signalling pathway, where they modulate inflammatory responses and fibrotic processes. They mediate a broad range of cellular responses that involve the actin cytoskeleton and are important regulators of cellular growth, migration, metabolism, and apoptosis. Aberrant downstream signalling has important roles in a range of fibrotic dysfunctions. There are two kinase forms, ROCK1 and ROCK2, which have broadly similar functions (especially in fibrosis) but the simultaneous systemic inhibition of both ROCK1 and ROCK2 appears to be more closely associated with cardiovascular effects (notably hypotension). The pharmacological inhibition of both ROCK isoforms prevents airway remodelling and lung fibrosis, but the chemistry is particularly complex and historically identifying safe and effective selective inhibitors has proved challenging.

Fibrosis is a difficult to treat element in many serious and debilitating diseases

Fibrosis is the excessive deposition of connective tissue components and occurs when the normal healing process goes wrong. This formation of excessive scarring can affect virtually every organ system, including the skin, lungs, liver, and kidney. Such fibrotic tissue remodelling severely impairs the function of the affected organ and often leads to organ malfunction. The initial causes of fibrosis are manifold, and while the precise disease process is not fully understood, it typically involves a common series of events, including secretion of cytokines which provoke a pro-fibrotic, chronic inflammatory immune response that leads to production of excessive extracellular matrix (ECM) proteins (eg collagen) and the tissue becoming fibrous in nature. Fibrotic diseases are commonly associated with high morbidity and mortality, and the need for effective anti-fibrotic therapies remains very high. This is particularly the case for pulmonary fibroses.

RXC007 could potentially be disease altering

Pulmonary fibrosis in need of novel and effective treatments

Despite such clear unmet clinical need, the available treatments offer only a slowing of disease progression, are poorly tolerated by patients (leading to treatment discontinuation), and lung transplants are often the only option. In this context, RXC007 could be a particularly attractive programme, with a preclinical profile that suggests the potential to be disease modifying. RXC007 was chosen from a series of highly selective and orally active ROCK2 inhibitors, with extensive preclinical data showing good ADME profiles and robust anti-fibrotic effects. Results from immune mediated models, together with the encouraging (final) Phase I safety and pharmacokinetic data, were presented at ICLAF (International Colloquium on Lung and Airway Fibrosis) on 2 October 2022.

Preclinical evidence suggests an impressive profile, with disease modifying impacts

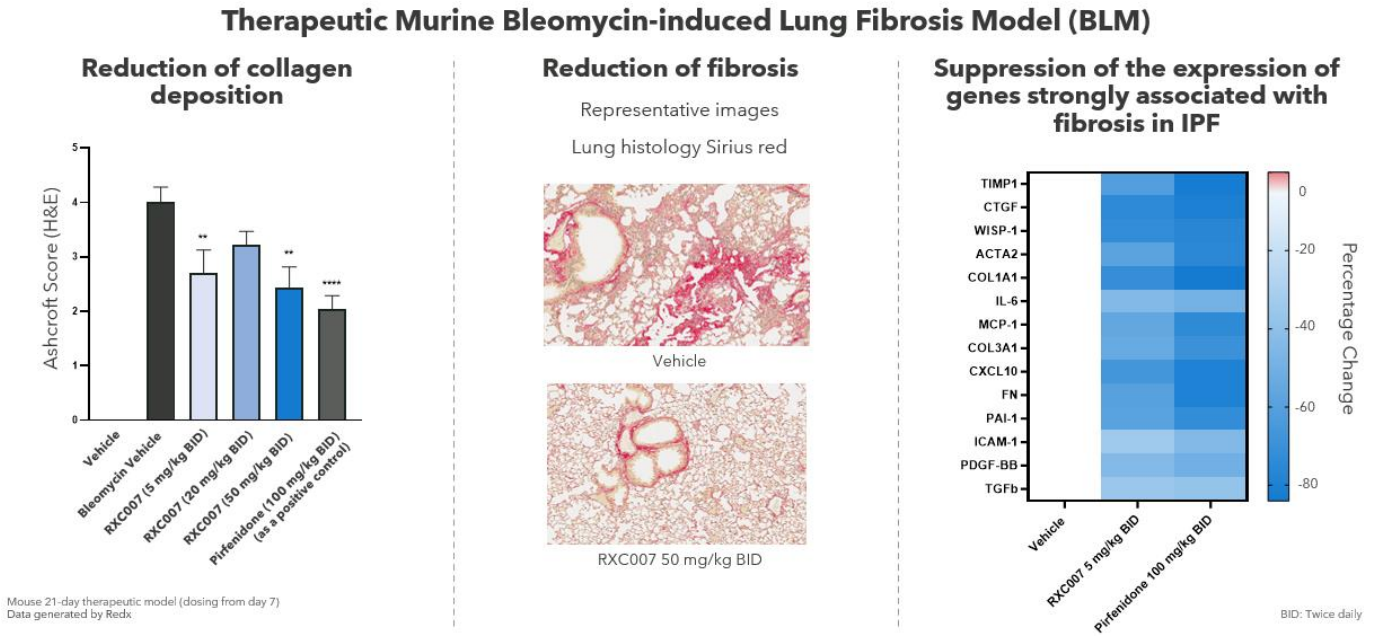
The preclinical data for RXC007 are impressive, albeit with the caveat that animal models (in isolation) fail to replicate many aspects of human disease, including its progressive and unremitting nature. The challenge is to perform a series of studies that collectively provide a representative insight into fibrosis remodelling, have consistent endpoints, generate reproducible and reliable results, and, importantly, can be subjected to robust analysis and interpretation. The best characterised preclinical model is the murine intratracheal bleomycin challenge (BLM), with

appropriate treatment timing, relevant measurements for collagen accumulation, and suitable histologic assessments.

A material reduction in collagen deposition and fibrosis is seen

RXC007 and pirfenidone (an approved IPF treatment), were dosed therapeutically from Day 7-21 via oral gavage. The results (Exhibit 1) showed that RXC007 reduced collagen deposition in a dose-dependent manner, materially reduced fibrosis, and successfully suppressed the panel of genes that are typically associated with fibrosis.

Exhibit 1: RXC007 in the Bleomycin-induced Lung Fibrosis Model (BLM)



Source: ICLAF October 2022 Abstract No.66 Redx Pharma

GVHD murine model provides additional clinical insights

The murine models of GVHD (Graft vs Host disease) are typically employed to assess likely GVHD therapeutic efficacy, however they also provide invaluable clinical insights into the mechanisms that underlie a number of fibrotic diseases. The Murine Sclerodermatous cGVHD model is an immune mediated model that explores associated skin and lung fibrosis. The results here provide additional greater clinical relevance as they employ similar disease mechanisms to those that underlie auto-immune pathologies that result in fibrosis.

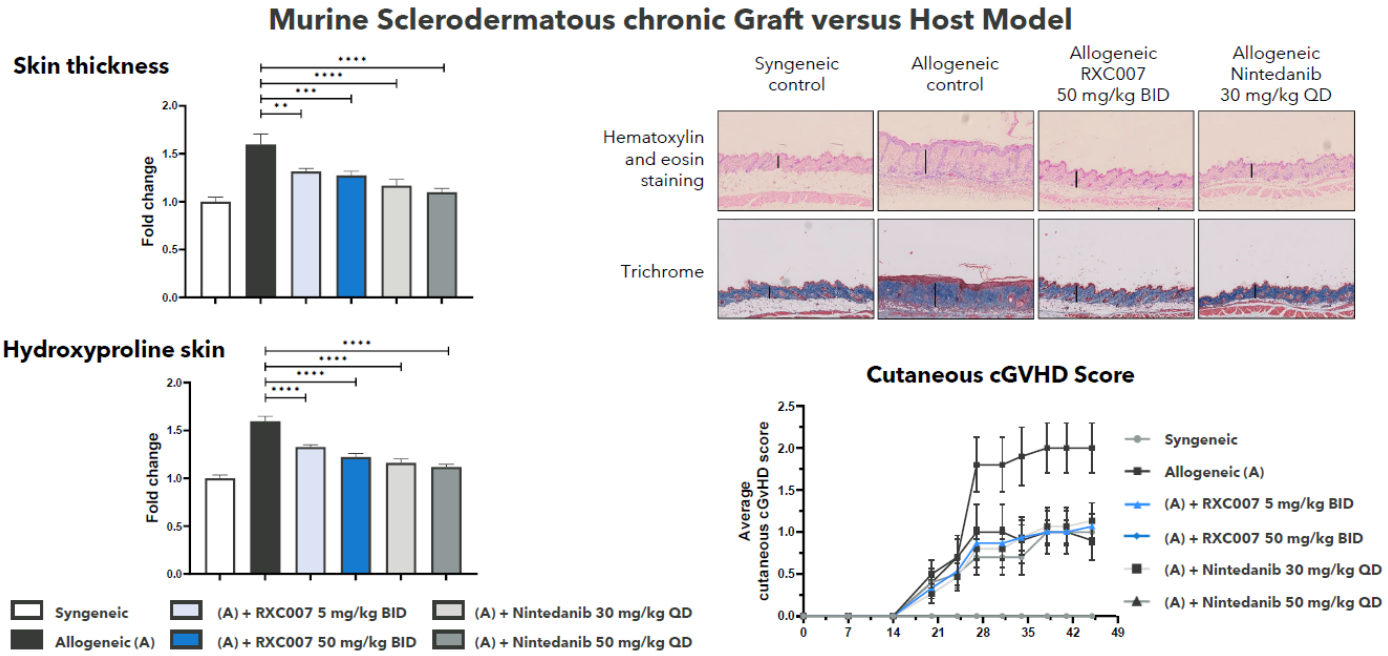
Model replicates many aspects of human fibrotic disease

To reflect the clinical situation with treatment only upon clinical signs of cGVHD, administration of RXC007 and nintedanib started 21 days after bone marrow transplantation and thus several days after the first clinically detectable manifestations of cGVHD in allogeneically transplanted mice. RXC007 and nintedanib were administered by oral gavage BID for 28 days.

Again collagen deposition and fibrosis are materially reduced

The results (Exhibit 2) showed RXC007 administration resulted in a significant reduction of collagen content and collagen deposition in the skin, a significant reduction of fibrosis score and collagen content in the lungs around the bronchioles, and a similar effect on the cutaneous cGVHD score between nintedanib and RXC007. The strength of this collective data led to RXC007 being progressed into clinical development for lung fibrosis, including idiopathic pulmonary fibrosis (IPF) and auto-immune related interstitial lung disease (ILD).

Exhibit 2: RXC007 in the Murine Sclerodermatous chronic Graft versus Host Model



Source: ICLAF October 2022 Abstract Number 66; Redx Pharma

Phase I safety and tolerability data are confirmed as clean

The ICLAF presentation also discussed the final Phase I data, first presented at the Interstitial Lung Disease (ILD) Summit in March 2022, which confirmed RXC007's excellent safety and pharmacokinetic profile. This study consisted of a double-blind, placebo-controlled trial in healthy volunteers with two parts:

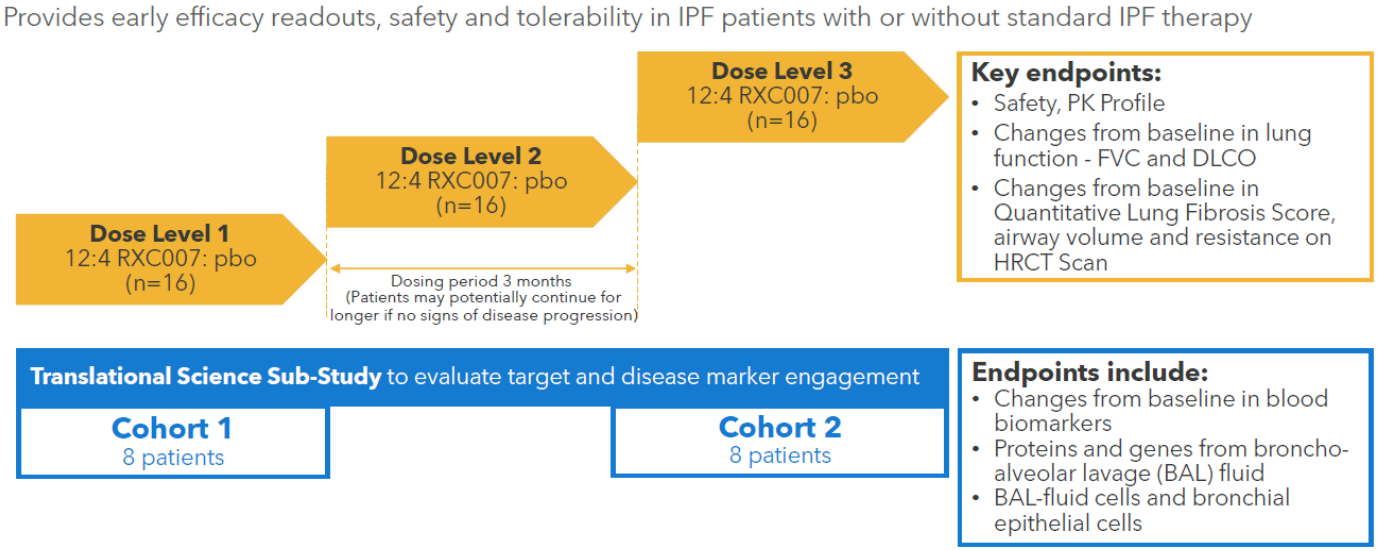
- a single dose (SAD) with dose escalation cohorts, and
- multiple doses (MD) over 14 days with dose expansion cohorts.

No adverse events were observed in the SAD stage, following single doses of 2-70mg (dosed once or twice in a day), and no serious adverse events were observed in the MD stage (dosed at 50mg twice daily for 14 days), with only transient, reversible, mild adverse events observed. The pharmacokinetics were as predicted from preclinical data, with linear exposure for 2mg QD to 70mg BID, with biologically relevant exposures achieved from 20mg. No significant effect on exposure was seen when dosed with food. The data also showed a mean half-life of approximately 9-11 hours, which suggests it is suitable for once-daily dosing.

Phase IIa programme topline data expected H223

These encouraging data clear the path for a staged Phase II trial programme. The first Phase IIa study will be of 12 weeks duration and will assess early efficacy signals, safety, and tolerability in IPF (Exhibit 3). The insights, especially around the suitability of biomarkers and target engagement, both with and without standard of care (SoC) agents, will guide design (and dose selection) of the larger 12-month Phase IIb trial. Top-line data from the Phase IIa study is expected in H223. The Phase IIb study will likely also explore RXC007 plus SoC over 12 months in IPF with lung function (FVC) as primary endpoint. However, other fibrotic indications could also feature as more clinical data becomes available.

Exhibit 3: RXC007 Phase IIa study design



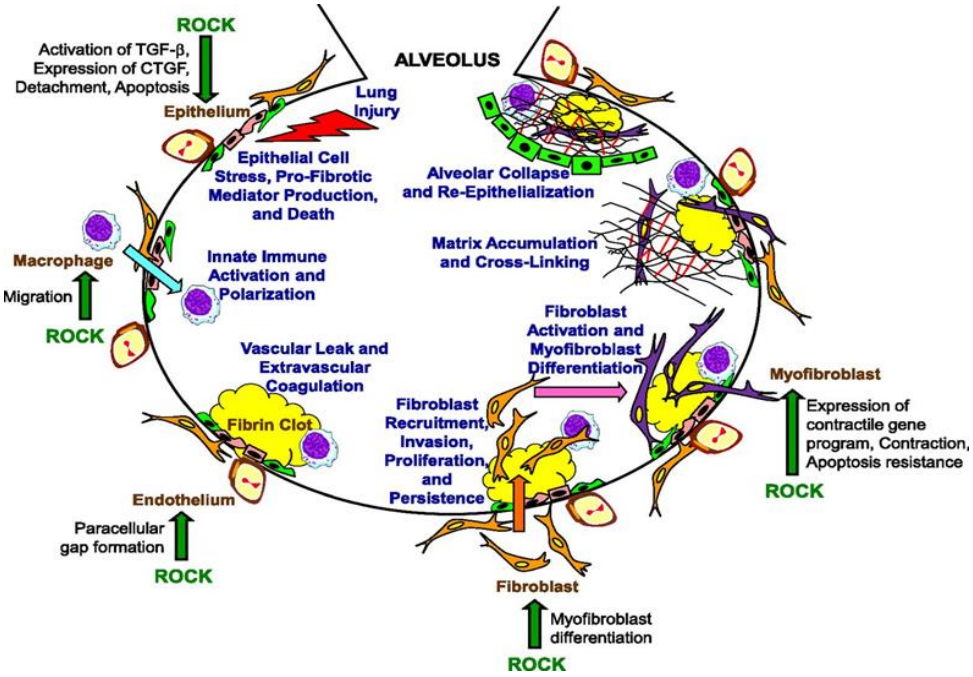
Source: Redx Pharma Note: DLCO = carbon monoxide diffusion coefficient; FVC = forced vital capacity; HRCT = high resolution computerised tomography; Pbo = placebo

The roles of ROCK in IPF (and other fibroses)

Addressing ROCK as a target provides multiple, yet precise, points of interaction...

In IPF (idiopathic pulmonary fibrosis), disease progression is viewed as a consequence of aberrant wound healing responses leading to repetitive lung injury. The responses to this tissue injury, such as vascular leakage, fibroblast recruitment, myofibroblast differentiation, and re-epithelialisation, all fundamentally involve a reorganisation of the actin cytoskeleton of participating cells, including epithelial cells, fibroblasts, and endothelial cells.

Exhibit 4: ROCK are critical mediators and rational targets for new therapies



Source: The Rho Kinases: Critical Mediators of Multiple Profibrotic Processes and Rational Targets for New Therapies for Pulmonary Fibrosis, Pharmacological Reviews 15, 67 (1) 103-117

...suggesting a meaningful clinical response yet clean side effect prolife

The actin filament assembly and actomyosin contraction are directed by the Rho-associated coiled-coil forming protein kinase (ROCK) family of serine/threonine kinases, including ROCK1 and ROCK2. ROCK signalling occurs across multiple sites and pathways, acting as nodal points that impact a number of critical downstream functions. ROCK1 is ubiquitously expressed, whereas ROCK2 appears to be more selectively expressed in brain and muscle, particularly smooth muscle. The rationale for a selective ROCK2 inhibitor with pleiotropic effects (ie acting across multiple target pathways) is highly compelling. Exhibit 4 shows the various processes where ROCK inhibition impacts. It is these critical roles that underscore the therapeutic potential of ROCK inhibition for fibrosis.

IPF: significant unmet need for novel therapies

IPF causes lung scarring and is a chronic disease which is typically fatal

Idiopathic pulmonary fibrosis (IPF) is a severe, chronic, often fatal lung disease which causes scarring (fibrosis) in lungs that worsens over time. Fibrosis occurs when the normal healing process goes awry, with the formation of excessive scarring. The lung scarring leads to difficulty in breathing, shortness of breath, and life-threatening conditions including respiratory failure. IPF belongs to a large group of conditions, referred to as interstitial lung disease (ILD), which are all characterised by progressive inflammation and fibrosis in the lungs, notably around the alveoli (air sacs). According to the American Lung Association, IPF is the most common form of pulmonary fibrosis, and studies suggest IPF represents between 20-50% of all ILDs.

The cause of IPF is unknown

Exposure to certain environmental factors can lead to lung scarring (pulmonary fibrosis, PF) including hazardous dust and fumes, and smoking also increases the risk. Prior viral infection or other medical conditions can also cause PF; for example COVID-19 has been associated with the development of pulmonary fibrosis, and acid reflux (GERD) is thought to increase the risk owing to patients breathing in acid drops that may injure the lungs. Genetic factors are also thought to play a role in the development of pulmonary fibrosis. In the case of IPF, the cause is unknown, hence 'idiopathic'.

IPF generally affects older males; in the US there are c 50k new cases each year

The risk of developing IPF generally increases with age. It rarely affects people aged below 50 and affects more men than women. In the US, around 100,000 people are thought to have IPF, with approximately 50,000 new cases of IPF diagnosed each year. Symptoms are generally similar to other lung conditions, such as a cold or an upper respiratory infection, and include persistent dry cough, shortness of breath, tiredness, and loss of appetite/weight loss. These generally develop gradually and worsen over time. Given the similarity to other respiratory conditions, diagnosing IPF can be a challenge and is generally via a specialist physician through a series of tests which can include:

- Lung function tests, which include spirometry (how much air is inhaled and/or exhaled), pulse oximetry (oxygen in the blood), and exercise stress/capacity tests eg six-minute walk test;
- Imaging, including chest X-rays, CT (computerised tomography) and high-resolution CT (HRCT) scans, in addition to ECGs;
- Bronchoscopy, where a tube with a camera is passed into the airways;

- Tissue sample, either via bronchoscopy to collect cells and fluid from the lungs, or via a surgical lung biopsy.

The disease is progressive and prognosis is usually poor

IPF generally worsens over time, although given it is a complex and heterogenous disease, progression can be highly variable amongst patients. Only limited treatment options exist with the anti-fibrotics Esbriet (pirfenidone) and Ofev (nintedanib) approved. These slow the decline in lung function rather than improving or reversing the fibrosis. Without anti-fibrotic treatment prognosis is generally poor, with a meta-analysis suggesting a five-year overall survival rate of 31% and a pooled mean overall survival of four years.

Current treatments, Esbriet and Ofev, generate combined WW sales of >$4bn

Roche's Esbriet (pirfenidone) was approved for the treatment of IPF in Europe in 2011 and in the US in 2014. Revenues in 2021 were CHF1.04bn (c $1.2bn), although this has now gone generic in the US, with Sandoz launching the first fully substitutable equivalent in May 2022. Boehringer Ingelheim's Ofev (nintedanib) was approved in the US for IPF in 2014 and shortly after in Europe, marketed as Vargatef. Revenues in 2021 were €2.5bn (c $2.9bn). Patent expiry is expected in 2025. Ofev is also approved for chronic ILD in which lung fibrosis continues to worsen and to slow the rate of decline in lung function in adults with systemic sclerosis-associated ILD (SSc-ILD).

Both Esbriet and Ofev slow progression but do not reverse the disease…

According to the FDA approved labels, both Esbriet and Ofev significantly slowed down the rate of lung function decline, as measured by Forced Vital Capacity (FVC), with both showing around a 40-50% relative reduction in FVC decline. In the clinical studies that formed the basis of the FDA approvals, neither demonstrated a statistically significant difference in all-cause mortality (survival), albeit mortality benefits have been observed in various pooled and meta-analyses for both Esbriet and Ofev and in the real-world setting.

…and tolerability is generally poor, with severe GI side effects

Significant gastrointestinal side effects are observed with both, notably high rates of nausea, which affects around a third of patients treated with Esbriet, whilst around two-thirds of patients treated with Ofev experience diarrhoea. These side effects can lead to dose reductions and treatment discontinuations. Overall, treatment discontinuation within 12 months is around 50% for both agents.

Exhibit 5: Selected Phase III IPF development programmes

Product	Mechanism/Target	Company	Trials	Start	Completion*	Notes
Pamrevlumab	Connective tissue growth factor inhibitor antibody	FibroGen	ZEPHYRUS I ZEPHYRUS II	Jul 2019 Dec 2020	Dec 2022 Apr 2023	Top-line ZEPHYRUS I data expected mid-2023
INOPulse	Pulsed inhaled nitric oxide	Bellerophon Therapeutics	REBUILD	Dec 2020	Dec 2022	Top-line data Q323
RG6354 (PRM-151)	Anti-fibrotic immunomodulator	Roche	STARSCAPE	Mar 2021*	Dec 2023	Filing 2024 (correct as of July 2022)
Tyvaso (trepostinil)	Prostacyclin receptor agonist	United Therapeutics	TETON-1 TETON-2	Jun 2021 TBC	Jun 2024 Sep 2025	Tyvaso already approved in PAH
BI 1015550	Phosphodiesterase 4B	Boehringer Ingelheim	NCT05321069	Sep 2022*	Nov 2024	

Source: Trinity Delta, company websites & press releases, and clinicaltrials.gov. Note: * from clinicaltrials.gov

Unmet need in IPF remains high, with several candidates in development

Given the current limited treatment options in IPF, which do not reverse the disease and are associated with poor tolerability, there remains a high unmet need for novel therapies with better patient outcomes. According to Evaluate Pharma

there are 336 products in development for IPF, of which 138 are in clinical trials and 198 are at the preclinical and research project stages. There are only two other ROCK2 inhibitors in clinical development globally (Sanofi's Rezurock and Graviton/Sino Pharmaceutical's TDI01), to our knowledge, albeit their development status in IPF is uncertain. Select compounds in Phase III development are summarised in Exhibit 5.

IPF could have blockbuster potential

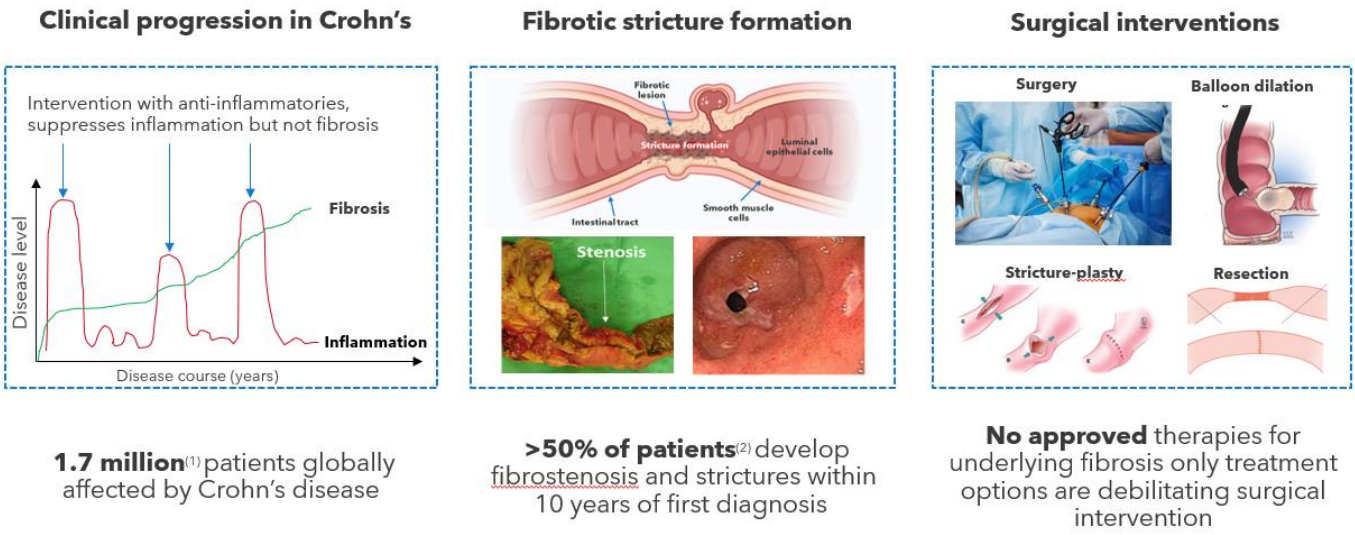
With current treatments reaching >$4bn in sales per annum, there could be blockbuster potential for a novel IPF therapy that improves on existing options. We note that Pliant Therapeutics completed a $230m (gross) offering on NASDAQ in July 2022 following positive Phase IIa data in IPF for its lead asset PLN-74809. Pliant Therapeutics has a current market capitalisation of c $1bn.

RXC008: pan-ROCK for fibrostenotic Crohn's disease

ROCK a highly attractive target for fibrosis in Crohn's disease

RXC008 is the development candidate in Redx Pharma's novel GI-targeted ROCK programme. It is a pan-ROCK inhibitor designed to only work locally in the gut wall and, as it is quickly degraded by metabolic enzymes, to have a short systemic half-life once absorbed, thus minimising the unwanted effects (ie hypotension) seen when ROCK1 is also targeted. The preclinical data have been particularly impressive, suggesting a disease modifying potential. IND enabling studies are underway, with a Phase I programme scheduled to start before end-2023.

Exhibit 6: RXC008 a potential novel therapy for fibrostenotic Crohn's disease



Source: Redx Pharma Notes: 1 GlobalData Crohn's Disease Dynamic Market Forecast to 2026 report; 2 Chan et al, 2018

Fibrosis is a major element in the poor clinical outcomes

Chronic inflammatory bowel disease (IBD) consists mainly of ulcerative colitis (UC), where the fibrosis is located mainly in rectal mucosa and submucosa, and Crohn's disease, where it can occur in all regions of the intestinal wall (most commonly the small intestine). Normally the GI tract has a remarkable ability for self-regeneration following short-lived and mild insults, as in peptic ulceration, infectious enteritis, or mild diverticulitis. However, if the inflammation becomes chronic and severe, the inflammatory mechanisms drive an excessive production of extracellular matrix (ECM) components and activate intestinal stromal cells that produce fibrosis. Even in the absence of inflammation, tissue damage and fibrosis continue to progress with increased accumulation and crosslinking of ECM.

Even targeted biologics have limited effects on progression

Typically Crohn's disease follows a relapsing and remitting course, with treatments ranging from simple anti-inflammatories (eg steroids) and immune suppressors (eg azathioprine) to targeted biologics such as vedolizumab (Entyvio), ustekinumab (Stelara), and risankizumab (Skyrizi). These can be very effective at providing symptomatic relief, but once fibrosis is established, control of inflammation even with biologics is not sufficient to halt fibrosis progression as matrix stiffness can drive fibrosis independently of intestinal inflammatory activity. Hence anti-inflammatory treatment is best suited for early-stage disease, as fibrosis might become self-perpetuating once ECM activity has become established.

High impacts on patients and healthcare providers

Clinical reviews state more than half of patients with Crohn's develop stricturing or penetrating complications requiring hospital interventions within the first ten years after diagnosis. The current treatment options for symptomatic fibrotic strictures are surgical resection and endoscopic dilation (EBD). Unfortunately, these are not only highly invasive and fraught with complications but are also associated with high rates of recurrence. Up to 80% of such patients will require at least one surgical resection, with a recurrence rate of up to 70%. The patient, and economic, burden of fibrotic strictures in Crohn's disease is significant and identified as an area of clinical focus.

Preclinical models show a reversal in disease progression

The ROCK receptors are expressed in fibroblastic, epithelial, endothelial, and muscle cells of the human intestinal tract and are activated in inflamed and fibrotic tissue. Redx Pharma has evaluated pan-ROCK inhibitors, which address both ROCK1 and ROCK2 pathways, in several preclinical and animal models. These have shown that ROCK inhibition prevented myofibroblast accumulation, expression of pro-fibrotic factors, and accumulation of fibrotic tissue; repeated administration resulted in the prevention and reversal of the fibrotic damage.

Designed for maximal effect at local gut site only

Lead candidate RXC008 is designed to be retained locally in the gut wall and, as it is quickly degraded by metabolic enzymes (paraoxonase), to have a very short half-life once absorbed. The local effect allows the targeting of both ROCK receptors while avoiding the systemic side-effects, notably cardiovascular, associated with ROCK1 inhibition. Early preclinical data were presented at ECCO (European Crohn's and Colitis Organisation) in 2018 which showed the mechanisms by which RXC008 works and how a compound with similar properties to RXC008 reduces tissue damage and fibrosis in various animal models. With the obvious caveat that this is preclinical data, there was also evidence of a reversal of established fibrosis (suggesting a therapeutic role in addition to a preventative function alone).

IND/CTA ready for end-2023

The preclinical work is continuing, and an IND/CTA submission is planned for end-2023. RXC008 is one of the three new clinical assets Redx Pharma management plan to progress into the clinic by 2025.

Valuation and Financials

rNPV valuation of £458m, or 138p per share

We value Redx Pharma as a classic drug discovery and development play, with our sum of the parts rNPV-based model generating a valuation of £458m ($596m), equivalent to 138p per share. Exhibit 7 summarises the outputs and underlying assumptions of our valuation model. Our September 2020 Initiation provides a detailed overview of our valuation methodology.

Exhibit 7: rNPV-based valuation of Redx Pharma

Programme	Total NPV ($m)	Total NPV (£m)	Approval likelihood	rNPV ($m)	rNPV (£m)	rNPV/ share (p)	Notes
RXC004 (porcupine inhibitor - oncology)	836.2	643.3	30%	169.1	130.1	39.0	Peak sales: $2.55bn (£1.96bn) Launch year: 2027
RXC007 (ROCK2 inhibitor - IPF/NASH)	1,173.5	902.7	15%	121.1	93.2	27.9	Peak sales: $3.13bn (£2.41bn) Launch year: 2028
AZD5055 (AstraZeneca: porcupine inhibitor - IPF)	325.2	250.1	15%	53.9	41.5	12.4	Peak sales: $1.66bn (£1.28bn) Launch year: 2028
JZP815 (Jazz Pharma: pan-RAF - oncology)	165.0	126.9	7%	30.0	23.1	6.9	Peak sales: $707m (£544m) Launch year: 2029
RX008 (ROCK1/2 - Crohn's disease)	163.7	125.9	5%	38.8	29.8	8.9	Peak sales: $1.61bn (£1.24bn) Launch year: 2029
Discovery engine				171.3	131.8	39.5	
Operating costs	(45.1)	(34.7)		(45.1)	(34.7)	(10.4)	
Net cash	56.7	43.6		56.7	43.6	13.1	FY22e cash
Total	**2,675.2**	**2,057.9**		**595.8**	**458.3**	**137.5**	
Total (fully diluted)				**613.4**	**471.8**	**97.9**	Based on all options and CLNs

Source: Trinity Delta Note: The rNPV of RXC004 and RXC007 includes a deal success factor of 80%, and of 75% for GI-targeted ROCK; other valuation assumptions include a 12.5% discount factor, £/$ FX rate of 1.30, and 10% taxation from 2028 (UK patent box).

Clinical progress, clarity on timelines and patient sizes will refine our valuation

The clinical progress of the various pipeline assets should unlock upside, as further data would prompt us to adjust the respective success probabilities that reflect the inherent clinical, commercial, and execution risks that each programme carries. Additionally, as these programmes progress, there should be more insight into the specific oncology or fibrosis patient populations that will be addressed, and this in turn would mean that peak sales (pricing, penetration) and timeline assumptions could be revisited.

Clinical data set to be delivered throughout 2023

The news flow over the next 12 months should see RXC004 top line data from the monotherapy element of the Phase II PORCUPINE 2 trial, with biliary cancer results in H123, and the monotherapy genetically selected pancreatic cancer results due in H223. While these data should provide valuable information on toxicities and tolerance, we suspect the true indications of likely efficacy will arise from the combination studies (with CPIs). This should become apparent when the combination arm of PORCUPINE 2 in biliary cancer and the monotherapy and combination arms of PORCUPINE, in MSS mCRC, report in H223. We also expect preliminary results from the RXC007 Phase IIa study in H223, which should provide useful insights into its likely efficacy and positioning in various fibrotic diseases. RXC008 is expected to be granted IND/CTA permission for progression into the clinic by end-2023, with patient enrolment starting in 2024.

All key programmes funded through to end-23

Our June 2022 Update provides a summary of Redx Pharma's financial position and reviews H122 results. At end-March 2022, Redx Pharma had £31.6m in cash (H121: £39.9m), which included $19m in milestone payments from partnered programmes. This was subsequently boosted by the June 2022 equity placement which raised £34.3m, with support from all existing investors and a new specialist healthcare fund, Invus, joining the shareholder list. Additionally, in June 2022, a further milestone, $5m, was received from Jazz Pharmaceuticals. These funds, plus modest risk-adjusted milestones, are sufficient to maintain the development momentum being built and fund planned operations through key data points to end-2023.

Exhibit 8: Multiple - fully funded - potential milestones in 2022-2023

	2022 (CY)	2023 (CY)
Porcupine Inhibitor (RXC004)	• Data from Phase 1 combination study with nivolumab (anti-PD-1) ✓ Initiation of PORCUPINE2 monotherapy Phase 2 study in genetically selected pancreatic and biliary cancer • Initiation of anti-PD-1 combination arms	**Ph2 data - from H1 2023** PORCUPINE • **H2** mono & combination - MSS mCRC PORCUPINE2 • **H1** monotherapy - biliary • **H2** combination - biliary • **H2** monotherapy - pancreatic
ROCK2 Selective Inhibitor (RXC007)	✓ **H1** Data from Phase 1 healthy volunteer study ✓ Initiation of Phase 2a study in IPF • **H2** US IND	**H2** Phase 2a topline data read out
GI-targeted ROCK Inhibitor (RXC008)	✓ **H1** Select development candidate	IND/CTA submission – **end 2023**
DDR Inhibitor (Discoidin Domain Receptor) **Research Targets**	• Progress DDR inhibitor for fibrosis • Advance multiple programmes in early discovery	Progress target of two additional wholly-owned INDs by 2025
Porcupine Inhibitor (RXC006/AZD5055) **Pan-RAF Inhibitor** (JZP815) **MAPK Pathway Target**	✓ IND cleared triggering $5m June 2022	Redx remains eligible for regulatory and development milestones

Source: Redx Pharma

Exhibit 9: Summary of financials

Year-end: Sept 30	£'000s	2019	2020	2021	2022E	2023E
INCOME STATEMENT						
Revenues		**3,131**	**5,685**	**10,035**	**19,219**	**3,950**
Cost of goods sold		(350)	0	0	0	0
Gross Profit		**2,781**	**5,685**	**10,035**	**19,219**	**3,950**
R&D expenses		(8,339)	(10,460)	(24,445)	(34,223)	(42,437)
G&A expenses		(1,831)	(4,238)	(6,455)	(7,717)	(8,051)
Underlying operating profit		**(7,389)**	**(8,445)**	**(17,080)**	**(20,829)**	**(44,607)**
Share-based payments		(45)	(568)	(3,785)	(1,893)	(1,930)
Exceptionals		948	0	0	0	0
Other revenue/expenses		241	812	1,120	1,142	1,165
EBITDA		**(6,154)**	**(7,536)**	**(19,112)**	**(19,912)**	**(44,280)**
Operating Profit		**(6,245)**	**(8,201)**	**(19,745)**	**(21,579)**	**(45,372)**
Financing costs/income		(90)	(967)	(1,698)	(125)	(83)
Profit Before Taxes		**(6,335)**	**(9,168)**	**(21,443)**	**(21,704)**	**(45,455)**
Adj. PBT		**(7,479)**	**(8,844)**	**(14,993)**	**(20,954)**	**(44,690)**
Current tax income		2,017	(45)	(133)	342	424
Net Income		**(4,318)**	**(9,213)**	**(21,576)**	**(21,362)**	**(45,031)**
EPS (p)		**(3.4)**	**(5.4)**	**(8.4)**	**(7.0)**	**(13.1)**
Adj. EPS		**(4.0)**	**(5.2)**	**(5.9)**	**(6.8)**	**(12.9)**
DPS (p)		**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Average no. of shares (m)		126.4	170.1	256.4	304.3	342.5
BALANCE SHEET						
Current assets		**5,807**	**29,468**	**35,815**	**53,183**	**33,025**
Cash and cash equivalents		3,704	27,513	29,552	43,594	31,007
Accounts receivable		1,232	1,923	6,231	9,215	1,623
Other current assets		871	32	32	374	395
Non-current assets		**551**	**3,459**	**3,730**	**2,001**	**853**
Property, plant & equipment		134	3,048	3,325	1,813	884
Intangible assets		417	411	405	401	397
Other non-current assets		0	0	0	(214)	(427)
Current liabilities		**(4,867)**	**(10,934)**	**(9,592)**	**(26,400)**	**(34,161)**
Short-term debt		(468)	0	0	(14,247)	(25,000)
Accounts payable		(3,445)	(3,362)	(4,699)	(7,529)	(8,487)
Other current liabilities		(954)	(7,572)	(4,893)	(4,624)	(674)
Non-current liabilities		**0**	**(19,967)**	**(16,821)**	**(1,544)**	**(1,331)**
Long-term debt		0	(16,758)	(14,247)	0	0
Other non-current liabilities		0	(3,209)	(2,574)	(1,544)	(1,331)
Equity		**1,491**	**2,026**	**13,132**	**27,239**	**(1,614)**
CASH FLOW STATEMENTS						
Operating cash flow		**(4,668)**	**395**	**(21,379)**	**(18,567)**	**(37,429)**
Profit before tax		(6,335)	(9,168)	(21,443)	(21,704)	(45,455)
Non-cash adjustments		(782)	2,123	6,116	3,684	3,105
Change in working capital		(265)	6,425	(6,065)	(290)	4,600
Interest paid		13	7	13	(125)	(83)
Taxes paid		2,701	1,008	0	(133)	404
Investing cash flow		**32**	**(55)**	**(754)**	**(151)**	**(158)**
CAPEX on tangible assets		(28)	(59)	(754)	(151)	(158)
Acquisitions/disposals		60	4	0	0	0
Other investing cash flows		0	0	0	0	0
Financing cash flow		**1,869**	**23,469**	**24,143**	**32,761**	**25,000**
Proceeds from equity		0	1,876	24,929	33,577	0
Increase in loans		1,000	22,563	0	0	25,000
Other financing cash flow		869	(970)	(786)	(816)	0
Net increase in cash		**(2,767)**	**23,809**	**2,010**	**14,042**	**(12,588)**
Cash at start of year		6,471	3,704	27,513	29,552	43,594
Cash at end of year		**3,704**	**27,513**	**29,552**	**43,594**	**31,007**
Net cash at end of year		**3,236**	**10,755**	**15,305**	**29,347**	**6,007**

Source: Company, Trinity Delta Note: Short-term debt in FY23E is indicative of our view of Redx Pharma's funding requirement. Redmile/Sofinnova Convertible Loan Note has August 2023 conversion date, with a 15.5p conversion price, equating to a potential 110.3m of new shares. Revenue forecasts do not include any contribution from milestone payments yet to be received.

Philippa Gardner pgardner@trinitydelta.org +44 (0) 20 3637 5042

Lala Gregorek lgregorek@trinitydelta.org +44 (0) 20 3637 5043

Franc Gregori fgregori@trinitydelta.org +44 (0) 20 3637 5041

Disclaimer

More information is available on our website: www.trinitydelta.org