Online Supplementary File

Blinding and drug reconstitution

Physician and patient blinding were maintained throughout the study by ensuring that all syringes were identical. Reconstitution of the placebo or romilkimab powder with water for injection was either done at the investigational site by an unmasked pharmacist who did not have any contact with study participants or at the patient's home by a healthcare professional (eg, visiting nurse) out of the patient's view (this was required as products were similar before reconstitution but slightly different afterwards). For the reconstitutions and injections performed at home, each visiting nurse was dedicated to a single patient in the study and thus remained masked and blinded during the entire study.

Allanore Y, *et al. Ann Rheum Dis* 2020; 79:1600–1607. doi: 10.1136/annrheumdis-2020-218447

Key exclusion criteria

Key exclusion criteria included: systemic sclerosis disease duration >36 months from first non-Raynaud's phenomenon manifestation; modified Rodnan skin score <10 or >35 at screening and baseline visits; vasculitis or another connective tissue disease (eg, polymyositis); forced vital capacity ≤75% predicted and diffusing lung capacity for carbon monoxide after haemoglobin correction ≤40% predicted at screening; history of heart failure, including left ventricular ejection fraction ≤45% or any clinically significant electrocardiogram findings at screening; previous treatment with rituximab, bone marrow transplantation, total lymphoid irradiation, or ablative ultra–high-dose cyclophosphamide, or any investigational drug.

Allanore Y, *et al. Ann Rheum Dis* 2020; 79:1600–1607. doi: 10.1136/annrheumdis-2020-218447

Supplementary table S1 Summary of key safety findings in the DRI11772 study[1]

DRI11772 study **Serious cardiac TEAEs, n (%)**	**Placebo QW** **(N=109)**	**Romilkimab** **200 mg Q2W** **(N=108)**	**Romilkimab** **200 mg QW** **(N=108)**
Cardiac disorders	**3 (3%)**	**3 (3%)**	**10 (9%)**
Atrial fibrillation	0	1 (1%)	1 (1%)
Acute coronary syndrome	1 (1%)	0	2 (2%)
Cardiac failure	0	0	1 (1%)
Coronary artery stenosis	1 (1%)	1 (1%)	1 (1%)
Arteriosclerosis coronary artery	0	0	1 (1%)
Myocardial infarction	1 (1%)	0	1 (1%)
Acute right ventricular failure	0	1 (1%)	0
Arrhythmia	0	0	1 (1%)
Atrial flutter	0	0	1 (1%)
Cardiac failure congestive	0	0	1 (1%)
Congestive cardiomyopathy	0	0	1 (1%)
Right ventricular failure	0	0	1 (1%)
Supraventricular tachycardia	0	0	1 (1%)
Ventricular fibrillation	0	0	1 (1%)
DRI11772 study **AE profile, patients, n (%)**	**Placebo QW** **(N=109)**	**Romilkimab** **200 mg Q2W** **(N=108)**	**Romilkimab** **200 mg QW** **(N=108)**
Any TEAE	99 (91%)	102 (94%)	100 (93%)
Serious TEAE	26 (24%)	27 (25%)	46 (43%)
TEAE leading to death	11 (10%)	6 (6%)	13 (12%)
TEAE leading to discontinuation	15 (14%)	13 (12%)	23 (21%)

AE, adverse event; QW, once weekly; Q2W, once every 2 weeks; TEAE, treatment-emergent adverse event.

[1]Raghu G, Richeldi L, Crestani B, *et al*. SAR156597 in idiopathic pulmonary fibrosis: a phase 2 placebo-controlled study (DRI11772). *Eur Respir J* 2018;52:1801130.

Supplementary table S2 Country institutional review boards and ethics committees

Country	Institutional review board or independent ethics committee
Argentina	Centro Médico Privado de Reumatología, Tucumán, Argentina; Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; Organización Médica de Investigación (OMI), Buenos Aires, Argentina; Hospital Britanico Perdriel, Buenos Aires, Argentina
Belgium	UZ Gent Corneel, Heymanslaan, Belgium; UZ Leuven Rheumatology department, Leuven, Belgium
Estonia	SA Põhja-Eesti Regionaalhaigla Sisehaiguste kliinik, Tallinn, Estonia
France	CHU Hautepierre Service de Rhumatologie 1, Strasbourg Cedex, France; Hôpital Lapeyronie Fédération de Rhumatologie 371, Montpellier, France; Groupe Hospitalier Cochin 27, Paris, France
Germany	Universitätsklinikum Charité Medizinische Klinik mit Schwerpunkt Rheumatologie und Klinische Immunologie Charitéplatz 1, Berlin, Germany; Universitätsklinikum Köln Klinik für Dermatologie und Venerologie, Köln, Germany; Kerckhoff-Klinik gGmbH Abteilung für Rheumatologie und Klinische Immunologie, Bad Nauheim, Germany; Universitätsklinikum Ulm Klinik für Dermatologie und Allergologie, Ulm, Germany
Italy	Ospedale Maggiore Policlinico Immunologia Clinica, Milan, Italy; Azienda Ospedaliera San Martino, Genova, Italy; Istituto Ortopedico Gaetano Pini U. O. Reumatologia, Milan, Italy; AOU S.Luigi Gonzaga di Orbassano, Torino, Italy
Mexico	Investigacion y Biomedicina de Chihuahua, Chihuahua, Mexico; Centro de Estudios de Investigacion Basica y Clinica, Jalisco, Mexico; Hospital Universitario, Nuevo Leon, Mexico; Centro Integral en Reumatologia Jalisco, Mexico
Poland	Prywatna Praktyka Lekarska, Wielkopolskie, Poland; REUMATIKA-Centrum Reumatologii, Mazowieckie, Poland; Centrum Medyczne Oporow, Dolnoslaskie, Poland
Romania	Spitalul Clinic Judetean de Urgenta Cluj-Napoca Sectia Clinica Reumatologie, Cluj Napoca, Romania; MEDIAB SRL, Targu Mures, Romania; Spitalul Clinic Sfanta Maria, Bucharest, Romania; Spitalul Clinic "dri Cantacuzion", Bucharest, Romania
Russian Federation	Research Institute of Rheumatology, Moscow, Russian Federation; Regional Clinical Hospital for Wars Veterans 10, Kemerovo, Russian Federation; Republican clinical hospital, Ufa, Russian Federation; City clinical hospital, Moscow, Russian Federation; Practicheskaya Meditsina, Ltd 1, Moscow, Russian Federation
Ukraine	TOV Revmocenter 5, Ukraine; Policlinic, Administration of Medical Services and Rehabilitation (ARTEM), Ukraine
UK	Royal Free NHS Trust, Greater London, UK
USA	Cleveland Clinic, Ohio, USA; Georgetown University Medical Center, District of Columbia, USA; University of California, California, USA; UT Health CRU at Memorial Hermann-TMC, Texas, USA

Supplementary table S3 Summary of key changes from protocol amendment (9 August 2017)

Following exclusion criteria were added: • History of heart failure (including acutely decompensated in the setting of preserved ejection fraction), left ventricular ejection fraction ≤45%, coronary artery disease, angina, myocardial infarction, ischemic cardiomyopathy, and/or hypertrophic cardiomyopathy. • Ischaemic ECG changes (except those not supported by the findings of a left heart catheterisation performed in the last year within screening) and/or other clinically significant ECG findings at screening. All abnormal ECG finding were to be reviewed and confirmed by a local cardiologist. • FVC (% predicted) ≤75% and DL_{CO} (% predicted after haemoglobin correction) ≤40% at screening.
Following procedures were added or modified: • PFT and echocardiogram (2-dimensional transthoracic) were added at the screening visit, and ECG assessment was modified. • FVC (% predicted and observed) and DL_{CO} (% predicted [corrected for haemoglobin] and observed) assessment were added to the screening visit to screen for the newly added exclusion criterion.

DL_{CO}, diffusing lung capacity for carbon monoxide; ECG, electrocardiogram; FVC, forced vital capacity; PFT, pulmonary function test.

Supplementary table S4 Critical or major protocol deviations by category

n (%)	**Placebo QW (n=49)**	**Romilkimab 200 mg QW (n=48)**
Any critical or major deviation	19 (39)	9 (19)
Inclusion/exclusion criteria	1 (2)	1 (2)
DcSSc according to Leroy's criteria	1 (2)	1 (2)
Randomisation procedure	8 (16)	2 (4)
Wrong stratum of randomisation	8 (16)	2 (4)
IMP management	1 (2)	4 (8)
IMP administered under a protocol-specific contraindication	0	1 (2)
Invalid administered IMP for use	1 (2)	1 (2)
Kit dispensation without IRT transaction during treatment	0	2 (4)
Concomitant medications/therapy	3 (6)	0
Prohibited use of immunosuppressive therapies as concomitant medications	1 (2)	0
Protocol-specific co-administered medication not administered as per protocol	3 (6)	0
Assessments/procedures	7 (14)	1 (2)
PFTs / DL_{CO} not performed	2 (4)	0
PFTs / DL_{CO} not performed	1 (2)	1 (2)
Study procedure performed against protocol instructions	4 (8)	0
Clinical safety	1 (2)	2 (4)
Failure to follow up on related AE/SAE/AESI	1 (2)	0
Failure to report AE/AESI/SAE/pregnancy/overdose to sponsor within protocol-specified time window	0	2 (4)
Source data records	2 (4)	1 (2)
Lost, non-existent, missing or incomplete source data	2 (4)	1 (2)

AE, adverse event; AESI, adverse event of special interest; DcSSc, diffuse cutaneous systemic sclerosis; DL_{CO}, diffusing lung capacity for carbon monoxide; IMP, investigational medicinal product; IRT, interactive response technology; PFT, pulmonary function test; SAE, serious adverse event; QW, once weekly.

Supplementary table S5 Mean change from baseline to week 24 in additional exploratory efficacy endpoints in the ITT population treated with romilkimab versus placebo

	Placebo QW (n=49)	**Romilkimab 200 mg QW (n=48)**
UCLA SCTC GIT 2.0 score		
Baseline mean (SD)	0.42 (0.36) [n=48]	0.29 (0.25) [n=45]
LS mean (SE) change from baseline	–0.02 (0.04) [n=44]	–0.04 (0.04) [n=44]
LS mean (SE) difference [95% CI], p value	–0.02 (0.06) [–0.14, 0.10], 0.39	
Tender joint count 28		
Baseline mean (SD)	6.37 (7.41)	2.52 (4.10)
LS mean (SE) change from baseline	–1.32 (0.57) [n=48]	–2.41 (0.58) [n=47]
LS mean (SE) difference [95% CI], p value	–1.08 (0.84) [–2.74, 0.58], 0.10	
Digital ulcer count		
Baseline mean (SD)	1.00 (1.51)	0.65 (1.58)
LS mean (SE) change from baseline	–0.27 (0.17) [n=48]	–0.17 (0.17) [n=47]
LS mean (SE) difference [95% CI], p value	0.10 (0.24) [–0.37, 0.57], 0.33	
CRISS – predicted probability of improvement, n	47	47
Mean (SD)	0.3811 (0.4372)	0.4245 (0.4266)
p value	0.27	
CRISS – probability of improvement ≥60%, n	49	48
n (%)	18 (37)	19 (40)
CRISS events, n	49	48
Decline in FVC, n (%)	2 (4)	0
Scleroderma renal crisis, n (%)	0	1 (2)
New onset left ventricular failure, n (%)	0	0
New onset of PAH (right arm), n (%)	0	0

CI, confidence interval; CRISS, composite response index in diffuse cutaneous systemic sclerosis; FVC, forced vital capacity; ITT, intent-to-treat; LS, least-squares; PAH, pulmonary arterial hypertension; QW, once weekly; SD, standard deviation; SE, standard error; UCLA SCTC GIT 2.0, University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0.

Supplementary table S6 Mean change from baseline to week 24 in mRSS for prespecified ITT subpopulations treated with romilkimab versus placebo

	Placebo QW (n=49)	**Romilkimab 200 mg QW (n=48)**
Disease duration <20 months, n	23	25
LS mean (SE) change from baseline	–1.75 (1.24)	–5.09 (1.19)
LS mean (SE) difference [95% CI]	–3.34 (1.72) [–6.74, 0.07]	
Disease duration ≥20 months, n	25	22
LS mean (SE) change from baseline	–3.09 (1.19)	–4.40 (1.26)
LS mean (SE) difference [95% CI]	–1.31(1.73) [–4.74, 2.12]	
Interaction p value for disease duration	0.41	
With background medication,* n	29	25
LS mean (SE) change from baseline	–3.43 (1.08)	–5.81 (1.17)
LS mean (SE) difference [95% CI]	–2.38 (1.59) [–5.55, 0.79]	
Without background medication,* n	19	22
LS mean (SE) change from baseline	–0.95 (1.34)	–3.64 (1.24)
LS mean (SE) difference [95% CI]	–2.69 (1.83) [–6.31, 0.94]	
Interaction p value for background medication	0.90	
With medical history of SSc-ILD, n	18	17
LS mean (SE) change from baseline	–4.08 (1.41)	–5.82 (1.42)
LS mean (SE) difference [95% CI]	–1.74 (2.00) [–5.71, 2.24]	
Without medical history of SSc-ILD, n	30	30
LS mean (SE) change from baseline	–1.48 (1.09)	–4.09 (1.08)
LS mean (SE) difference [95% CI]	–2.61 (1.53) [–5.65, 0.44]	
Interaction p value for medical history of SSc-ILD	0.73	

*Includes methotrexate, mycophenolate mofetil, azathioprine, and cyclophosphamide.
CI, confidence interval; ILD, interstitial lung disease; ITT, intent-to-treat; LS, least-squares; mRSS, modified Rodnan skin score; QW, once weekly; SE, standard error; SSc, systemic sclerosis.

Supplementary table S7 Distribution of events reflecting disease progression

Events reflecting disease progression used in time to progression analysis, n (%)	**Placebo QW (n=49)**	**Romilkimab 200 mg QW (n=48)**
Patients with a decrease >10% in % predicted FVC from baseline	4 (8)	3 (6)
Patients with a decrease >15% in % predicted DL_{CO} (haemoglobin corrected) from baseline	3 (6)	3 (6)
Patients with an increase >20% or >+5 in mRSS from baseline	5 (10)	3 (6)
Patients with a CRISS event	1 (2)	0
Death events	0	0
Patients with a decrease >10% in % predicted FVC and a decrease >15% in % predicted DL_{CO} (haemoglobin corrected) from baseline	1 (2)	0
Patients with a decrease >10% in % predicted FVC and a decrease >15% in % predicted DL_{CO} (haemoglobin correct) from baseline and a CRISS event	1 (2)	0

CRISS, composite response index in diffuse cutaneous systemic sclerosis; DL_{CO}, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; mRSS, modified Rodnan Skin Score; QW, once weekly.

Supplementary table S8 Mean change from baseline to week 24 in protein biomarkers in the ITT population treated with romilkimab versus placebo

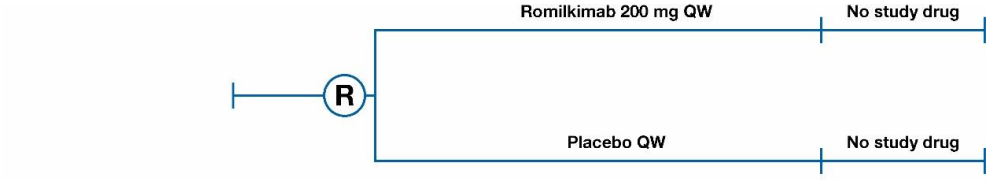
	Placebo QW (n=49)	**Romilkimab 200 mg QW (n=48)**
TARC (ng/L)		
Baseline mean (SD)	576.07 (330.29) [n=46]	583.00 (406.42) [n=46]
LS mean (SE) change from baseline	–20.38 (36.03) [n=45]	–135.94 (36.04) [n=45]
LS mean difference [95% CI], p value	–115.56 [–216.87, –14.26], 0.0258	
Periostin (µg/L)		
Baseline mean (SD)	138.82 (91.81) [n=45]	156.22 (96.14) [n=46]
LS mean (SE) change from baseline	–7.39 (6.49) [n=45]	–24.31 (6.49) [n=45]
LS mean difference [95% CI], p value	–16.92 [–35.19, 1.35], 0.07	
Eotaxin-3 (ng/L)		
Baseline mean (SD)	29.11 (16.60) [n=45]	30.44 (24.92) [n=46]
LS mean (SE) change from baseline	–2.05 (10.91) [n=45]	12.49 (10.80) [n=45]
LS mean difference [95% CI], p value	14.55 [–16.01, 45.10], 0.35	
COMP (µg/L)		
Baseline mean (SD)	377.39 (200.09) [n=46]	406.31 (230.56) [n=45]
LS mean (SE) change from baseline	–29.59 (15.62) [n=46]	–24.62 (15.90) [n=44]
LS mean difference [95% CI], p value	4.97 [–39.38, 49.33], 0.82	
CCL2 (ng/L)		
Baseline mean (SD)	360.27 (160.55) [n=44]	394.89 (647.82) [n=46]
LS mean (SE) change from baseline	–15.28 (28.78) [n=44]	47.13 (28.97) [n=43]
LS mean difference [95% CI], p value	62.40 [–18.81, 143.62], 0.13	

CCL2, chemokine (C-C motif) ligand 2; CI, confidence interval; COMP, cartilage oligomeric matrix protein; ITT, intent-to-treat; LS, least-squares; QW, once weekly; SD, standard deviation; SE, standard error; TARC, thymus and activation regulated chemokine.

Supplementary table S9 Number of randomised patients by institution

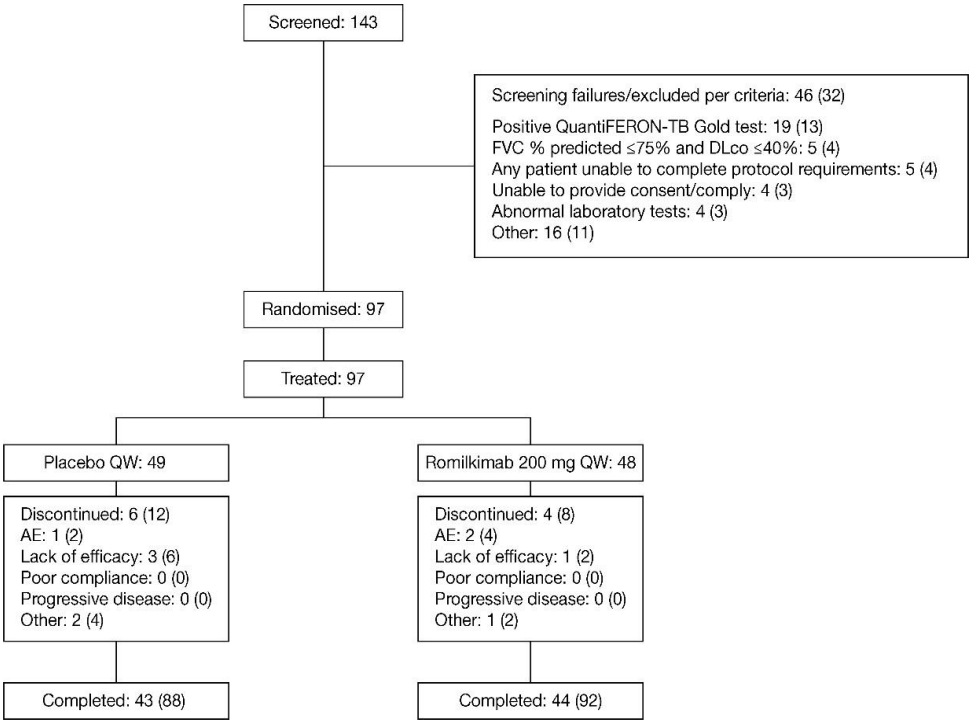
Patients randomised (n)	**Institution**	**Country**
11	Centro Médico Privado de Reumatología	Argentina
	Hospital Britanico	Argentina
	Hospital Italiano De Buenos Aires	Argentina
	Organización Médica de Investigación (OMI)	Argentina
8	UZ Gent	Belgium
	UZ Leuven	Belgium
3	SA Põhja-Eesti Regionaalhaigla	Estonia
4	CHU Hautepierre	France
	Groupe Hospitalier Cochin	France
	Hôpital Lapeyronie	France
3	Universitätsklinikum Köln	Germany
	Universitätsklinikum Ulm	Germany
8	AOU S.Luigi Gonzaga di Orbassano	Italy
	Azienda Ospedaliera San Martino	Italy
	Istituto Ortopedico Gaetano Pini	Italy
	Ospedale Maggiore Policlinico Immunologia Clinica	Italy
9	Centro de Estudios de Investigacion Basica y Clinica, S.C.	Mexico
	Centro Integral en Reumatologia S.A. De C.V.	Mexico
	Hospital Universitario “Dr. José Eleuterio González”	Mexico
	Investigacion y Biomedicina de Chihuahua	Mexico
14	Centrum Medyczne Oporow	Poland
	Prywatna Praktyka Lekarska	Poland
	REUMATIKA-Centrum Reumatologii NZOZ	Poland
7	Spitalul Clinic Judetean de Urgenta Cluj-Napoca	Romania
	Spitalul Clinic Sfanta Maria Sectia de Medicina	Romania
	Spitalul Clinic Sfanta Maria Sectia de Medicina	Romania
14	City Clinical Hospital n.a. Botkin of Moscow	Russian Federation
	Regional Clinical Hospital for Wars Veterans	Russian Federation
	Republican clinical hospital named after Kuvatov	Russian Federation
	Research Institute of Rheumatology named after V.A. Nasonova	Russian Federation
6	Kyiv City Clinical Hospital 3	Ukraine
	National Scientific Center Institute of Cardiology	Ukraine
	Policlinic of Administration of Medical Services and Rehabilitation of ARTEM	Ukraine
	TOV Revmocenter	Ukraine
5	Royal Free NHS Trust	UK
5	Cleveland Clinic	USA
	Georgetown University Medical Center	USA
	University of California, San Francisco	USA
	UT Health CRU at Memorial Hermann-TMC	USA

Supplementary figure S1 Study design. ADA, anti-drug antibody; CRISS, composite response index in diffuse cutaneous systemic sclerosis; D, day; D1, baseline; EQ-5D-5L, European Quality of Life-5 Dimension-5 Level; HAQ-DI, Health Assessment Questionnaire-Disability Index; mRSS, modified Rodnan skin score; PK, pharmacokinetics; QW, once weekly; SHAQ, Scleroderma Health Assessment Questionnaire; UCLA SCTC GIT 2.0, University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0; R, randomisation; W, week.



	Screening			Treatment period							Follow-up		
	Screening	D1	W2	W4	W6	W8	W12	W16	W18	W20	W24	W30	W35
mRSS	x	x		x		x	x				x		x
Lung function	x	x					x				x		x
SHAQ / HAQ-DI		x		x		x	x				x		x
EQ-5D-5L		x					x				x		x
UCLA SCTC GIT 2.0		x		x		x	x				x		x
Digital ulcer count		x		x		x	x				x		x
Tender joint count 28		x		x		x	x				x		x
CRISS							x				x		x
Blood samples – PK		x		x		x	x				x		x
Blood samples – ADA	x	x		x		x	x				x		x
Blood samples – biomarkers		x					x				x		x

Supplementary figure S2 Patient disposition during the 24-week study, n (%). AE, adverse event; DL_{CO}, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity.



Supplementary figure S3 Kaplan-Meier curve for time to first event reflecting progression in the romilkimab and placebo groups. Censored=patients that left the study before an event occurred or the study ended before an event occurred. CI, confidence interval; HR, hazard ratio; QW, once daily.