FG-3019 anti-connective tissue growth factor monoclonal antibody: results of an open-label clinical trial in idiopathic pulmonary fibrosis

Ganesh Raghu[1], Mary Beth Scholand[2], João de Andrade[3], Lisa Lancaster[4], Yolanda Mageto[5], Jonathan Goldin[6], Kevin K. Brown[7], Kevin R. Flaherty[8], Mark Wencel[9], Jack Wanger[10], Thomas Neff[11], Frank Valone[11], John Stauffer[11] and Seth Porter[11]

Affiliations: [1]University of Washington, Seattle, WA, USA. [2]University of Utah, Salt Lake City, UT, USA. [3]University of Alabama at Birmingham, Birmingham, AL, USA. [4]Vanderbilt University, Nashville, TN, USA. [5]University of Vermont, Burlington, VT, USA. [6]David Geffen School of Medicine, Los Angeles, CA, USA. [7]National Jewish Health, Denver, CO, USA. [8]University of Michigan Health System, USA. [9]Via Christi Clinic, Wichita, KS, USA. [10]Pulmonary Function and Clinical Trial Consultant, Rochester, MN, USA. [11]FibroGen, Inc., San Francisco, CA, USA.

Correspondence: Ganesh Raghu, Division of Pulmonary and Critical Care Medicine, Campus Box 356522, Seattle, WA 98195-6522, USA. E-mail: graghu@u.washington.edu.

ABSTRACT FG-3019 is a fully human monoclonal antibody that interferes with the action of connective tissue growth factor, a central mediator in the pathogenesis of fibrosis.

This open-label phase 2 trial evaluated the safety and efficacy of two doses of FG-3019 administered by intravenous infusion every 3 weeks for 45 weeks in patients with idiopathic pulmonary fibrosis (IPF). Subjects had a diagnosis of IPF within the prior 5 years defined by either usual interstitial pneumonia (UIP) pattern on a recent high-resolution computed tomography (HRCT) scan, or a possible UIP pattern on HRCT scan and a recent surgical lung biopsy showing UIP pattern. Pulmonary function tests were performed every 12 weeks, and changes in the extent of pulmonary fibrosis were measured by quantitative HRCT scans performed at baseline and every 24 weeks.

FG-3019 was safe and well-tolerated in IPF patients participating in the study. Changes in fibrosis were correlated with changes in pulmonary function.

Further investigation of FG-3019 in IPF with a placebo-controlled clinical trial is warranted and is underway.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fatal lung disease of unknown aetiology, characterised by progressive dyspnoea and relentless loss of lung function [1]. The natural course of IPF, while variable over time, is universally progressive and the prognosis is poor with 5-year survival rates in the range of approximately 20–40% [2].

Connective tissue growth factor (CTGF) is an essential mediator of human fibrotic conditions [3] and represents a common pathway for fibrogenesis. When expressed in excess, CTGF co-ordinately upregulates growth factors such as transforming growth factor β and insulin-like growth factor 1. While normally expressed at low levels in healthy adults, excess CTGF has been shown to promote significant production of extracellular matrix (ECM) forms of both collagen and fibronectin, as well as inhibitors of metalloproteinases that normally inhibit breakdown of ECM components. The accumulation of ECM inherent in fibrosis is driven by both increased secretion and decreased degradation [3–5].

FG-3019 is a fully human monoclonal antibody specific for CTGF. Pre-clinical studies suggest that FG-3019 penetrates into tissues to reduce effective tissue levels of CTGF resulting in reduction of pro-fibrotic factors, enabling a rebalancing of ECM secretion and processing, and a return toward tissue homeostasis. In a mouse model of radiation-induced pulmonary fibrosis, administration of FG-3019 for 8 weeks beginning 16 weeks after lethal irradiation, when severe tissue remodelling was already advanced, resulted in altered gene expression in the lungs, reversal of lung pathology, decrease in abnormal lung density, abrogation of fibrosis, improvement in lung function and prolonged survival [6]. Notably, in irradiated animals, FG-3019 treatment altered the elevated expression of an array of fibrosis-related genes in the lungs, including ⩾3-fold reductions in expression levels of fibronectin, CTGF, lysyl oxidase and collagen 1α1.

In an open-label, phase 1b, dose-escalation study in 21 IPF patients, FG-3019 demonstrated no dose-limiting toxicity, dose-dependent adverse events (AEs) or drug-related serious adverse events (SAEs) [7]. Herein, we present data from a phase 2, prospective, open-label safety and efficacy study of FG-3019 in 89 subjects with IPF, and demonstrate good safety and tolerability, promising outcomes in changes of forced vital capacity (FVC) and a decrease in the extent of the radiographic pattern of pulmonary fibrosis in some patients.

Methods

Study design

Study FGCL-3019-049 was an open-label, single-arm, multicentre, phase 2a clinical trial conducted in the USA in subjects with IPF to evaluate the safety, tolerability and efficacy of FG-3019. Subjects received 15 mg·kg^{-1} (cohort 1) or 30 mg·kg^{-1} (cohort 2) of FG-3019 intravenously every 3 weeks over 45 weeks. For both cohorts, eligible subjects were 35–80 years old at screening with a clinical diagnosis of IPF within the prior 5 years along with either usual interstitial pneumonia (UIP) pattern on a high-resolution computed tomography (HRCT) scan within 5 years of screening, or a possible UIP pattern on an available HRCT scan plus a recent surgical lung biopsy showing UIP pattern. The protocol stipulated HRCT evidence of ⩾10% to <50% parenchymal fibrosis (reticulation) and <25% honeycombing within the whole lung. For cohort 1, inclusion criteria stipulated FVC of 45–85% of predicted value [8], diffusing capacity of the lung for carbon monoxide (*D*LCO) ⩾30% predicted, objective evidence of disease progression (by either computed tomography (CT) scan, pulmonary function tests (PFTs) or dyspnoea) and decline in pulmonary function or worsening dyspnoea in the prior 3–12 months. For cohort 2, the FVC inclusion criterion was adjusted to ⩾55% of predicted value, with evidence of IPF disease progression within preceding 18 months, defined as above.

Exclusion criteria for both cohorts included *D*LCO <30% of the predicted value, corrected for haemoglobin; infiltrative lung disease other than IPF; acute exacerbation of IPF within the prior 3 months; forced expiratory volume in 1 s/FVC ratio <0.65; extent of emphysema greater than the extent of fibrosis on HRCT; significant comorbid medical conditions; and concurrent treatment with immunomodulatory or immunosuppressive drugs.

Daily treatment with prednisone (⩽10 mg) and/or *N*-acetylcysteine (⩽1800 mg) was allowed provided that this treatment had been continuous for ⩾4 months prior to screening and was to be continued throughout the treatment period. Treatment of exacerbations of IPF at the discretion of the investigator (including use of corticosteroids) was acceptable for up to 4 weeks.

Efficacy end-points included PFT, HRCT and measures of health-related quality of life. An expert pulmonary physiology consultant certified each clinical site based on rigorous performance standards according to a study-specific PFT procedure manual and the consensus guidelines of the American Thoracic Society/European Respiratory Society [9]. All PFTs measured at baseline (BL) and every 12 weeks were read by an independent central reader.

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Visual reading of the screening HRCT scan by a central reader (MedQIA, Los Angeles, CA, USA) determined the eligibility of each subject. HRCT was performed using a standardised image acquisition protocol with careful attention to use of the same HRCT platform at each visit, and using a standardised acquisition technique and reconstruction algorithm. In order to standardise the lung volume at which images were obtained, HRCT technologists were trained to coach subjects to hold their breath as close to total lung capacity (TLC) as possible, which has previously been shown to be feasible [8]. Quality control was carefully monitored during the study, including confirmation of good correlation between the TLC measured by HRCT and the TLC measured by PFT to ensure the reproducibility of the breath-holding manoeuver. Both modalities of TLC assessment have been shown previously to be strongly correlated [10]. In this study, correlation values (r) for TLC measured by HRCT and by PFT were 0.89 at both BL and week 48. For the correlation of PFT- and HRCT-based TLC changes from baseline to week 48, r=0.34 (p=0.006). Changes in the extent of fibrosis from screening were measured at 24 weeks and at 48 weeks (3 weeks after the last dose) using quantitative analysis of thoracic HRCT by the central reader with a 510k-cleared computer algorithm (MedQIA) that provides an overall determination of the percentage of the lung that contains ground glass (GG), reticular fibrosis with architectural distortion (QLF), honeycomb fibrosis (HC), and a composite score that represents a summation of QLF, GG and HC (QILD) [11, 12].

Data in tables and figures are presented as observed values only. Where discussed in the results section, imputation included observed values plus imputed values for missing data based on mixed-model, repeated measures.

This study was performed in accordance with the Declaration of Helsinki. Ethics committees at each participating institution reviewed and approved the protocol before subjects were enrolled in the trial. Each subject was fully informed of the risks and benefits of participating in this trial, and provided written informed consent prior to screening (www.ClinicalTrials.gov number NCT01262001).

Results

Subject information

Between March, 2011, and December, 2012, 127 patients were screened and 90 subjects were enrolled in two cohorts, 89 of which received at least one dose of FG-3019 (figure 1). The study population was predominantly male and white, with a mean age of 67.9 years. Demographic data for each cohort are summarised in table 1. BL PFT and HRCT values are shown in tables 2 and 3 (BL PFT values represent a mean of values obtained at screening and on day 1). Mean BL FVC for cohort 1 was 62.8% predicted (range 42.6–89.6% predicted) and for cohort 2 it was 72.7% predicted (range 52.9–111.7% predicted). Mean BL D_{LCO} for cohort 1 was 48.3% predicted (range 31.1–94.5% predicted) and for cohort 2, it was 49.7% predicted (range 30.4–89.6% predicted). 67 (75%) subjects completed the study and 66 of these had week 48 PFTs and HRCT determinations. Inclusion criteria included evidence of IPF disease progression during the preceding 12 (cohort 1) or 18 months (cohort 2), defined as visually apparent worsening of abnormalities on HRCT or decline in FVC % predicted value by 10% or more. These criteria were intended to enrich for patients with progressive rather than stable disease. The change of inclusion criteria between cohort 1 and cohort 2 was based on two observations. In cohort 1, subjects with BL FVC <55% predicted generally did poorly in the trial with regard to changes in pulmonary function and changes in fibrosis. Of the 22 subjects who prematurely discontinued from the study, 13 had a BL FVC <55% predicted. In addition, the criteria for evidence of progressive disease within 3–12 months proved to be unduly restrictive and so were loosened to 18 months in the second cohort. As a pilot study precursor to a more robust placebo-controlled trial, these adjustments seemed prudent.

Our hypothesis was that FG-3019 treatment could reverse parenchymal fibrosis. Consequently, the inclusion criteria stipulated an extent of whole-lung parenchymal fibrosis (≥10% to <50%), assuming that some fraction of that fibrosis could be reversible, with no more than 25% HC, which was assumed to be irreversible.

Safety

Safety outcomes are summarised for each cohort in table 4. 24 (27.0%) out of 89 treated subjects experienced a total of 38 treatment-emergent SAEs during the trial. 13 (54%) of the 24 subjects with SAEs dropped out of the study before the week 48 time-point, and 24 of the 38 SAEs occurred in those 13 subjects. SAEs in 11 subjects were respiratory in nature, the most common of which were pneumonia (nine subjects), IPF exacerbation (six subjects) and respiratory failure (three subjects). SAEs in 12 subjects were nonrespiratory in nature, which reflected the underlying comorbid conditions known to be associated with this patient population (*e.g.* cerebrovascular accident, hypotension, major depression and transient ischaemic attack), with no clear trends. Of the 22 subjects who prematurely discontinued the study, 13 (59%) had a BL FVC <55% predicted. Eight deaths occurred during the trial, including three from respiratory failure, and one each for end-stage IPF, worsening IPF, IPF exacerbation, pneumonia and acute

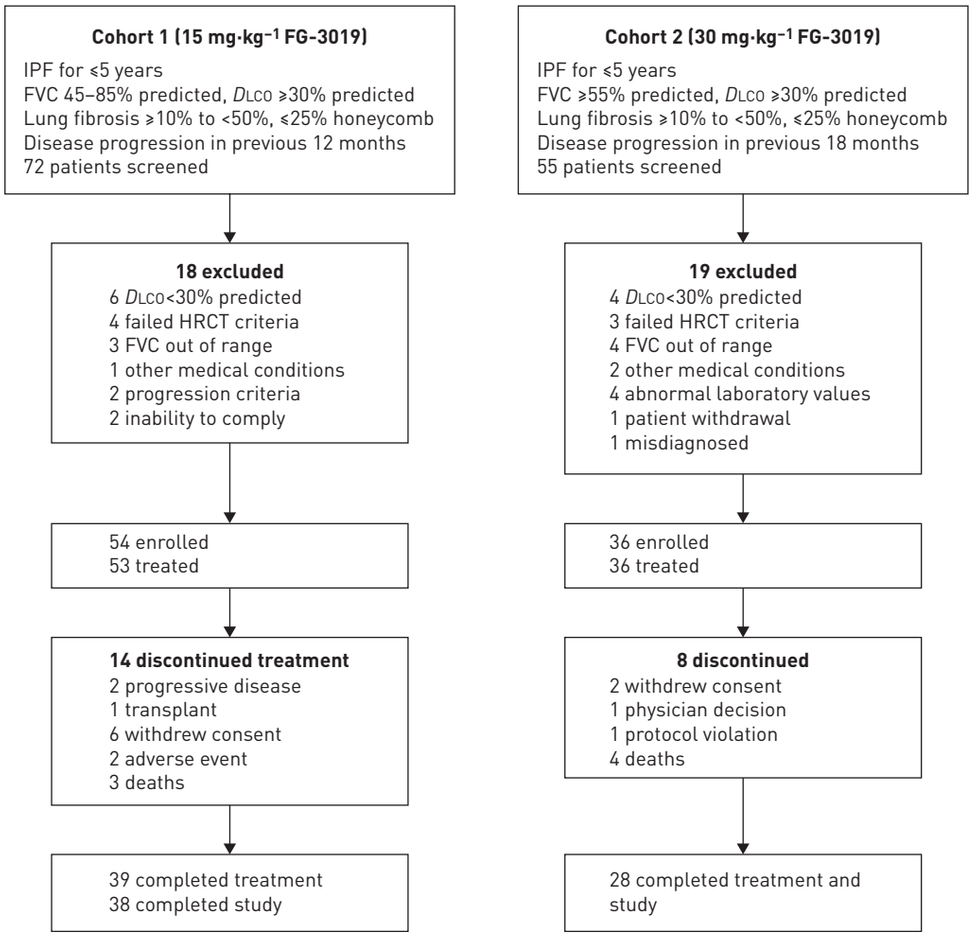

FIGURE 1 Enrolment and outcomes. IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography.

TABLE 1 Patient characteristics

	Cohort 1	Cohort 2	All
Subjects n	53	36	89
Age years			
Mean±SD	67.7±7.0	68.3±7.2	67.9±7.0
Median (range)	69 (47–82)	68.0 (49–81)	68.0 (47–82)
Male	44 (83.0)	27 (75.0)	71 (79.8)
Race			
American Indian	1 (1.9)		1 (1.1)
Black		1 (2.8)	1 (1.1)
White	52 (98.1)	35 (97.2)	87 (97.8)
Height cm			
Mean±SD	173.8±8.2	172.8±9.6	173.4±8.8
Median (range)	175.3 (152–193)	175.3 (155–189)	175.3 (152–193)
Weight kg			
Mean±SD	89.4±14.8	89.6±15.1	89.5±14.8
Median (range)	89.1 (57–122)	89.0 (63–122)	89.1 (57–122)
Subjects with time since IPF diagnosis of			
<1 year	19 (35.8)	15 (41.7)	34 (38.2)
1–3 years	21 (39.6)	12 (33.3)	33 (37.1)
>3 years	13 (24.5)	9 (25)	22 (24.7)

Data are presented as n (%) unless otherwise stated. IPF: idiopathic pulmonary fibrosis.

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TABLE 2 Pulmonary function test results

	Cohort 1			Cohort 2			All		
	BL	Change from BL		BL	Change from BL		BL	Change from BL	
		24 weeks	48 weeks		24 weeks	48 weeks		24 weeks	48 weeks
FVC									
Subjects n	53	45	38	36	30	28	89	75	66
FVC L									
Mean±SE	2.60±0.10	−0.08±0.03	−0.15±0.04	2.93±0.16	−0.07±0.05	−0.13±0.06	2.73±0.08	−0.08±0.02	−0.14±0.04
Median (range)	2.37 (1.50–4.22)	−0.08 (−0.54–0.36)	−0.17 (−0.68–0.57)	2.62 (1.32–5.51)	−0.08 (−0.37–0.82)	−0.11 (−0.75–0.64)	2.53 (1.32–5.51)	−0.08 (−0.54–0.82)	−0.14 (−0.75–0.64)
FVC % predicted									
Mean±SE	62.8±1.80	−1.80±0.65	−3.00±1.04	72.7±2.69	−1.71±1.15	−2.25±1.34	66.8±1.56	−1.77±0.60	−2.69±0.82
Median (range)	63.2 (42.6–89.6)	−1.54 (−15.7–6.8)	−3.62 (−15.1–10.7)	69.4 (52.9–111.7)	−1.55 (−13.2–17.3)	−1.89 (−16.7–14.1)	65.9 (42.6–111.7)	−1.54 (−15.7–17.3)	−3.30 (−16.7–14.1)
***D*LCO % predicted, Hb corrected**									
Subjects n	53	43	37	36	29	27	89	72	64
Mean±SE	48.3±1.7	−4.71±0.88	−4.50±0.96	49.7±2.4	−2.01±0.99	−5.61±1.08	49.8±1.41	−3.62±0.67	−4.9±0.72
Median (range)	47.0 (31.1–94.5)	−4.55 (−19.7–7.4)	−3.50 (−19.0–11.6)	49.5 (30.4–89.6)	−3.24 (−11.1–10.1)	−4.91 (−20.5–4.4)	47.4 (30.4–94.5)	−3.68 (−19.7–10.1)	−4.71 (−20.5–11.6)
FEV1 % predicted									
Subjects n	53	45	38	36	30	28	89	75	66
Mean±SE	69.4±1.80	−2.36±0.76	−3.44±1.08	79.7±2.54	−1.43±1.33	−1.65±1.32	73.6±1.57	−1.99±0.70	−2.68±0.84
Median (range)	72.5 (47.5–103.0)	−2.28 (−15.4–9.7)	−3.65 (−17.0–10.8)	77.9 (60.5–115.4)	−2.36 (−19.2–19.4)	−1.59 (−15.6–17.7)	74.4 (47.5–115.4)	−2.35 (−19.2–19.4)	−2.16 (−17.0–17.7)
TLC % predicted									
Subjects n	53	43	37	36	30	28	89	73	65
Mean±SE	65.2±1.6	−1.55±1.21	−2.89±1.20	71.6±2.5	−1.86±0.92	−4.32±1.16	67.8±1.41	−1.68±0.80	−3.51±0.84
Median (range)	64.3 (43.1– 98.9)	−1.04 (−21.9– 13.8)	−3.92 (−15.0– 17.9)	68.9 (53.3– 118.5)	−1.93 (−15.5– 9.7)	−4.23 (−18.3– 8.9)	65.3 (43.1– 118.5)	−1.79 (−21.9– 13.8)	−4.02 (−18.3– 17.9)

All data are from observed values. BL: baseline; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon dioxide; Hb: haemoglobin; FEV1: forced expiratory volume in 1 s; TLC: total lung capacity.

TABLE 3 Quantitative high-resolution computed tomography results for whole-lung fibrosis

	Cohort 1			Cohort 2			All		
	BL	Change from BL		BL	Change from BL		BL	Change from BL	
		24 weeks	48 weeks		24 weeks	48 weeks		24 weeks	48 weeks
Subjects n	53	46	39	36	30	28	89	76	67
QLF %									
Mean±SE	20.2±1.6	2.46±0.94	3.59±1.08	18.8±1.8	2.30±1.10	3.75±1.42	19.6±1.2	2.39±0.71	3.66±0.86
Median (range)	19.0 (2–51)	1.0 (−10–26)	2.0 (−6–27)	17.0 (2–44)	2.0 (−10–19)	2.0 (−13–26)	18.0 (2–51)	1.5 (−10–26)	2.0 (−13–27)
GG %									
Mean±SE	18.3±1.1	−0.80±0.71	−0.90±0.82	18.0±1.3	0.73±0.78	1.71±0.72	18.2±0.8	−0.20±0.53	0.19±0.58
Median (range)	18.0 (5–42)	0.0 (−13–8)	0.0 (−12–12)	17.5 (7–33)	1.0 (−10–10)	1.0 (−6–10)	18.0 (5–42)	0.0 (−13–10)	0.0 (−12–12)
HC %									
Mean±SE	3.9±1.1	−0.17±0.42	−0.26±0.26	2.3±0.52	0.20±0.35	−0.61±0.29	3.3±0.67	−0.03±0.29	−0.40±0.20
Median (range)	1.0 (0.0–37)	0.0 (−13–7)	0.0 (−5–5)	1.0 (0–13)	0.0 (−5–7)	0.0 (−7–1)	1.0 (0–37)	0.0 (−13–7)	0.0 (−7–5)
QILD score									
Mean±SE	42.4±2.5	1.48±1.25	2.44±1.61	39.0±2.9	3.23±1.69	4.86±1.76	41.0±1.9	2.17±1.01	3.45±1.19
Median (range)	44.0 (9–93)	1.0 (−19–26)	2.0 (−16–28)	37.0 (11–74)	3.5 (−16–31)	3.5 (−22–22)	39.0 (9–85)	1.5 (−19–31)	3.0 (−22–28)
TLC mL									
Mean±SE	3673±119	−64±61	−190±76	4020±168	−129±81	−133±91	3813±99	−89±48	−166±58
Median (range)	3513 (2421–6485)	−120 (−966–1423)	−161 (−1380–889)	3741 (2398–6422)	−145 (−1410–875)	−142 (−1002–1467)	3565 (2398–6485)	−135 (−1410–1423)	−158 (−1380–1467)

All data are from observed values. BL: baseline; QLF: reticular fibrosis with architectural distortion; GG: ground glass; HC: honeycombing; QILD: QLF+GG+HC; TLC: total lung capacity.

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TABLE 4 Treatment-emergent adverse events (TEAEs) in 89 treated patients

	Cohort 1	Cohort 2	Total n (%)
TEAEs reported in >10% of subjects	45	33	78 (87.6)
Cough	19	9	28 (31.5)
Fatigue	8	10	18 (20.2)
Dyspnoea	11	5	16 (18.0)
Upper respiratory tract infection	9	5	14 (15.7)
Nasopharyngitis	7	6	13 (14.6)
Bronchitis	6	6	12 (13.5)
Headache	8	3	11 (12.4)
Peripheral oedema	4	6	10 (11.2)
Diarrhoea	7	3	9 (10.1)
Dizziness	5	4	10 (11.2)
Nausea	6	4	10 (11.2)
Urinary tract infection	5	4	9 (10.1)
Pneumonia	6	2	8 (9.0)
Idiopathic pulmonary fibrosis exacerbation	3	5	8 (9.0)
Nasal congestion	1	7	8 (9.0)
Treatment-emergent serious adverse events[#]	**13**	**11**	24 (27.0)
Cardiac disorders	0	4	4 (4.5)
Gastrointestinal disorders	1	0	1 (1.1)
Infections and infestations	7	3	10 (11.2)
Pneumonia	6	2	8 (9.0)
Influenza	0	1	1 (1.1)
Neoplasms[¶]	0	1	1 (1.1)
Nervous system disorders	2	0	2 (2.2)
Psychiatric disorders	1	0	1 (1.1)
Renal and urinary disorders	0	1	1 (1.1)
Respiratory, thoracic and mediastinal disorders	5	6	11 (12.4)
Idiopathic pulmonary fibrosis	**2**	**4**	6 (6.7)
Acute respiratory failure	2	0	2 (2.2)
Dyspnoea	0	1	1 (1.1)
Epistaxis	0	1	1 (1.1)
Hypoxia	0	1	1 (1.1)
Pulmonary hypertension	0	1	1 (1.1)
Respiratory arrest	1	0	1 (1.1)
Respiratory failure	0	1	1 (1.1)
Vascular disorders	2	0	2 (2.2)

TEAEs included medical conditions, signs and symptoms not previously observed in the subject that emerged during the protocol-specified adverse event reporting period. A serious adverse event was defined as any adverse event or suspected adverse reaction that resulted in death, a life-threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity, or substantial disruption of the ability to conduct normal life functions. [#]: 24 subjects with serious adverse events; some subjects experienced more than one serious adverse events. [¶]: benign, malignant and unspecified, including cysts and polyps.

respiratory distress syndrome/sepsis secondary to colon cancer surgery. None of the deaths was considered by the investigator to be related to the study drug. No National Cancer Institute grade 3 or 4 laboratory abnormalities [13] were reported from the Safety Population. No infusions were stopped due to safety concerns. There were no obvious differences in AEs or SAEs between the two cohorts.

Outcomes

Results for pulmonary function outcomes are shown in table 2 and summarised in table 5, and quantitative HRCT outcomes are shown in table 3. Tables 2, 3 and 5 show mean baseline values and changes from baseline for each cohort individually as well as for pooled results. Table 5 shows the change of FVC, FVC % predicted, D_{LCO} % predicted and TLC % predicted from BL to week 48 for each cohort, and within each cohort for all subjects, for those with BL FVC $\geqslant$55% predicted and for those with BL FVC <55% predicted. Table 5 also shows the number of subjects that showed substantial negative changes in FVC % predicted ($\leqslant -10\%$) and positive changes FVC % predicted (>0%) at week 48.

Mean±SEM observed FVC change for the combined cohorts 1 and 2 was −140±35 mL (−2.7% predicted) from BL to week 48 for the entire study population (n=89 at BL and n=66 at week 48) and −110±37 mL

TABLE 5 Summary of mean pulmonary function changes (Δ) at week 48

Cohort	Subjects at BL n	FVC L		FVC % predicted		D_{LCO} % predicted		TLC % predicted		ΔFVC ⩽−10% predicted	ΔFVC >0% predicted
		Subjects n	ΔFVC L	Subjects n	ΔFVC % predicted	Subjects n	ΔD_{LCO} % predicted	Subjects n	ΔTLC % predicted		
Cohort 1	53	38	−0.15	38	−3.00	37	−4.50	36	−2.89	5 (13.2)	9 (23.7)
BL FVC ⩾55% predicted	38	33	−0.12	33	−2.19	33	−3.43	31	−2.22	4 (12.1)	9 (27.3)
BL FVC <55% predicted	15	5	−0.37	5	−8.42	4	−12.92	5	−8.08	1 (20.0)	0 (0.0)
Cohort 2	36	28	−0.13	28	−2.25	27	−5.61	28	−4.32	4 (14.3)	10 (35.7)
BL FVC ⩾55% predicted	32	27	−0.11	27	−1.93	27	−5.61	27	−4.00	3 (11.1)	10 (37.0)
BL FVC <55% predicted	4	1	−0.58	1	−11.01	0	0.0	1	−12.80	1 (100.0)	0 (0.0)
Cohort 1+2	89	66	−0.14	66	−2.69	64	−4.94	64	−3.51	9 (13.6)	19 (28.8)
BL FVC ⩾55% predicted	70	60	−0.11	60	−2.07	60	−4.41	58	−3.05	7 (11.7)	19 (31.7)
BL FVC <55% predicted	19	6	−0.40	6	−8.85	4	−12.92	6	−8.87	2 (33.0)	0 (0.0)

Data are presented as n (%) unless otherwise stated. BL: baseline; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity.

(−2.1% predicted) in subjects with BL FVC >55% predicted (n=70 at BL and n=60 at week 48). At week 48, 19 (28.8%) had no decline in FVC % predicted. In contrast, nine (13.6%) subjects had an absolute decline in FVC % predicted ⩾10%. Using imputation for all subjects with at least one post-BL determination, the mean FVC changes at week 48 were −205±33 mL (5.5% predicted) for all subjects (n=82) and −128±35 mL (2.8% predicted) for subjects with BL FVC ⩾55% predicted (n=65).

Extent and change of pulmonary fibrosis was assessed using quantitative HRCT. HRCT scores at BL, Week 24 and week 48 are summarised in table 3 by cohort and combined. In the combined results for cohorts 1 and 2, the BL QLF was 19.6% and the mean change at week 48 was +3.66%. For GG, the baseline extent was 18.2% and the mean change at week 48 was +0.19%. There was less HC at baseline (3.3%) and a mean change of −0.4% at week 48. The greatest magnitude of change at week 48, both positive and negative, occurred in QLF. While the majority of patients (65%) exhibited an increase in reticular fibrosis, 35% exhibited stable or improved reticular fibrosis at week 48. Regardless of the analysis method, observed or imputed, the same 16 subjects showed improved fibrosis (20% of full analysis set, 24% of completers) and seven showed stable fibrosis (9% of full analysis set, 11% of completers).

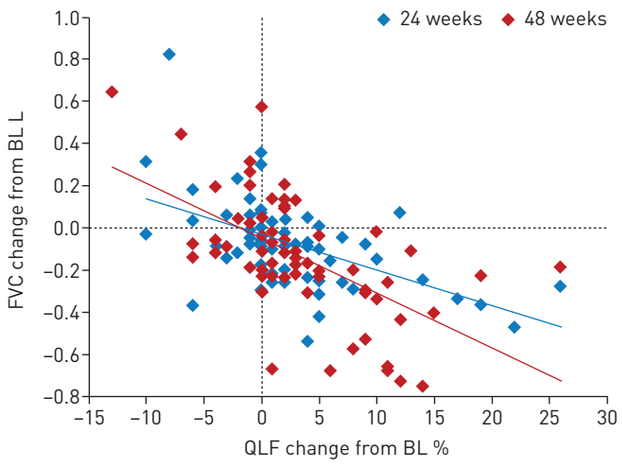

FIGURE 2 Correlations between fibrosis (QLF) change and forced vital capacity (FVC) change with all available data from baseline (BL) at week 24 (n=74) and week 48 (n=66).

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TABLE 6 Correlation of forced vital capacity change with fibrotic changes

Fibrosis subtype	Week	Subjects n	Pearson's r	p-value
QLF	24	74	−0.520	<0.0001
	48	66	−0.624	<0.001
GG	48	66	−0.233	0.074[#]
QILD	48	66	−0.514	<0.001

QLF: reticular fibrosis with architectural distortion; GG: ground glass; QILD: QLF+GG+honeycombing. [#]: nonsignificant.

Figure 2 and table 6 show the relationships between change from BL in FVC and QLF at weeks 24 and 48. An inverse correlation is noted between changes in the extent of QLF and changes in FVC, (r=−0.520 and r=−0.624, p<0.001) at both 24 and 48 weeks. To further characterise the relationship between apparent changes in fibrosis and changes in FVC, a *post hoc* analysis was performed whereby FVC changes in subjects that completed the week 24 and week 48 HRCT assessments were categorised by QLF change from BL at weeks 24 and 48 (figure 3) since those were the only time-points at which changes in both FVC and HRCT values could be assessed. Subjects with QLF change from BL >0 had a mean FVC change from BL at week 48 of −0.24 L. However, those with QLF change from BL ⩽0 had a positive average FVC change from BL, and at Week 48, the average FVC change from BL for these subjects was +0.04 L.

Patient reported outcomes were assessed using the St George's Respiratory Questionnaire and the University of California at San Diego Shortness of Breath Questionnaire (table 7). None of the outcomes was considered to reflect a significant change from BL.

We evaluated demographic properties, pulmonary function, quantitative fibrosis parameters at BL and plasma CTGF levels to determine if any BL factor or combination of BL factors could identify those patients who exhibited positive or negative changes in FVC or QLF; however, no BL property was found to be a reliable predictor or correlate of outcome.

Discussion

This study was initiated after observing reversal of established pulmonary fibrosis by FG-3019 in a mouse model of radiation-induced pulmonary fibrosis. The aim of this clinical study was to determine the safety and tolerability of FG-3019, and to assess whether modulation of CTGF activity by the antibody could impact established fibrosis in a fulminant human interstitial lung disease such as IPF. Two doses of the monoclonal antibody administered to IPF patients by intravenous infusion every 3 weeks for 45 weeks were well tolerated in the patients enrolled in this study. AEs were generally mild and the SAEs were typical of those seen in subjects with IPF. A wide range of disease severity was enrolled in the trial, with FVC values

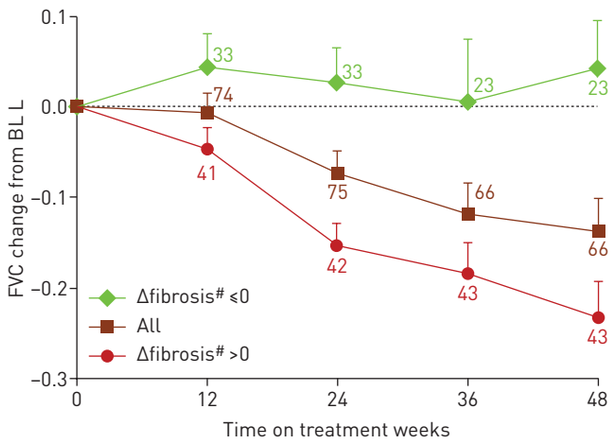

FIGURE 3 Categorical changes in forced vital capacity (FVC) based on reticular fibrosis with architectural distortion (QLF) change (Δ) from baseline (BL) at week 24 and week 48. [#]: change in QLF score from BL to week 24 and week 48; categorical FVC changes at weeks 12 and 24 were based on week 24 change in fibrosis, and categorical FVC change at weeks 36 and 48 were based on week 48 change in fibrosis.

TABLE 7 Patient-reported outcomes: observed values for subjects that completed week 48 assessments

	BL FVC ⩾55% predicted[#]			All[¶]		
	BL	Change		BL	Change	
		Week 24	Week 48		Week 24	Week 48
UCSD-SOBQ total	29.00±2.42	0.90±1.57	1.30±1.85	29.90±2.25	1.70±1.50	2.90±1.88
SGRQ symptoms	49.90±2.51	1.50±2.22	0.70±2.29	51.10±2.41	1.09±2.04	0.60±2.08
SGRQ activity	57.20±2.15	1.60±2.00	1.80±1.74	58.70±2.05	2.10±1.86	2.40±1.64
SGRQ impacts	30.10±2.12	0.50±1.98	0.50±2.07	32.00±2.08	0.20±1.82	0.20±1.92
SGRQ total	42.10±1.79	0.70±1.69	0.80±1.66	43.70±1.76	0.80±1.54	0.80±1.52

Data are presented as mean±SEM. BL: baseline; FVC: forced vital capacity; UCSD-SOBQ: University of California at San Diego Shortness of Breath Questionnaire; SGRQ: St George's Respiratory Questionnaire. [#]: n=60; [¶]: n=66.

ranging from 42.6% to 111.7% predicted. Patients with FVC values below 55% predicted generally had higher QLF scores at BL, and demonstrated worsening of both fibrosis and pulmonary function.

The study was designed to be open-label and thus did not include a placebo group. FG-3019-treated patients in this study showed an average decline of 140 mL over the treatment period of 48 weeks. Of the subjects who completed a 48-week course of treatment, 13.6% experienced a decline of FVC % predicted of ⩾10%. In contrast, 30% of treated subjects showed an increase of FVC (range 0.2–14.1% predicted).

A subset of subjects exhibited reduced reticular fibrosis 48 weeks after initiating dosing with FG-3019. Changes in fibrosis score correlated with changes in pulmonary function. In an analysis of the FVC outcomes based on the changes in fibrosis, subjects with stable or reduced fibrosis (QLF change from BL ⩽0) had a positive average FVC change from BL at week 48 of +40 mL. In contrast, subjects with increased fibrosis (QLF change from BL >0) had a mean FVC change from BL at week 48 of −240 mL. Quantifying pulmonary fibrosis by computer algorithms has greater sensitivity for identifying changes in fibrosis than visual scoring [14]. Consequently, some of the changes seen in pulmonary fibrosis may represent the variable natural progression of this heterogeneous disease.

Treatment of scleroderma lung disease with cyclophosphamide yielded improvement in quantified lung fibrosis in some subjects with a statistically significant correlation with changes in FVC [11]. However, quantitative change in fibrosis has not been studied longitudinally in IPF patients to enable an expected change in fibrosis in a manner analogous to the predicted changes in FVC. Recent studies have used quantitative HRCT to evaluate changes of fibrosis in untreated IPF subjects. MALDONADO *et al.* [15] used a computer-aided system for quantifying IPF fibrosis based on unique HRCT texture patterns for GG, QLF and HC, and the changes in those HRCT-derived patterns between two time-points 3–15 months apart. They showed that changes in reticular fibrosis and total fibrosis were predictive of survival. ODA *et al.* [16], using a similar HRCT scoring system approach, showed that HRCT fibrosis scores at 6 and 12 months after diagnosis were significantly increased compared to those observed at the initial diagnosis and that patients with elevated HRCT fibrosis score at 6 months had a poor prognosis. KIM *et al.* [17] showed that QLF scores closely correlate with disease extent and that 6-month change in QLF is predictive of FVC decline at 18 months, whereas quantitative CT measures based only on measures of lung density (kurtosis) predict mortality but not functional change. Quantitative HRCT has not been previously reported as a measure of outcomes in an interventional IPF clinical trial and has not been established or validated as a surrogate marker of clinically meaningful outcomes. Nonetheless, as noted in a recent position paper [18], the use of quantitative CT algorithms as an end-point in clinical trials is an area of growing interest and promise.

In summary, this open-label study designed to assess the safety and potential for efficacy of long-term use of FG-3019, a novel antifibrotic agent given intravenously for 45 weeks in patients with IPF, demonstrated a good safety profile and yielded encouraging outcomes with regard to changes in pulmonary function and extent of pulmonary fibrosis by imaging. The limitations incurred by the lack of a placebo control group as well as the need to validate the novel computerised scoring system for quantifying the extent of fibrosis in this study is evident. Further studies are warranted to confirm the observed findings, and a randomised placebo-controlled phase 2 clinical trial of FG-3019 in IPF patients is currently underway.

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