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STRATUS: A Phase II Study of Abituzumab in Patients With Systemic Sclerosis–associated Interstitial Lung Disease

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ABSTRACT. ***Objective.*** To investigate the effects of abituzumab in systemic sclerosis–associated interstitial lung disease (SSc-ILD).

Methods. STRATUS was a phase II, double-blind, parallel-group, multicenter trial (ClinicalTrials.gov: NCT02745145). Adults (≤ 75 yrs) with SSc-ILD on stable mycophenolate were randomized (2:2:1) to receive intravenous abituzumab 1500 mg, abituzumab 500 mg, or placebo every 4 weeks for 104 weeks. The primary endpoint was the annual rate of change in absolute forced vital capacity.

Results. STRATUS was terminated prematurely due to slow enrollment (n = 75 screened, n = 24 randomized), precluding robust analysis of efficacy. Abituzumab was well tolerated; no new safety signals were detected.

Conclusion. Further investigation of abituzumab for treatment of SSc-ILD is required.

Key Indexing Terms: clinical trial, integrins, interstitial lung disease, systemic sclerosis

Systemic sclerosis (SSc) is a chronic, progressive autoimmune disease leading to abnormal fibrosis and vasculopathy of the skin and internal organs.[1] Pulmonary involvement—particularly interstitial lung disease (ILD)—is the leading cause of death in SSc.[2,3,4] Preclinical models have provided robust evidence for the promotion of lung fibrosis by transforming growth factor β (TGF-β).[5] TGF-β is activated by αV-class integrins on pulmonary epithelial cells,[6] making αVβ6 a potential prognostic marker in ILD.[7,8] Blocking integrin αV is therefore an attractive strategy for treating SSc-ILD. Abituzumab is a humanized monoclonal antibody, previously evaluated in colorectal and prostate cancer,[9,10] that binds to and inhibits the activity of the αV-class integrin. The phase II STRATUS study aimed to investigate the effects of abituzumab in patients with SSc-ILD receiving stable mycophenolate therapy but was terminated prematurely due to slow patient enrollment.

The STRATUS study was sponsored by Merck KGaA (for all study sites residing in countries outside of the USA) or EMD Serono Research and Development Institute Inc. (a business of Merck KGaA, Darmstadt, Germany), Billerica, Massachusetts, USA (for study sites residing within the USA). Merck KGaA authors were involved in the study design, collection, analysis, and interpretation of the data, and in the writing of and decision to submit the manuscript.

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METHODS

STRATUS (ClinicalTrials.gov: NCT02745145; EUCTR: EMR200017-014) was a phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of abituzumab in patients with SSc-ILD conducted at 32 sites. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The protocol was approved by the lead study site ethics board (Division of Rheumatology, University of Michigan, Ann Arbor, Michigan; approval number: HUM00111923), as well as by the ethics boards of all other recruiting sites (Supplementary Data, available with the online version of this article). The primary objective was to demonstrate efficacy of abituzumab in improving lung function in patients with SSc-ILD receiving background mycophenolate therapy. Secondary objectives included evaluation of safety and tolerability.

Participants. Patients were men or women aged 18–75 years who fulfilled the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria for the classification of SSc. Patients had to take a stable dose of 1.5–3 g/day mycophenolate mofetil (MMF) or 1080–2160 mg/day mycophenolate sodium (MPS) for ≥ 2 months before screening and throughout the treatment period. The required duration of prior mycophenolate treatment was reduced from ≥ 6 months to ≥ 2 months following a protocol amendment.

Eligible patients fulfilled the following criteria: ≥ 5% lung fibrosis on high-resolution computed tomography (HRCT; central reading[11] performed by Jonathan G. Goldin, MD, PhD, of MedQIA, Los Angeles, California, USA) to enrich for risk of fibrotic progression; disease duration of < 7 years from the first non-Raynaud symptom; diffusing lung capacity for carbon monoxide (DLCO) ≥ 30% predicted; forced vital capacity (FVC) 40–85% predicted to ensure some reserve yet enrich for risk of progression and thus the need for biologic therapy; and ratio of percent predicted FVC:DLCO < 1.8 to ensure that individuals with a low likelihood of pulmonary hypertension (PH) were selectively enrolled. All patients provided written informed consent and agreed to use robust contraceptive methods during the study.

Patients with underlying conditions constituting an inappropriate risk or contraindication for study participation (e.g., significant renal impairment, obstructive lung disease/emphysema, PH, inflammatory connective tissue disease other than SSc-associated myopathy, fibromyalgia, and secondary Sjögren syndrome, and/or tuberculosis) were excluded. Drugs other than MPS or MMF considered by the investigator to have immunomodulating, immunosuppressive, or potential SSc disease-modifying properties were not permitted within 2 months before screening (5 months for cyclophosphamide). Medications for pulmonary arterial hypertension (e.g., endothelin receptor antagonists, phosphodiesterase type 5 inhibitors) were not permitted.

Study design and endpoints. Patients were randomized (2:2:1) to receive intravenous (IV) infusions of abituzumab 1500 mg, abituzumab 500 mg, or placebo every 4 weeks for 104 weeks (Figure 1). The primary endpoint was the annual rate of change in absolute FVC (mL), with the primary analysis conducted after all patients had completed the 52-week study visit or discontinued the study treatment. Safety and tolerability were evaluated as follows: treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs of special interest; changes in clinical laboratory measures, electrocardiogram measures, and vital signs; and incidence of patients with positive antidrug antibody titers. TEAEs of special interest were defined as blistering grade 3+ skin and subcutaneous tissue disorders, or any cutaneous reaction of grade 1–2 that worsened or did not respond to specific treatment.

RESULTS

Patient disposition. Planned enrollment was 175 patients, but the study was terminated early due to enrollment difficulties. Of 75 patients screened, 24 were randomized to treatment between November 2016 and January 2018 (abituzumab 1500 mg, n = 9; abituzumab 500 mg, n = 5; placebo, n = 10). In total, 40 (78%) screen failures reflected patients not meeting all eligibility criteria. The most common reason for screening failure was FVC > 85% predicted. Baseline characteristics are shown in Table 1.

All patients were withdrawn from study treatment before completion of the treatment period. The median treatment duration was 25.9 weeks (abituzumab 1500 mg, 27.9 weeks; abituzumab 500 mg, 16.0 weeks; placebo, 26.6 weeks; range 8.0–64.1 weeks). Adherence to treatment (percentage of planned infusion volume received) was high (mean 95%), with 75% of patients having > 80% adherence. Withdrawal for 19 patients (79%) was because of the sponsor's decision to terminate the study. Of the remaining 5 patients, 3 (13%) had worsening of ILD, 1 (4%) died (considered nondrug-related) and 1 withdrew because of an adverse event (4%).

Efficacy. The number of patients enrolled precluded robust analysis of efficacy. The primary endpoint, however, was examined in line with the full study analysis plan. At baseline, mean (SD) FVC was 2122 mL (449.0), 1958 mL (123.8), and 2117 mL (575.5) for the placebo, abituzumab 500 mg, and abituzumab 1500 mg groups, respectively. Absolute changes from baseline in FVC over time are shown in Figure 2.

Safety. Overall, 21 of the 24 patients (88%) experienced at least 1 TEAE. The most frequently occurring TEAEs were diarrhea (n = 7, 29%), which lasted for a few days in most cases, and cough (n = 6, 25%), which generally lasted for a few weeks or

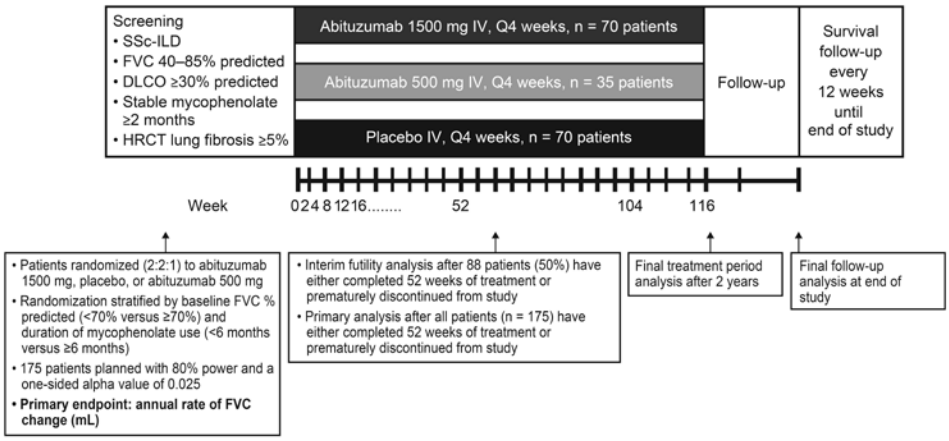

Figure 1. STRATUS study design. DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IV: intravenous; Q4 weeks: every 4 weeks; SSc-ILD: systemic sclerosis–associated interstitial lung disease.

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Table 1. Baseline demographic and disease characteristics.

	Placebo, n = 10	Abituzumab 500 mg, n = 5	Abituzumab 1500 mg, n = 9
Mean age, yrs (SD)	51 (11)	60 (8)	55 (8)
Age category, yrs, n (%)			
< 35	1 (10)	0 (0)	0 (0)
35–49	3 (30)	0 (0)	2 (22)
50–75	6 (60)	5 (100)	7 (78)
Female, n (%)	8 (80)	4 (80)	7 (78)
Ethnicity, (%)			
White (Hispanic or Latino)	1 (10)	0 (0)	3 (33)
White (Other)	9 (90)	5 (100)	6 (67)
Type of SSc, n (%)			
Diffuse cutaneous	6 (60)	1 (20)	7 (78)
Limited cutaneous	4 (40)	4 (80)	2 (22)
Duration of SSc, yrs, mean (SD)	3.77 (2.1)	3.53 (0.8)	3.87 (3.4)
QLF (%), mean (SD)	35.44 (13.7)	29.09 (15.8)	34.15 (14.5)
FVC, mL, mean (SD)	2122 (449.0)	1958 (123.8)	2117 (575.5)
DLCO, mmol/min/kPa, mean (SD)	3.3 (0.7)	3.2 (1.0)	4.1 (1.2)

DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; QLF: quantitative lung fibrosis (whole lung); SSc: systemic sclerosis.

did not resolve; these were followed by fatigue, gastroenteritis, arthralgia, and headache, each occurring in 4 patients (17%). There were no notable differences in the incidence of TEAEs between treatment arms. No TEAEs of special interest were reported (Supplementary Table 1, available from the authors on request). Three patients discontinued treatment because of TEAEs, 2 in the abituzumab 500 mg arm (1 with fatal outcome [described below] and 1 with progressive ILD) and 1 in the placebo arm (nonserious cough and dyspnea). Two additional patients discontinued treatment due to progressive disease; however, these cases were not reported as TEAEs leading to withdrawal.

Four patients had serious TEAEs, none of which were considered related to study treatment. One patient receiving abituzumab 500 mg had pneumonia, device-related infection (catheter for total parenteral nutrition), and multiorgan failure due to sepsis, leading to death. One patient receiving placebo had pneumonia. One patient receiving abituzumab 1500 mg had skin ulcer and 1 patient had small fiber neuropathy.

Observed changes from baseline in clinical laboratory values were not considered to be clinically relevant.

DISCUSSION

In the STRATUS study, abituzumab IV infusions of 500 mg and 1500 mg every 4 weeks were well tolerated and treatment adherence was high. There were no new safety findings as compared with previous oncology trials.[9,10]

The study was terminated early due to low enrollment,

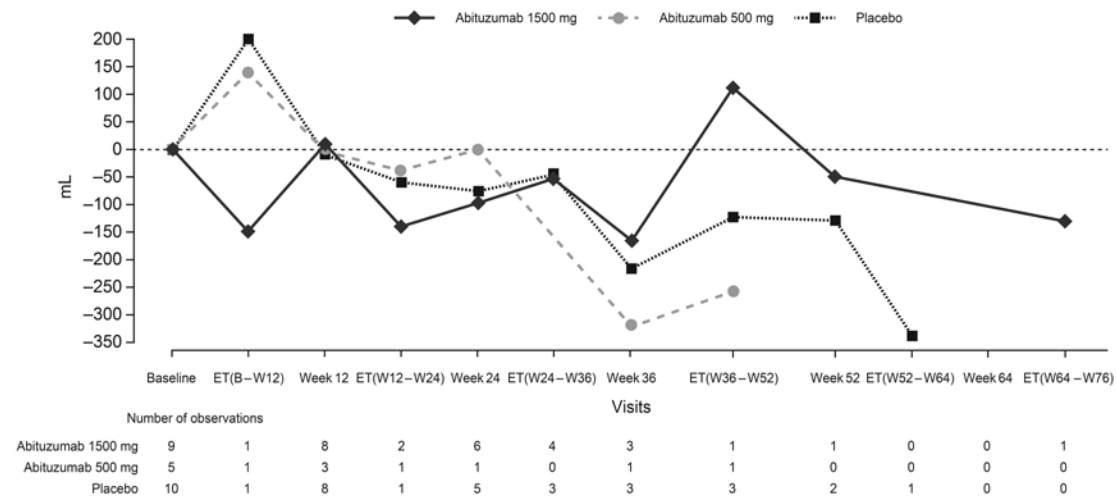

Figure 2. Mean absolute change from baseline in FVC over time, by treatment arm. B: baseline; ET: early termination; FVC: forced vital capacity; W; week.

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and several factors contributed to this, including the rarity of SSc-ILD. Whereas ILD affects 80% of patients with SSc, the global prevalence of SSc itself is only 1 in 10,000.[12] In addition, patients were initially required to have ≥ 6 months of previous mycophenolate use, based on data from the Scleroderma Lung Study II, in which MMF's effect on FVC was seen to be near maximal by 6–12 months.[13] We hypothesized that requiring 6 months of previous mycophenolate would limit its confounding effect on the primary outcome measure. Mycophenolate uptake as standard-of-care was, however, slower than expected. Following slow recruitment, the protocol was amended to reduce mycophenolate therapy to ≥ 2 months on a stable dose. Another factor was the concomitant recruitment into a large (n = 580) SSc-ILD study of nintedanib,[5,14] which may have been more attractive to patients and physicians, as nintedanib has proven efficacy in idiopathic pulmonary fibrosis[15] and is taken orally (whereas abituzumab had not yet been evaluated in pulmonary fibrosis and STRATUS required IV infusions). Further, the nintedanib study had broader inclusion criteria: patients could receive mycophenolate, methotrexate, or no concomitant immunosuppressant, with no upper limit for FVC.[14]

The small patient numbers yielded few efficacy data points per timepoint. Only descriptive (not inferential) statistics were performed and, as expected with such a small sample size, no meaningful conclusions could be drawn.

In conclusion, abituzumab's effects on αV-class integrins make it a rational choice for SSc-ILD treatment, particularly in cases with ongoing epithelial damage, since integrin αV expression has been shown to be upregulated in injured and inflamed epithelia, including in ILD. Targeting this integrin should be beneficial in individuals at risk of fibrotic progression. The STRATUS study enrollment therefore required both lung fibrosis on HRCT and decreased predicted FVC. However, the study was terminated early following slow enrollment, likely due to multiple factors, including enrollment in other SSc trials, and eligibility criteria intended for enrichment of patients with SSc-ILD at risk of progression and for reduction of variability of background medication (immunosuppressant). Abituzumab was well tolerated with no new safety signals, but no efficacy conclusions can be drawn from the limited data obtained before termination.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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