Safety and Tolerability of Thrombin Inhibition in Scleroderma-Associated Interstitial Lung Disease

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Objective. Interstitial lung disease (ILD) is a frequent complication of systemic sclerosis (SSc) (scleroderma) and the leading cause of scleroderma-related deaths. There exists an unmet need for a new drug therapy for ILD-complicated SSc. Substantial evidence supports an important role for thrombin in the pathogenesis of SSc-associated ILD (hereafter SSc-ILD), and targeting thrombin with a direct thrombin inhibitor could prove to be a novel and effective treatment strategy. As a first step toward designing a clinical trial to test the efficacy of thrombin inhibition in SSc-ILD, we conducted this study to test the safety and tolerability of dabigatran in patients with SSc-ILD.

Methods. We performed a prospective, single-center, open-label treatment trial with the direct thrombin inhibitor, dabigatran, in patients with SSc-ILD. Any patient with a history of gastrointestinal hemorrhage or gastric antral vascular ectasia was excluded. Blood monitoring was performed monthly, and patient-reported outcomes, pulmonary function tests, and skin scores were obtained at baseline and at 1- and 6-month visits. Bronchoscopy with bronchoalveolar lavage (BAL) was performed at baseline and at 6 months for measurement of lung thrombin activity.

Results. Of 15 patients with SSc-ILD, 14 completed 6 months of treatment with dabigatran at 75 mg taken orally twice daily. Adverse events were uncommon and usually mild or unrelated to the study medication. No serious adverse event was observed. Dabigatran was well tolerated, and we observed no significant gastrointestinal, pulmonary, or other safety issues or intolerability. BAL fluid thrombin activity decreased or remained stable in 13 of 14 (92.8%) subjects.

Conclusion. Dabigatran appears to be safe and well tolerated in patients with SSc-ILD. A larger randomized controlled trial to test the efficacy of direct thrombin inhibition with dabigatran can be considered.

INTRODUCTION

Systemic sclerosis (SSc) (scleroderma) is a multisystem connective-tissue disease characterized by microvascular injury, autoimmunity, and fibrosis (1). Pulmonary involvement occurs frequently in patients with SSc, and interstitial lung disease (ILD) is the leading cause of SSc-related deaths (2). Despite the substantial disease burden associated with SSc-associated ILD (hereafter SSc-ILD), there is currently no US Food and Drug Administration (FDA)-approved medication for treating this condition (3).

Substantial data implicate the serine protease thrombin in the pathogenesis of SSc-ILD as well as in other ILDs, for example, idiopathic pulmonary fibrosis (IPF) (4–6). Lung injury, when coupled with increased vascular permeability, leads to extravasation of plasma-clotting factors into injured airspaces, where exposure to tissue factor initiates the coagulation cascade and the generation of thrombin and fibrin (4, 5). Thrombin, in turn, promotes lung fibrosis through interaction with specific cell-surface receptors (4, 5, 7).

Thrombin inhibition results in attenuation of lung fibrosis in vitro and in vivo animal experiments, leading others and us to propose thrombin inhibition as an attractive strategy for the treatment of SSc-ILD and other fibrosing lung diseases (5, 8, 9). Whereas general inhibition of the coagulation cascade in patients with lung fibrosis may be detrimental (10), inhibiting thrombin’s fibrotic properties while avoiding a significant effect on hemostasis could have important clinical implications (5, 11, 12). As a first step toward testing a strategy of thrombin inhibition in a patient population inherently at increased risk of gastrointestinal bleeding, we sought to determine whether treatment of patients with SSc-ILD...
### Table 1. Baseline characteristics of the study cohort

| Patient | Sex  | Race | Age  | SSc Classification | ANA\(^a\) | Disease Duration | FVC (l), %Ref | FEV\(_1\), %Ref | DLCO, (ml/min/mm Hg), %Ref | Mahler Dyspnea Index | HRCT Chest Scan | Rx            | Duration (mo) | Prior Therapy |
|---------|------|------|------|---------------------|----------|------------------|--------------|----------------|--------------------------|------------------|---------------|----------------|----------------|---------------|
| 1       | Female | White | 41.3 | lcSSc | PMSc1 | 7.75 | 58 | 60 | 45 | 7 | NSIP | MMF | 53 | ... |
| 2       | Female | Black | 50.6 | dcSSc | Scl70\(^b\) | 6.90 | 41 | 47 | 37 | 14 | NSIP | MMF | 54 | ... |
| 3       | Male   | White | 49.1 | dcSSc | Speck | 1.58 | 51 | 60 | 39 | 6 | UIP | MMF | 1 | ... |
| 4       | Female | White | 45  | lcSSc | Scl70\(^b\) | 4.00 | 75 | 76 | 57 | 4 | NSIP | ... | ... | ... |
| 5       | Female | Black | 45.2 | dcSSc | Scl70\(^b\) | 9.08 | 65 | 61 | 42 | 5 | NSIP | ... | ... | ... |
| 6       | Female | Black | 44.2 | lcSSc | Scl70\(^b\) | 10.00 | 55 | 62 | 52 | 8 | UIP | MMF | 28 | ... |
| 7       | Female | White | 66.1 | lcSSc | Scl70\(^b\) | 2.33 | 82 | 77 | 60 | 8 | NSIP | ... | ... | ... |
| 8       | Male   | White | 56.7 | dcSSc | Scl70\(^b\) | 4.58 | 75 | 83 | 55 | 7 | NSIP | MMF | 35 | Cyclophosphamide |
| 9       | Female | White | 57.6 | dcSSc | Scl70\(^b\) | 0.92 | 82 | 76 | 55 | 4 | UIP | Ritux | ... | ... | ... |
| 10      | Female | Black | 35.7 | lcSSc | Nucleo | 3.00 | 84 | 88 | 86 | 10 | NSIP | MMF | 29 | ... |
| 11      | Female | White | 42  | lcSSc | PMSc1 | 5.25 | 99 | 94 | 64 | 10 | NSIP | MMF | 50 | Cyclophosphamide |
| 12      | Female | Black | 30.7 | dcSSc | Speck | 1.58 | 70 | 66 | 63 | 14 | UIP | MMF | 9 | ... |
| 13      | Female | Black | 40  | dcSSc | Nucleo | 1.33 | 83 | 80 | 69 | 5 | ... | MMF | 12 | Tocilizumab |
| 14      | Female | White | 60.6 | dcSSc | Scl70\(^b\) | 4.17 | 60 | 67 | 31 | 8 | NSIP | MMF | 7 | ... |
| 15      | Female | White | 48.2 | lcSSc | Scl70\(^b\) | 2.25 | 79 | 78 | 59 | 8 | NSIP | MMF | 16 | ... |
| Total   | 13 female and 2 male | 9 white and 6 black | 47.5 ± 9.6 | 4.3 ± 2.9 | 70.6 ± 15.4 | 54.3 ± 14.1 | 7.86 ± 3.11 | ... | ... | ... | ... | ... | ... | ... |

Abbreviation: ANA, antinuclear antibody; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusion capacity for carbon monoxide; FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; lcSSc, limited cutaneous systemic sclerosis; MMF, mycophenolate mofetil; nucleo, nucleolar antinuclear antibody pattern; NSIP, nonspecific interstitial pneumonia; Ritux, rituximab; Rx, Treatment; speck, speckled antinuclear antibody pattern; UIP, usual interstitial pneumonia; %Ref, predicted.

\(^a\)ANAs include PMSc1 and anti-PM/Scl antibodies.

\(^b\)Anti-topoisomerase antibodies.
PATIENTS AND METHODS

To test the prediction that dabigatran (dabigatran etexilate) is safe, we conducted a prospective, single-center, open-label treatment trial with a specific focus on the incidence of bleeding and gastrointestinal side effects in 15 patients with SSc-ILD treated for 6 months at a dose of 75 mg taken orally twice daily. Because patients with SSc-ILD may potentially have a greater risk of bleeding and dyspepsia than the population with atrial fibrillation studied in the pivotal trials for dabigatran etexilate, we chose the lowest available dose for this safety study (75 mg twice daily). The study was approved by the Institutional Review Board of the Medical University of South Carolina and by a data and safety monitoring board (DSMB) established on behalf of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH).

Recruitment strategy, eligibility, schedule of study visits, assessments, study-related procedures, data collection, and study forms are detailed in a manual of procedures developed by the investigators and approved by the DSMB (see Supplemental Material). Potential study subjects were recruited from the Scleroderma Clinic at the Medical University of South Carolina and by a data and safety monitoring board (DSMB) established on behalf of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH).

Between March 2016 and December 2017, 15 subjects with SSc-ILD were enrolled in a single-center open-label treatment trial to test the safety and tolerability of dabigatran at a dose of 75 mg taken orally twice daily. The baseline demographic and pulmonary features of the patients are shown in Table 1. A majority of subjects were white women (87%) with a mean age of 47.5 ± 9.6 years and a mean disease duration of 4.3 ± 2.9 years. Most study subjects had an autoantibody known to be associated with an increased risk for SSc-ILD: Scl-70 (9 of 15; 60%) or PM/Scl (2 of 15; 13%). All had dyspnea (Mahler Dyspnea Index of 4–14; mean: 7.86 ± 3.11), and most had a restrictive pattern on the pulmonary function test (10 of 15; 67%), with a nonspecific interstitial pneumonia pattern on the HRCT chest scan (10 of 15; 67%). Most were receiving mycophenolate mofetil (MMF) as the treatment of SSc-ILD (11 of 15; 73%) (20). Of the 15 subjects, 14 (93.3%) completed the 6-month treatment protocol. One subject (patient 10; Table 1) was excluded for inability to comply with study protocol visits.

RESULTS

Patient cohort. Between March 2016 and December 2017, 15 subjects with SSc-ILD were enrolled in a single-center open-label treatment trial to test the safety and tolerability of dabigatran at a dose of 75 mg taken orally twice daily. The baseline demographic and pulmonary features of the patients are shown in Table 1. A majority of subjects were white women (87%) with a mean age of 47.5 ± 9.6 years and a mean disease duration of 4.3 ± 2.9 years. Most study subjects had an autoantibody known to be associated with an increased risk for SSc-ILD: Scl-70 (9 of 15; 60%) or PM/Scl (2 of 15; 13%). All had dyspnea (Mahler Dyspnea Index of 4–14; mean: 7.86 ± 3.11), and most had a restrictive pattern on the pulmonary function test (10 of 15; 67%), with a nonspecific interstitial pneumonia pattern on the HRCT chest scan (10 of 15; 67%). Most were receiving mycophenolate mofetil (MMF) as the treatment of SSc-ILD (11 of 15; 73%) (20). Of the 15 subjects, 14 (93.3%) completed the 6-month treatment protocol. One subject (patient 10; Table 1) was excluded for inability to comply with study protocol visits.
Safety of dabigatran. Of the 14 subjects who completed the 6-month treatment protocol, 7 patients experienced a total of 11 adverse events (AEs) (Table 2). AEs included fatigue, headache, menorrhagia, and epistaxis. All AEs were graded as mild, except for one moderate-grade AE (headache), which the study team and DSMB members felt was not related to the study drug (headache attributed to a preexisting Chiari malformation that resolved after a neurosurgical procedure that required a brief interruption of the study drug). No serious adverse event (SAE) was recorded for any of the study subjects; thus, the sequential probability ratio test never yielded an indication that the SAE event rate was greater than 5%. Monthly laboratory monitoring of CBC and CMP showed no signs of drug toxicity. No significant change in hemoglobin or hematocrit levels was observed. Coagulation studies (Table 3) demonstrated no significant change in the PT. The mean PT was increased (5.1 ± 4.9 seconds; \( P < 0.004 \)), which was not felt to be clinically significant. Prolongation of the plasma TT was observed in 6 of 9 (67%) of subjects, for whom baseline and 6-month data were available. All data were periodically reviewed by the DSMB, which found no significant safety issues and no reason to invoke the stopping rules set forth in the Manual of Procedures (MOP).

The mean pulmonary function measures for the group did not change significantly over time (Table 4, Figure 1); however, some individuals did experience declines greater than 10% in FVC, forced expiratory volume (FEV), or DLCO (n = 4) or improvements greater than 10% (n = 4) from baseline to the end of the study. Results from the linear mixed models confirmed that there was no significant change in pulmonary function over time (\( P = 0.24, P = 0.24, P = 0.79 \) for predicted FVC percentage, predicted forced expiratory volume in 1 second (FEV\(_1\)) percentage, and predicted DLCO percentage, respectively). Consistent with the findings on the pulmonary function test, we found no significant change in self-reported dyspnea during the 6-month treatment period (\( P = 0.41 \)). Of 14 subjects, 4 reported worsening dyspnea, 3 reported no change, and 6 reported improvement.

Tolerability of dabigatran. Dabigatran in a dose of 75 mg taken orally twice daily was well tolerated. We observed no patient dropout due to intolerance or AE. Table 5 lists GIT and SHAQ scores and the modified Rodnan Skin Score (mRSS) at the various study time points, and they are displayed in Figure 2. The 3-month and 6-month GIT assessments showed no significant change from baseline GIT scores, and a linear mixed model confirmed that there was no significant (\( P = 0.45 \)) change over time in GIT scores. No significant change was noted in the SHAQ score at individual time points or overall during treatment with dabigatran (\( P = 0.89 \) from the linear mixed model). The mRSS declined (improved) by the 6-month visit compared with

| Table 2. Listing of adverse events |
|-----------------------------------|
| Patient | Event | Relationship | Intervention Discontinued | Severity | Outcome | Serious |
|---------|-------|--------------|---------------------------|----------|---------|---------|
| 3       | Fatigue | Not related | No | Mild | Unresolved | No |
| 5       | Menorrhagia | Possibly | No | Mild | Resolved | No |
| 5       | Headache | Not related | No | Mild | Unresolved | No |
| 6       | Chiari malformation | Not related | No | Moderate | Resolved | No |
| 7       | Epistaxis | Possibly | No | Mild | Resolved | No |
| 7       | Cystitis | Not related | No | Moderate | Resolved | No |
| 7       | Epistaxis | Possibly | No | Mild | Resolved | No |
| 9       | Epistaxis | Possibly | No | Mild | Resolved | No |
| 14      | Epistaxis | Possibly | No | Mild | Resolved | No |
| 15      | Menorrhagia | Possibly | No | Mild | Resolved | No |
| 15      | Contact dermatitis | Not related | No | Moderate | Unresolved | No |

| Table 3. Coagulation studies at baseline and at the 6-mo visit |
|-------------------------------------------------------------|
| Prothrombin time (mean ± SD), s (normal range: 91-12.0) | 13.8 ± 1.2 | 14.4 ± 1.3 | 0.7 ± 1.4 | 0.10 |
| Partial thromboplastin time (mean ± SD), s (normal range: 24-33) | 30.6 ± 2.8 | 35.8 ± 4.9 | 5.1 ± 4.9 | 0.004 |
| Thrombin time, No. elevated (% elevated)² | 1 (7.7) | 8 (50.0) | 6 (66.7) | 0.03 |

| 
| aP for change from baseline. |
| bElevated is defined as > 20 s. |
the mRSS at baseline. Results from a linear mixed model indicated that the average monthly decline in mRSS was 1.1 units (95% confidence interval [CI]: 0.4–1.7 units; \( P = 0.004 \)).

**BAL fluid thrombin activity.** BAL fluid thrombin activity was elevated (>6.4 ng/ml) at baseline in only 6 of 14 of our study subjects (43%) (Table 6). After treatment with dabigatran, mean thrombin activity was not significantly different from that at baseline, with reduced thrombin activity in 5 of 6 of those with elevated thrombin activity at baseline (83.3%) and a return to the normal range in 4 of 6 (66.7%). One subject (patient 12; Table 1) had a substantial increase in BAL fluid thrombin activity after 6 months of therapy with dabigatran. Excluding this single case, the BAL fluid thrombin activity decreased or remained stable in 13 of 14 (92.8%) subjects.

### Discussion

SSc-ILD is a major cause of morbidity and mortality for which no FDA-approved treatment exists (2,3). Cyclophosphamide (2), MMF(20), and myeloablative autologous stem-cell transplantation (21) have been shown to improve lung function in a variable percentage of patients, but such therapies are often toxic or ineffective. Two FDA-approved drugs for IPF, nintedanib and pirfenidone, and a number of other drugs are currently under investigation (3). Given the substantial disease burden and unmet need, there is an urgency for novel treatment strategies for SSc-ILDs.

One such strategy involves targeting the serine protease thrombin. The rationale for this strategy is based on extensive evidence showing that thrombin plays an important role in the

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**Table 4.** Pulmonary function tests

| Study Visits | N | Mean ± SD | Change From Baseline |
|--------------|---|-----------|----------------------|
|              |   |           | Mean ± SD | \( P \) |
| FVC, % predicted | Baseline | 15 | 70.6 ± 15.4 | ... | ... |
|               | 3-mo visit | 14 | 70.0 ± 15.4 | 0.4 ± 9.9 | 0.89 |
|               | 6-mo visit | 14 | 67.3 ± 13.6 | -2.4 ± 5.9 | 0.16 |
| FEV\(_1\), % predicted | Baseline | 15 | 71.7 ± 12.6 | ... | ... |
|               | 3-mo visit | 14 | 70.3 ± 11.6 | -0.2 ± 9.5 | 0.93 |
|               | 6-mo visit | 14 | 68.5 ± 9.3 | -2.1 ± 6.0 | 0.22 |
| DLCO, % predicted | Baseline | 15 | 54.3 ± 14.1 | ... | ... |
|               | 3-mo visit | 14 | 52.3 ± 14.2 | 0.3 ± 6.4 | 0.87 |
|               | 6-mo visit | 14 | 52.6 ± 11.5 | 0.6 ± 5.0 | 0.68 |

Abbreviation: DLCO, diffusion capacity for carbon monoxide; FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity.
pathogenesis of SSc-ILD as well as IPF (see below). To assess potential risks of thrombin inhibition in patients with SSc-ILD, we conducted a pilot study in which 14 of 15 patients with SSc-ILD completed 6 months of treatment with dabigatran (75 mg taken orally twice daily). The demographics of our study population are similar to those of Scleroderma Lung Study I (SLS I) and Scleroderma Lung Study II (SLS II) (20,22), although the disease duration of our study population was somewhat longer. AEs were uncommon and were usually mild or unrelated to the study medication. There were no SAEs. Dabigatran was well tolerated, and we observed no significant gastrointestinal, pulmonary, or other safety issues or intolerability.

The primary aim of our study was to assess safety. Given the small cohort size, this study was not powered to assess efficacy. We did, however, obtain pulmonary function testing at the baseline, 3-month, and 6-month visits out of an abundance of caution because systemic anticoagulation with warfarin in a prior IPF clinical trial was found to be associated with an increase in risk of FVC decline and patient death (10). With dabigatran treatment, we observed no significant deterioration of pulmonary function or dyspnea at the 3-month or 6-month assessments, suggesting that, unlike warfarin, dabigatran is not associated with an increased risk of respiratory decline. The mean pulmonary function measures for the group did not change significantly over time (Table 4, Figure 1); however, some individuals did experience declines greater than 10% in FVC, FEV, or DLCO (n = 4) or improvements greater than 10% (n = 4) from baseline to the end of the study.

To assess gastrointestinal tolerability, patients completed the GIT, a validated self-administered 34-item tool that captures the gastrointestinal burden associated with SSc as well as the majority of the commonly reported gastrointestinal symptoms...
associated with dabigatran (18). GIT assessments indicated no significant change in gastrointestinal symptoms. Patients also completed the SHAQ, a widely used and well-characterized outcome measure for SSc (17). No significant change was noted in the SHAQ score at individual time points or overall during treatment with dabigatran, indicating an absence of any negative effect of treatment on overall SSc disease status. The mRSS declined at the 6-month visit compared with the baseline visit, with an average monthly decline in mRSS of 1.1 units (95% CI: 0.4–1.7 units; \( P = 0.004 \)). Given the small sample size and the lack of a control group, no conclusions can be drawn regarding an effect of dabigatran on the mRSS.

There is substantial evidence supporting vascular injury and overexpression of thrombin in the pathogenesis of both SSc-ILD and IPF (8,14,23–30). We previously reported that thrombin activity is highly expressed in the BAL fluid of patients with SSc-ILD (14). Additionally, we observed that after a brief exposure to thrombin in vitro, normal lung fibroblasts undergo differentiation to a myofibroblast phenotype, with such activation occurring via a protease activated receptor-1 (PAR-1)/protein kinase C-epsilon (PKC\( \varepsilon \))-dependent pathway (28). Dabigatran inhibits thrombin by preventing cleavage of the extracellular domain of the PAR-1 receptor, thereby inhibiting thrombin's cellular effects (28,29). We have shown that dabigatran inhibits thrombin-induced differentiation of normal lung fibroblasts to the SSc-like myofibroblast phenotype, and with thrombin inhibition, SSc lung fibroblasts exhibit decreased expression of connective tissue growth factor (CTGF) (CCN2), \( \alpha \)-smooth muscle actin, and collagen type I (28,29). We also demonstrated that dabigatran has anti-inflammatory and anti-fibrotic effects in a bleomycin model of pulmonary fibrosis, and no hemorrhagic complication was observed with such treatment (8). Thus, we and others have concluded that the antifibrotic effects of dabigatran are specific to inhibition of thrombin per se, rather than to its less-specific effects on coagulation and hemostasis, and thus the dissociation of the antifibrotic effects from hemostasis may have important clinical implications (5,11).

BAL fluid thrombin activity was elevated at the baseline assessment in only 6 of 14 of our study subjects (43%), perhaps owing to the frequent use of immunosuppressive therapy in these patients. After treatment with dabigatran, the mean thrombin activity was not significantly different from that at baseline. A single subject was found to have a substantial increase in BAL fluid thrombin activity at the 6-month visit. We do not have a definitive explanation for this increase; however, we can exclude non-compliance because the plasma TT measured at the time of the BAL procedure was more than 50 seconds. This patient’s overall disease may have been more active, because the mRSS had increased, dyspnea had worsened, and the BAL cell count differential contained 10% neutrophils. Excluding this single case, the BAL fluid thrombin activity decreased or remained stable in 13 of 14 (92.8%) subjects.

For those patients whose BAL fluid thrombin expression was elevated at baseline, dabigatran administration lowered thrombin activity. In some of our study subjects, the BAL fluid thrombin activity was normal at baseline. Future studies might employ a thrombin activity measurement for cohort enrichment, electing to treat only those patients with increased lung thrombin activity. A low dose of 75 mg twice daily was chosen for

| Patient | Baseline (ng/ml) | 6 mo (ng/ml) | Absolute Difference | % Difference |
|---------|-----------------|--------------|--------------------|-------------|
| 1       | 6.29            | 7.24         | 0.94               | 0.15        |
| 2       | 4.06            | 4.30         | 0.24               | 0.06        |
| 3       | 31.95           | 5.06         | -26.89             | -0.84       |
| 4       | 5.59            | 4.56         | -1.03              | -0.18       |
| 5       | 9.76            | 4.63         | -5.13              | -0.53       |
| 6       | 4.01            | 3.46         | -0.55              | -0.14       |
| 7       | 9.80            | 10.33        | 0.54               | 0.05        |
| 8       | 11.33           | 7.59         | -3.75              | -0.33       |
| 9       | 15.33           | 4.75         | -10.58             | -0.69       |
| 11      | 5.29            | 6.21         | 0.92               | 0.17        |
| 12      | 6.10            | 100.18       | 94.08              | 15.43       |
| 13      | 4.18            | 5.89         | 1.71               | 0.41        |
| 14      | 6.99            | 4.69         | -2.30              | -0.33       |
| 15      | 4.15            | 4.95         | 0.81               | 0.19        |

Median (IQR) 6.2 (4.2 to 9.8) 5.0 (4.6 to 7.2) -0.2 (-3.8 to 0.9) (NS) -0.05 (-0.3 to 0.2) (NS)

Median (IQR) (excluding patient No. 12) 6.3 (4.2 to 9.8) 5.0 (4.6 to 6.2) 0.6 (-3.8 to 0.8) (NS) -0.1 (-0.3 to 0.2) (NS)

Abbreviation: IQR, interquartile range; NS, not statistically significant.
this exploratory study because no previous safety studies had been reported in this patient group; however, some patients may require a higher dosage (eg, 150 mg twice daily) to maintain low expression of lung thrombin activity. Future studies should be designed to explore this issue as well as to further explore the safety and the efficacy of dabigatran in patients with SSC-ILD and other fibrosing lung diseases.

ACKNOWLEDGMENTS

The authors thank Carol A. Lambourne, MSc, PhD, for assistance in developing the MOP. The authors also wish to thank the members of the staff at KAI, Inc; James Witter, MD, PhD and the staff at the NIAMS; and the DSMB (Eliza Chakravarty, MD, Chairperson; Thomas S. Kickler, MD, DSMB Safety Officer; and Weng Kee Wong, PhD, MS, Statistician) for their time and efforts to ensure the successful and safe conduct of this study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Silver, Highland, Nietert, Bogatkevich.

Acquisition of data. Silver, Wilson, Akter, Atanelishvili, Huggins, Kajdasz, Highland, Nietert, Bogatkevich.

Analysis and interpretation of data. Silver, Wilson, Akter, Atanelishvili, Huggins, Kajdasz, Highland, Nietert, Bogatkevich.

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