Arthritis & Rheumatology
Vol. 72, No. 1, January 2020, pp 125–136
DOI 10.1002/art.41055

American College of Rheumatology
Empowering Rheumatology Professionals

Abatacept in Early Diffuse Cutaneous Systemic Sclerosis: Results of a Phase II Investigator-Initiated, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

Dinesh Khanna,[1] Cathie Spino,[1] Sindhu Johnson,[2] Lorinda Chung,[3] Michael L. Whitfield,[4] Christopher P. Denton,[5] Veronica Berrocal,[1] Jennifer Franks,[4] Bhavan Mehta,[4] Jerry Molitor,[6] Virginia D. Steen,[7] Robert Lafyatis,[8] Robert W. Simms,[9] Anna Gill,[5] Suzanne Kafaja,[10] Tracy M. Frech,[11] Vivien Hsu,[12] Robyn T. Domsic,[13] Janet E. Pope,[14] Jessica K. Gordon,[15] Maureen D. Mayes,[16] Elena Schiopu,[1] Amber Young,[1] Nora Sandorfi,[17] Jane Park,[18] Faye N. Hant,[19] Elana J. Bernstein,[20] Soumya Chatterjee,[21] Flavia V. Castelino,[22] Ali Ajam,[23] Yue Wang,[4] Tammara Wood,[4] Yannick Allanore,[24] Marco Matucci-Cerinic,[25] Oliver Distler,[26] Ora Singer,[1] Erica Bush,[1] David A. Fox,[1] and Daniel E. Furst[27]

Objective. T cells play a key role in the pathogenesis of early systemic sclerosis. This study was undertaken to assess the safety and efficacy of abatacept in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Methods. In this 12-month, randomized, double-blind, placebo-controlled trial, participants were randomized 1:1 to receive either subcutaneous abatacept 125 mg or matching placebo, stratified by duration of dcSSc. Escape therapy was allowed at 6 months for worsening disease. The coprimary end points were change in the modified Rodnan skin thickness score (MRSS) compared to baseline and safety over 12 months. Differences in longitudinal outcomes were assessed according to treatment using linear mixed models, with outcomes censored after initiation of escape therapy. Skin tissue obtained from participants at baseline was classified into intrinsic gene expression subsets.

Results. Among 88 participants, the adjusted mean change in the MRSS at 12 months was –6.24 units for those receiving abatacept and –4.49 units for those receiving placebo, with an adjusted mean treatment difference of –1.75 units ($P = 0.28$). Outcomes for 2 secondary measures (Health Assessment Questionnaire disability index and a composite measure) were clinically and statistically significantly better with abatacept. The proportion of subjects in whom escape therapy was needed was higher in the placebo group relative to the abatacept group (36% versus 16%). In the inflammatory and normal-like skin gene expression subsets, decline in the MRSS over 12 months was clinically and significantly greater in the abatacept group versus the placebo group ($P < 0.001$ and $P = 0.03$, respectively). In the abatacept group, adverse events occurred in 35 participants versus 40 participants in the placebo group, including 2 deaths and 1 death, respectively.

Conclusion. In this phase II trial, abatacept was well-tolerated, but change in the MRSS was not statistically significant. Secondary outcome measures, including gene expression subsets, showed evidence in support of abatacept. These data should be confirmed in a phase III trial.

ClinicalTrials.gov identifier: NCT02161406.

Presented in part at the 82nd Annual Scientific Meeting of the American College of Rheumatology in Chicago, IL, October 2018, and the European Congress of Rheumatology Meeting of the European League Against Rheumatism in Madrid, Spain, June 2019.

Supported by Bristol-Myers Squibb and the NIH (National Institute of Allergy and Infectious Diseases Clinical and Autoimmunity Center of Excellence grant 5-UM1-AI-110557 to the University of Michigan for biomarker data and National Institute of Arthritis and Musculoskeletal and Skin Diseases grants K24-AR-063120 and R01-AR-07047 to Dr. Khanna).

[1]Dinesh Khanna, MD, MS, Cathie Spino, ScD, Veronica Berrocal, PhD, Elena Schiopu, MD, Amber Young, MD, Ora Singer, MD, Erica Bush, BS, David A. Fox, MD: University of Michigan, Ann Arbor; [2]Sindhu Johnson, MD, PhD: Mount Sinai Hospital and University Health Network, Toronto, Ontario, Canada; [3]Lorinda Chung, MD: Stanford University School of Medicine, Palo Alto, California; [4]Michael L. Whitfield, PhD, Jennifer Franks, BS, Bhavan Mehta, MS, Yue Wang, PhD, Tammara Wood, MS: Geisel School of Medicine at Dartmouth, Hanover, New Hampshire; [5]Christopher P. Denton, PhD, Anna Gill, MD: Royal Free Campus, London, UK; [6]Jerry Molitor, MD: University of Minnesota, Minneapolis; [7]Virginia D. Steen, MD: MedStar Georgetown University Hospital, Washington, DC; [8]Robert Lafyatis, MD: Pittsburgh University Medical Center, Pittsburgh, Pennsylvania; [9]Robert W. Simms, MD: Boston University School of Medicine, Boston, Massachusetts; [10]Suzanne Kafaja, MD: David Geffen School of Medicine at University of California, Los Angeles; [11]Tracy M. Frech, MD: University of Utah, Salt Lake City; [12]Vivien Hsu, MD: Robert Wood Johnson University, New Brunswick, New Jersey; [13]Robyn T. Domsic, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; [14]Janet E. Pope, MD: University of Western Ontario, London, Ontario, Canada; [15]Jessica K. Gordon, MD: Hospital for Special Surgery, New York, New York; [16]Maureen D. Mayes, MD: University of Texas McGovern Medical School, Houston; [17]Nora Sandorfi, MD: Perelman School of Medicine at the University of Pennsylvania, Pittsburgh; [18]Jane Park, MD: Seattle Rheumatology Associates,

INTRODUCTION

Systemic sclerosis (SSc; scleroderma) is an immune-mediated rheumatic disease characterized by fibrosis of the skin and internal organs and by vasculopathy (1). It has the highest case fatality rate of any rheumatic disease. One subclassification of this disease, diffuse cutaneous SSc (dcSSc), has a 10-year mortality rate of 50% (1). There are no licensed treatments for SSc, and disease management is focused on organ-specific complications (2).

Several published studies support the concept that T cells play a key role in the pathogenesis of dcSSc, including cutaneous disease and at least some of its visceral complications (3–5). Skin biopsy samples obtained from patients with early dcSSc demonstrate a perivascular, mononuclear cell infiltrate comprising T cells and macrophages (3,4). The numbers of T cells have been found to correlate with the degree of skin thickening at the biopsy sites. T cells are the dominant population of lymphocytes in the skin and are activated in SSc. The adaptive immune system gene expression signature in the skin is higher in early dcSSc than in established dcSSc (6). Animal studies support the notion that abatacept (a CTLA4 immunoglobulin fusion protein) could be effective in the management of dcSSc, as it attenuates skin and lung fibrosis in models of scleroderma (7,8). Additionally, a 24-week, placebo-controlled pilot study consisting of 10 participants showed that abatacept was safe (9). When incorporating the molecular gene expression data in skin, 4 of 5 participants with the inflammatory subset of dcSSc showed improvement with abatacept (9).

Based on these observations, we conducted a phase II trial to evaluate weekly subcutaneous (SC) abatacept versus placebo in dcSSc. The primary objectives were to assess the safety of abatacept and its efficacy on skin thickening, as assessed by the modified Rodnan skin thickness score (MRSS), in a 12-month, double-blind study in patients with relatively early disease (≤36 months). We hypothesized that baseline MRSS scores might be lower in patients with early dcSSc (≤18 months) and higher among those with longer disease duration (>18 and ≤36 months) and that the impact of abatacept might differ by duration of disease. We therefore stratified by disease duration, which allowed us to control for disease duration in the overall analysis and also to explore the ability of abatacept to prevent or reverse disease progression in patients with early dcSSc and to reverse established disease in patients with longer disease duration. Our a priori hypothesis was that patients with an inflammatory gene signature would have a statistically significant decline in MRSS over 12 months.

PATIENTS AND METHODS

Study design. This was a phase II, investigator-initiated, randomized, double-blind, placebo-controlled trial of abatacept in patients with dcSSc. DcSSc was defined by the presence of skin thickening, proximal as well as distal, to the elbows or knees with

Seattle, Washington; [19]Faye N. Hant, MD: Medical University of South Carolina, Charleston; [20]Elana J. Bernstein, MD: Columbia University, New York, New York; [21]Soumya Chatterjee, MD: Cleveland Clinic, Cleveland, Ohio; [22]Flavia V. Castelino, MD: Harvard Medical School, Boston, Massachusetts; [23]Ali Ajam, MD: Ohio State University Wexner Medical Center, Columbus; [24]Yannick Allanore, MD, PhD: Hôpital Cochin, Paris, France; [25]Marco Matucci-Cerinic, MD, PhD: University of Florence, Florence, Italy; [26]Oliver Distler, MD: University Hospital Zurich, Zurich, Switzerland; [27]Daniel E. Furst, MD: University of California, Los Angeles.

Drs. Fox and Furst contributed equally to this work.

Dr. Khanna has received consulting fees from Actelion, Acceleron, Arena, Boehringer Ingelheim, CSL Behring, Corbus, Cytori, GlaxoSmithKline, Galapagos, Merck, Mitsubishi Tanabi, and UCB (less than $10,000 each) and from Bayer, Bristol-Myers Squibb, and Genentech/Roche (more than $10,000 each) as well as research support on behalf of the University of Michigan from Bayer, Bristol-Myers Squibb, and Pfizer, and owns stock options in Eicos Sciences, Inc. and Civi BioPharma, Inc. Dr. Spino has received consulting fees from Bristol-Myers Squibb and Eicos Sciences, Inc. (less than $10,000 each). Dr. Chung has received consulting fees from Bristol-Myers Squibb, Boehringer Ingelheim, Mitsubishi Tanabe, and Eicos Sciences, Inc. (less than $10,000 each) and Reata (more than $10,00) and research support from United Therapeutics. Dr. Whitfield has received consulting fees from Bristol-Myers Squibb, Boehringer Ingelheim, Corbus, and Third Rock Ventures (less than $10,000 each) and Celdara Medical LLC and UCB (more than $10,000 each) and research support from Celdara Medical LLC and UCB. Dr. Molitor has received consulting fees from Boehringer-Ingelheim and Amgen (less than $10,000 each) and research support from Pfizer. Dr. Steen has received consulting fees, speaking fees, and/or honoraria from CSL Behring, Bayer, and Boehringer Ingelheim (less than $10,000 each). Dr. Lafyatis has received consulting fees from PRISM BioLab, Merck, Bristol-Myers Squibb, Biocon, Boehringer Ingelheim, UCB, Formation, Sanofi, and Genentech/Roche (less than $10,000 each) and research support from PRISM BioLab, Regeneron, Elpidera, and Kiniksa. Dr. Domsic has received consulting fees from Eicos Sciences Inc. and Boehringer Ingelheim (less than $10,000 each). Dr. Pope has received consulting fees from Actelion, Baxter, Bristol-Myer Squibb, Merck, Bayer, and Roche (less than $10,000 each) and research support from Baxter, Bristol-Myer Squibb, Eicos Sciences Inc, Merck, Emerald, Roche, and Seattle Genetics. Dr. Gordon has received research support from Corbus and Cumberland Pharmaceuticals. Dr. Mayes has received honoraria from the Young Investigator Program, MedTelligence, and Actelion (less than $10,000 each) and consulting fees from Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Galapagos, and Genetec (less than $10,000 each). Dr. Schiopu has received research support from Bristol-Myers Squibb and Bayer. Dr. Bernstein has received consulting fees from Genentech (less than $10,000) and research support from Pfizer (the ASPIRE Rheumatology program). Dr. Castelino has received consulting fees from Genentech and Boehringer (less than $10,000 each). Dr. Allanore has received consulting fees from Bristol-Myer Squibb, Genentech/Roche, Sanofi, Bayer, Actelion, and Inventiva (less than $10,000 each) and research support from Genentech/Roche, Sanofi, and Inventiva. Dr. Matucci-Cerinic has received consulting fees from Bristol-Myer Squibb (less than $10,000) and research support from Bristol-Myers Squibb. Dr. Distler has received consulting fees, speaking fees, and/or honoraria from Menarini, Acceleron Pharma, Amgen, ANAMAR, Bayer, Catenion, CSL Behring, Ergonex, GlaxoSmithKline, Inventiva, Italfarmaco, IQVIA, Eli Lily, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Blade Therapeutics, CSL Behring, Target BioScience, and UCB (less than $10,000 each). Dr. Fox has received consulting fees, speaking fees, and/or honoraria from Pfizer (less than $10,000) and research support from Regeneron, Gilead, and Seattle Genetics. Dr. Furst has received consulting fees, speaking fees, and/or honoraria from Actelion, Amgen, Bristol-Myers Squibb, Corbus, Galapagos, Pfizer, GlaxoSmithKline, Novartis, Sanofi, and Genentech/Roche (less than $10,000 each). No other disclosures relevant to this article were reported.

Address correspondence to Dinesh Khanna, MD, MS, University of Michigan, Division of Rheumatology, Department of Internal Medicine, 500 South State Street, Ann Arbor, MI 48109. E-mail: khannad@med.umich.edu.

Submitted for publication March 5, 2019; accepted in revised form July 18, 2019.

or without involvement of the face and neck at the time of study entry. Patients were treated for 12 months with double-blind study medication and were offered an additional 6 months of open-label SC abatacept therapy. Patients were telephoned 30 days after the last dose of study drug to discuss any adverse events (AEs) that may have occurred.

The study received an Investigational New Drug Exemption from the Food and Drug Administration. The study protocol was approved by the institutional review board or ethics committee at each participating site (see the Protocol section of the Supplementary Text, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract) before research commenced. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guideline. Written informed consent was obtained from each participant.

Study participation criteria. Key inclusion criteria were 1) age ≥18 years, 2) a diagnosis of SSc (defined by the 2013 American College of Rheumatology/European Union League Against Rheumatism criteria for SSc [10]) and dcSSc (defined by the Criteria for Early SSc [11]), and 3) disease duration of ≤36 months (defined as time from the first non–Raynaud's phenomenon manifestation). For individuals with a disease duration of ≤18 months, an MRSS of ≥10 and ≤35 units was required at the screening visit. For those with a disease duration of >18 to ≤36 months, an MRSS of ≥15 and ≤45 units was required along with one of the following conditions, which must have been observed at screening compared to the patient's last visit in the previous 1–6 months: 1) increase of ≥3 MRSS units, 2) involvement of 1 new body area with increase of ≥2 MRSS units, 3) involvement of 2 new body areas with increase of ≥1 MRSS unit, and/or 4) presence of ≥1 tendon friction rubs.

Oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and nonsteroidal antiinflammatory drugs were permitted if the patient was on a stable dose regimen for ≥2 weeks prior to and at the baseline visit, but no background immunomodulatory therapies were allowed. More details are provided in the Protocol section of the Supplementary Text.

Randomization and blinding. Eligible participants were randomized at a 1:1 ratio to receive either SC abatacept 125 mg or matching placebo (provided by Bristol-Myers Squibb), stratified by duration of dcSSc disease (≤18 months versus >18 to ≤36 months). The first injection was given at the research office, and subsequent study medications were injected weekly at home. The Data Coordinating Center (DCC) at the University of Michigan prepared the randomization schedule, using computer-generated block randomization with random block sizes of 2 and 4 (known only by the DCC). The study staff (including the research pharmacists) and patients were blinded with regard to the treatment assigned.

Procedures. Patients were seen at regular intervals throughout the 12-month study period. Study assessments and their timing are summarized in the study protocol (see the Protocol section of the Supplementary Text, http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). Screening took place within 28 days before randomization. Eligible patients were assessed at baseline; months 1, 3, 6, 9, and 12 in clinic; and by telephone 30 days after the last dose (for those who did not continue into the open-label period).

Escape therapy with immunomodulatory agents was permitted as add-on therapy to study medications due to worsening of dcSSc starting at month 6 (Protocol section of the Supplementary Text). The decision to initiate escape therapy was based on investigator discretion. No biologic agents were allowed as escape therapy.

Outcome measures. The primary outcome measure was change in MRSS at 12 months. The same assessor performed the MRSS measurement at each time point during the trial. Live demonstration and standardization of the MRSS for the trial occurred during an investigator meeting prior to study initiation, at which it was agreed upon that the average score at each anatomic site would be used (12). Secondary outcome measures included 1) change in MRSS from baseline to months 1, 3, 6, and 9; 2) change from baseline to months 1, 3, 6, 9, and 12 in the swollen and tender joint counts in 28 joints; 3) change from baseline to months 3, 6, and 12 in the patient global assessment (PtGA) and physician global assessment (PhGA) for overall disease, the Patient-Reported Outcomes Measurement Information System 29-Item Profile, the Health Assessment Questionnaire disability index (HAQ DI), Scleroderma HAQ DI visual analog scale (VAS; which assesses pain, burden of digital ulcers, Raynaud's phenomenon, gastrointestinal involvement, breathing, and overall disease), and the University of California Los Angeles Gastrointestinal Tract 2.0 Questionnaire; and 4) change from baseline to months 6 and 12 in forced vital capacity percent predicted (FVC %), and the American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS; a composite end point that captures cardiovascular/pulmonary/renal involvement and change in MRSS, HAQ DI, PtGA, PhGA, and FVC %).

The exploratory end points included 1) change from baseline to months 3, 6, and 12 in interference in the patient's physical functioning related to skin involvement and pain intensity due to SSc over the previous week on a 0–150 mm VAS; 2) proportion of patients with cardiac involvement, significant interstitial lung disease (ILD), and new renal crisis at 12 months; 3) change from baseline in body mass index and digital ulcer burden at 12 months; and 4) change from baseline to months 6 and 12 in % predicted diffusing capacity for carbon monoxide (corrected for hemoglobin) and FVC (ml).

Safety end points were 1) proportion of patients experiencing AEs; 2) incidence of AEs, serious AEs (SAEs), and AEs of special interest; 3) treatment discontinuation due to AEs; and 4) changes in clinical laboratory test results, vital signs, and physical examination results over time. The study was overseen by a Data and Safety Monitoring Committee that reviewed study conduct and safety outcomes approximately every 6 months.

RNA sequencing, read alignment, and gene expression calculation. Skin biopsy specimens measuring 3 mm were obtained from the involved forearm skin at each site, at baseline and at months 3 and 6. Biopsy specimens were stored in RNAlater and processed for RNA, as previously reported (13). Machine learning was used to classify biopsy specimens into intrinsic gene expression subsets. RNA-Seq data (reads per kilobase per million) were normalized, and baseline skin samples were classified into inflammatory, normal-like, or fibroproliferative intrinsic gene expression subsets (13). Details on the methodology are available in the Supplementary Methods at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract.

Statistical analysis. The size of the study population was based on practical considerations rather than a desired power for a prespecified difference. We planned to screen 121 patients and select 86 participants to randomize. With this sample size, we calculated that we could detect an effect size of at least 0.66 in the primary end point with 80% power, assuming a 5% 2-sided Type I error and a dropout rate of 15% (2-sample *t*-test; East software version 5.4). This effect size translates into a treatment difference in change in the MRSS from baseline to month 12 of 5.3, with an SD of 8 points (14). Sample sizes that were used in the detection of minimally important clinical differences of end points in previously published studies on dcSSc are detailed in the Supplementary Methods, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract, and provide context on the sample size needed for a confirmatory study.

The main analysis set for efficacy was the modified intent-to-treat (mITT) population, defined as all participants who were randomized to receive at least 1 dose of study medication. We analyzed the primary end point using a linear mixed model as described in Supplementary Methods. Escape therapy after 6 months was an indication of treatment failure; therefore, we censored primary end point data after initiation of escape therapy. In an additional sensitivity analysis, we applied the same model using all MRSS values (i.e., no censoring after escape therapy). Adjusted least squares means (LSMs), SEMs, 95% confidence intervals (95% CIs), and 2-sided *P* values for between-treatment comparisons are provided. Safety outcomes are summarized by treatment group using descriptive statistics (no tests were performed).

Analyses of all secondary end points utilized the same approach used for the primary end point, except for the ACR CRISS, for which a nonparametric approach was used (detailed in Supplementary Methods, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). No adjustments for multiplicity were made; thus, *P* values for secondary and exploratory outcomes should be interpreted with caution. The Supplementary Methods also provide the analysis approach for gene signature data. The full statistical analysis plan was finalized before unblinding. All statistical analyses were performed using SAS software version 9.4.

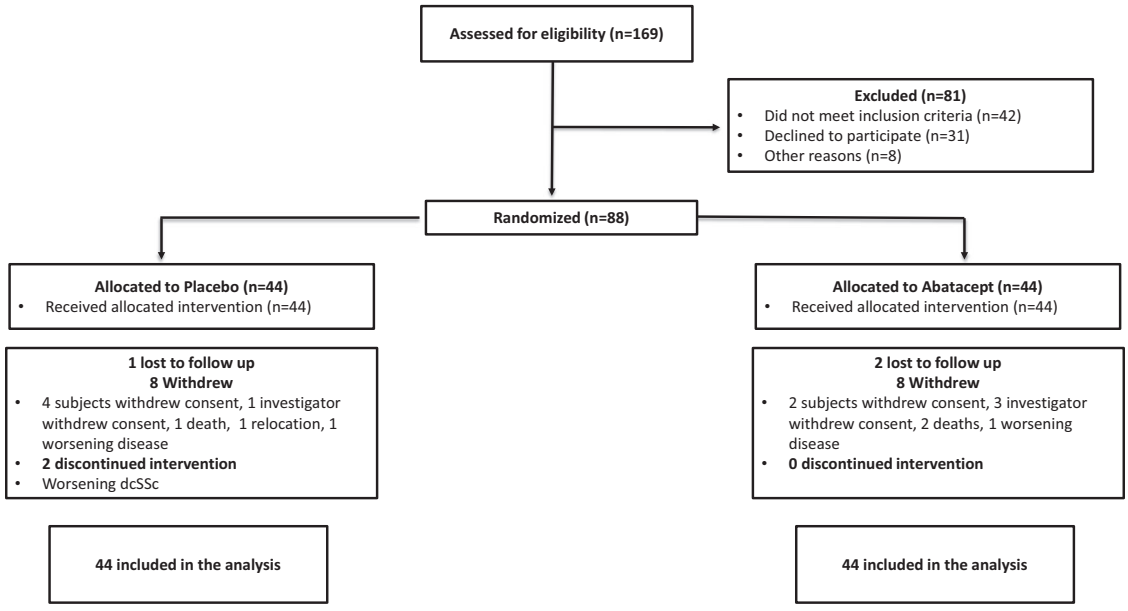

Figure 1. Flow chart showing the disposition of study participants.

Table 1. Demographic and baseline disease characteristics of the study patients*

	Overall (n = 88)	Placebo (n = 44)	Abatacept (n = 44)
Age, years	49 ± 13	49 ± 13	50 ± 12
Women, no. (%)	66 (75)	35 (80)	31 (70)
White, no. (%)	72 (82)	37 (84)	35 (80)
Not Hispanic or Latino, no. (%)	76 (86)	36 (82)	40 (91)
Disease duration, years†	1.59 ± 0.81	1.52 ± 0.79	1.66 ± 0.84
Disease duration ≤18 months, no. (%)	53 (60)	27 (61)	26 (59)
MRSS	22.45 ± 7.65	21.57 ± 7.33	23.34 ± 7.95
FVC % predicted	85.4 ± 15.10	86.5 ± 16.60	84.2 ± 13.50
Predicted DLco, corrected for Hgb	78.0 ± 18.24	76.5 ± 18.44	79.6 ± 18.12
PtGA, theoretical range 0–10	4.09 ± 2.38	4.31 ± 2.56	3.88 ± 2.21
HAQ DI, theoretical range 0–3	1.05 ± 0.71	0.97 (0.70)	1.14 (0.72)
PhGA, theoretical range 0–10	4.77 ± 1.67	4.76 ± 1.67	4.77 ± 1.67
Tendon friction rubs, no. (%)	32 (36)	13 (30)	19 (43)
Large joint contractures, no. (%)	63 (72)	32 (73)	31 (70)
Swollen joints, theoretical range 0–28	3.75 ± 5.70	3.86 ± 5.85	3.64 ± 5.62
Proportion of participants with ≥1 swollen joints, no. (%)	42 (48)	21 (48)	21 (48)
Use of prednisone, no. (%)	12 (14)	5 (11)	7 (16)
Prednisone dose, mg/day	7.9 ± 2.6	7.0 ± 2.7	8.6 ± 2.4

* Except where indicated otherwise, values are the mean ± SD. MRSS = modified Rodnan skin thickness score; FVC % predicted = forced vital capacity percent predicted; DLco = diffusing capacity for carbon monoxide; Hgb = hemoglobin; PtGA = patient global assessment; HAQ DI = Health Assessment Questionnaire disability index; PhGA = physician global assessment.
† Disease onset was defined as first non–Raynaud's sign or symptom.

RESULTS

Patient screening, enrollment, and continuation in the study. A total of 169 patients were screened for eligibility, and 88 were randomized to receive abatacept or placebo (44 in each treatment group) at 22 centers in the US, Canada, and the UK between September 22, 2014 and March 15, 2017 (Figure 1). Thirty-four patients in the abatacept group (77%) and 35 in the placebo group (80%) completed the 12-month trial. At 12 months, 7 patients in the abatacept group (16%) and 16 patients in the placebo group (36%) received escape therapy for worsening dcSSc (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). Eighty-eight patients were included in the mITT and safety analyses and 85 in the per-protocol analysis (43 in the abatacept group and 42 in the placebo group). A similar number of patients withdrew in each group. In the abatacept group, 10 patients withdrew due to the following reasons: investigator withdrew consent (n = 3), patient withdrew consent (n = 2), lost to follow-up (n = 2), death (n = 2), and worsening dcSSc (n = 1). In the placebo group, 9 patients withdrew due to the following reasons: investigator withdrew consent (n = 1), patient withdrew consent (n = 4), lost to follow-up (n = 1), death (n = 1), relocation (n = 1), and worsening dcSSc (n = 1). Compliance with the study drug was >98% (1 patient in the placebo group had a compliance of <80%). The median estimated duration of study medication exposure was 10.7 months (interquartile range [IQR] 5.2–11.1 months) in the abatacept group and 10.6 months (IQR 9.1–10.8 months) in the placebo group. The demographic and baseline disease characteristics were similar between treatment groups (Table 1).

Efficacy. Findings for the primary outcome measure did not differ significantly between the abatacept and placebo groups (LSM ± SEM change in MRSS –6.24 ± 1.14 and –4.49 ± 1.14, respectively with a treatment difference of –1.75 [95% CI –4.93, 1.43]) (Table 2 and Figure 2). Sensitivity analyses using the per-protocol population and incorporating all values after escape therapy in the mITT population showed comparable results (Table 2). There were also no statistically significant differences in MRSS change at months 1, 3, 6, and 9 (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract).

There were statistically significant and clinically meaningful treatment differences in LSM improvements in the HAQ DI at 12 months (–0.28; $P = 0.005$) (Table 2). There were no significant differences between the abatacept and placebo groups at 12 months in the swollen joint counts (LSM ± SEM 0.75 ± 0.84; $P = 0.37$) and tender joint counts (LSM ± SEM 0.76 ± 1.28; $P = 0.55$). There was statistically significant and clinically meaningful improvement in a new composite index, the ACR CRISS, that showed evidence in support of abatacept. The median change at 12 months in the ACR CRISS score was 0.72 (IQR 0.99) versus 0.02 (IQR 0.75) ($P = 0.03$) with the proportion of patients whose score improved by ≥0.60 (the clinically meaningful cutoff point [15]) significantly higher in the abatacept group compared to the placebo group (62.8%

Table 2. Changes from baseline to month 12 in primary and secondary efficacy end points in patients with diffuse cutaneous systemic sclerosis*

Efficacy end points	Placebo (n = 44)†	Abatacept (n = 44)†	Abatacept − placebo, LSM (95% CI)
Primary analysis of the mITT population with values censored after escape therapy	−4.49 ± 1.14	−6.24 ± 1.14	−1.75 (−4.93, 1.43)
Sensitivity analysis 1 of the per-protocol population with values censored after escape therapy	−4.63 ± 1.15	−6.25 ± 1.13	−1.62 (−4.79, 1.55)
Sensitivity analysis 2 of the mITT population with values not censored after escape therapy	−4.22 ± 1.04	−6.64 ± 1.10	−2.42 (−5.38, 0.54)
Secondary end point			
PtGA (0–10)‡	−0.09 ± 0.46	−0.31 ± 0.42	−0.22 (−1.45, 1.01)
PhGA (0–10)‡	−0.35 ± 0.32	−1.30 ± 0.29	−0.95 (−1.80, −0.10)§
FVC %	−4.13 ± 1.22	−1.34 ± 1.24	2.79 (−0.69, 6.27)
FVC (ml)	−121.6 ± 46.39	−36.39 ± 43.82	85.21 (−42.75, 213.16)
HAQ DI (0–3)‡	0.11 ± 0.07	−0.17 ± 0.07	−0.28 (−0.47, −0.09)¶
Scleroderma HAQ‡			
Overall VAS (0–150)	3.52 ± 6.05	−7.42 ± 5.64	−10.94 (−27.27, 5.38)
Breathing VAS (0–150)	16.95 ± 5.85	9.30 ± 5.51	−7.65 (−23.60, 8.30)
Raynaud's VAS (0–150)	−3.64 ± 7.17	7.58 ± 6.60	11.22 (−8.04, 30.47)
Digital ulcers VAS (0–150)	8.67 ± 5.52	−3.18 ± 5.13	−11.85 (−26.70, 3.01)
Gastrointestinal VAS (0–150)	8.01 ± 6.42	9.98 ± 6.00	1.96 (−15.40, 19.33)
Swollen joint count (0–28)‡	−0.86 ± 0.60	−0.11 ± 0.60	0.75 (−0.91, 2.41)
Tender joint count (0–28)‡	−1.47 ± 0.91	−0.71 ± 0.90	0.76 (−1.75, 3.27)
PROMIS-29			
Physical function	−0.17 ± 0.69	−1.54 ± 0.65	−1.36 (−3.23, 0.50)
Anxiety‡	−1.09 ± 1.37	−3.50 ± 1.31	−2.41 (−6.15, 1.32)
Depression‡	−0.41 ± 1.20	−0.02 ± 1.13	0.39 (−2.86, 3.64)
Fatigue‡	−0.98 ± 1.36	−0.65 ± 1.29	0.33 (−3.37, 4.03)
Sleep disturbance‡	−0.21 ± 0.62	−0.31 ± 0.57	−0.10 (−1.76, 1.57)
Pain interference‡	−1.56 ± 1.22	−4.10 ± 1.13	−2.53 (−5.81, 0.74)
Social roles‡	−1.26 ± 1.14	−1.11 ± 1.07	0.15 (−2.93, 3.24)
Pain intensity (0–10)‡	−0.18 ± 0.33	−0.72 ± 0.32	−0.54 (−1.44, 0.37)
UCLA GIT 2.0 total score (0.00–2.83)‡	0.05 ± 0.050	0.07 ± 0.047	0.12 (−0.01, 0.26)
ACR CRISS at 12 months, median (IQR)	0.02 (0.75)	0.72 (0.99)#	–

* For primary and sensitivity analyses, the estimates and *P* values are from a linear mixed model with treatment group, month (3, 6, 9, and 12), treatment group × month interaction, and baseline MRSS as fixed effects and study patient as a random effect. For secondary analyses, the estimates and *P* values are from a linear mixed model with treatment group, month, treatment group × month interaction, duration of dcSSc (≤18 versus >18–≤36 months), and baseline variable as fixed effects and study patient as a random effect. The modified intent-to-treat (mITT) population includes all of the randomized patients who received at least 1 dose of study medication. The per-protocol population includes mITT patients who did not experience a major protocol deviation, defined as eligibility criteria violations for which no exemption was granted, study drug compliance of <80% and >120%, and initiation of escape medication prior to month 3. LSM = least squares mean; 95% CI = 95% confidence interval; VAS = visual analog scale; PROMIS-29 = Patient-Reported Outcomes Measurement Information System 29-Item Profile; UCLA GIT 2.0 = University of California Los Angeles Gastrointestinal Tract 2.0 Questionnaire; IQR = interquartile range (see Table 1 for other definitions).
† Except where indicated otherwise, values are the LSM ± SEM.
‡ Higher score denotes worse symptoms.
§ *P* = 0.03 (not adjusted for multiplicity).
¶ *P* = 0.005 (not adjusted for multiplicity).
# *P* = 0.03 versus placebo, by Van Elteren test with adjustment for duration of diffuse cutaneous systemic sclerosis (dcSSc). Five participants in each group had cardiopulmonary-renal involvement and were given a probability score of 0.0. Multiple imputation was used to address missing follow-up data in MRSS, FVC % predicted, HAQ DI, PtGA, and PhGA, allowing calculation of American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS) scores.

versus 37.2%; *P* = 0.01 by Cochran-Mantel-Haenszel test with adjustment for dcSSc duration). Other secondary outcomes are presented in Table 2 and Supplementary Table 2.

In analyses of exploratory end points, the proportion of patients with a decrease in MRSS of ≥5 units (a clinically important improvement [16]) was similar in both groups (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). When the change in MRSS at 12 months was evaluated by disease duration (≤18 months versus >18–≤36 months) in an ad hoc analysis, numerically greater treatment effects were seen in early disease (n = 53) than in later disease (n = 35). LSM changes in

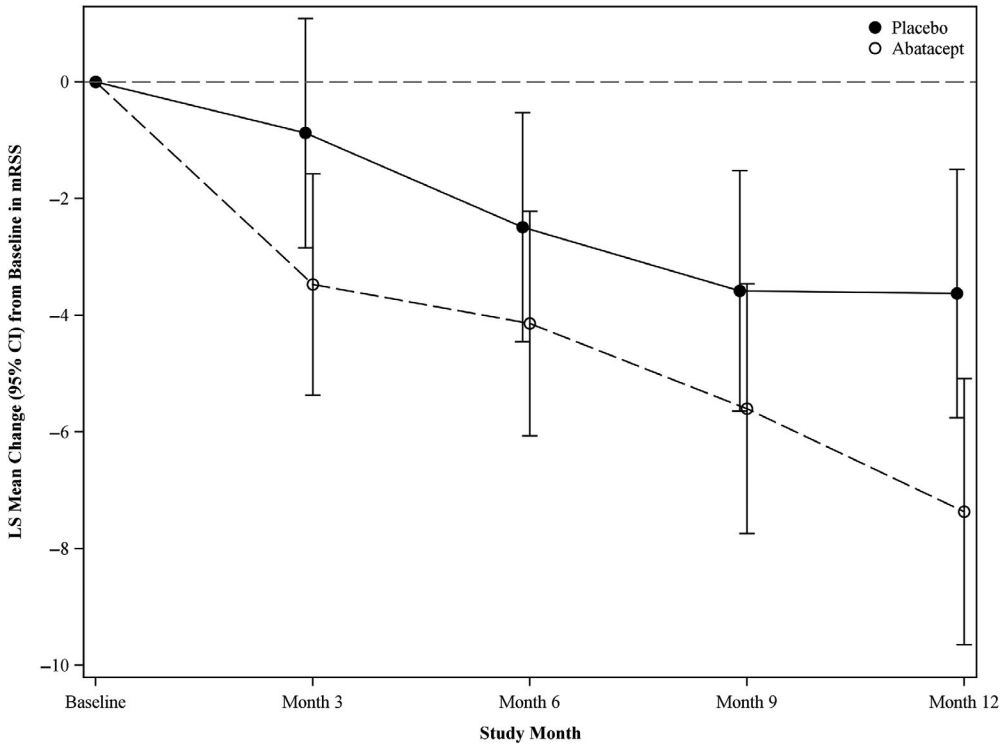

Figure 2. Change in modified Rodnan skin thickness score (MRSS) over a 12-month period in patients with diffuse cutaneous systemic sclerosis who received abatacept or placebo (modified intent-to-treat population). LS = least squares; 95% CI = 95% confidence interval.

MRSS in the abatacept group were –5.71 units and –6.62 units in the early and later disease groups, respectively, while in the placebo group, they were –2.98 units and –6.18 units. This resulted in an LSM treatment difference of –2.73 (95% CI –6.57, 1.11) in early disease and –0.44 (95% CI –6.10, 1.11) in later disease ($P = 0.16$ and $P = 0.88$, respectively).

A total of 23 patients (26%) needed escape therapy for worsening dcSSc, with a larger proportion needing escape therapy in the placebo group (16 [36%]) than in the abatacept group (7 [16%]). The reasons for escape therapy included worsening skin (8 in the placebo group and 4 in the abatacept group), worsening ILD (2 in placebo), polyarthritis (3 in placebo), and overall worsening disease (4 in placebo and 4 in abatacept). There was no increase in infections among those who received escape therapy and continued receiving abatacept (1 event; 0.4 person-year) versus those who did not receive escape therapy (27 events; 0.8 person-year). In comparison, patients who received placebo and started receiving escape therapy had 3 events (0.6; person-year) versus 40 events (1.2; person-year) among those who did not receive escape therapy.

Gene expression in skin biopsy specimens from 84 patients (43 in the abatacept group and 41 in the placebo group) was analyzed in 84 patients at baseline (43 in the abatacept group and 41 in the placebo group). No systemic biases were found related to collection site, time of biopsy, or the RNA-Seq analysis. Intrinsic gene expression subset (e.g., inflammatory, normal-like, fibroproliferative) was assigned using a machine learning classifier before the unblinding of the study. At baseline, 33 patients (39%) were classified as having the inflammatory subtype, 33 (39%) as having the normal-like subtype, and 18 (21%) as having the fibroproliferative subtype. Patients with early disease were more likely to be in the inflammatory subset (21 of 33; 64%) or the normal-like subset (23 of 33; 70%) than the fibroproliferative subset (7 of 18; 39%). There were no significant differences between the distribution of intrinsic gene expression subsets at baseline in each treatment arm (Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). The LSM change in MRSS over 12 months was significantly different between the abatacept and placebo groups for the inflammatory and normal-like subsets ($P < 0.001$ and $P = 0.03$, respectively) (Figure 3 and Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract), but there was no difference in the fibroproliferative subset ($P = 0.47$). In the abatacept arm, the fibroproliferative subset showed a numerical increase in FVC % predicted ($P = 0.19$) while FVC % predicted decreased in the other 2 subsets. All gene expression subgroups showed numerical decreases in the HAQ DI in the abatacept arm that were not observed in the placebo arm.

Safety. Abatacept was found to be generally safe with no new safety signals and a lower number of patients experiencing AEs, infectious AEs, and SAEs compared to the placebo group

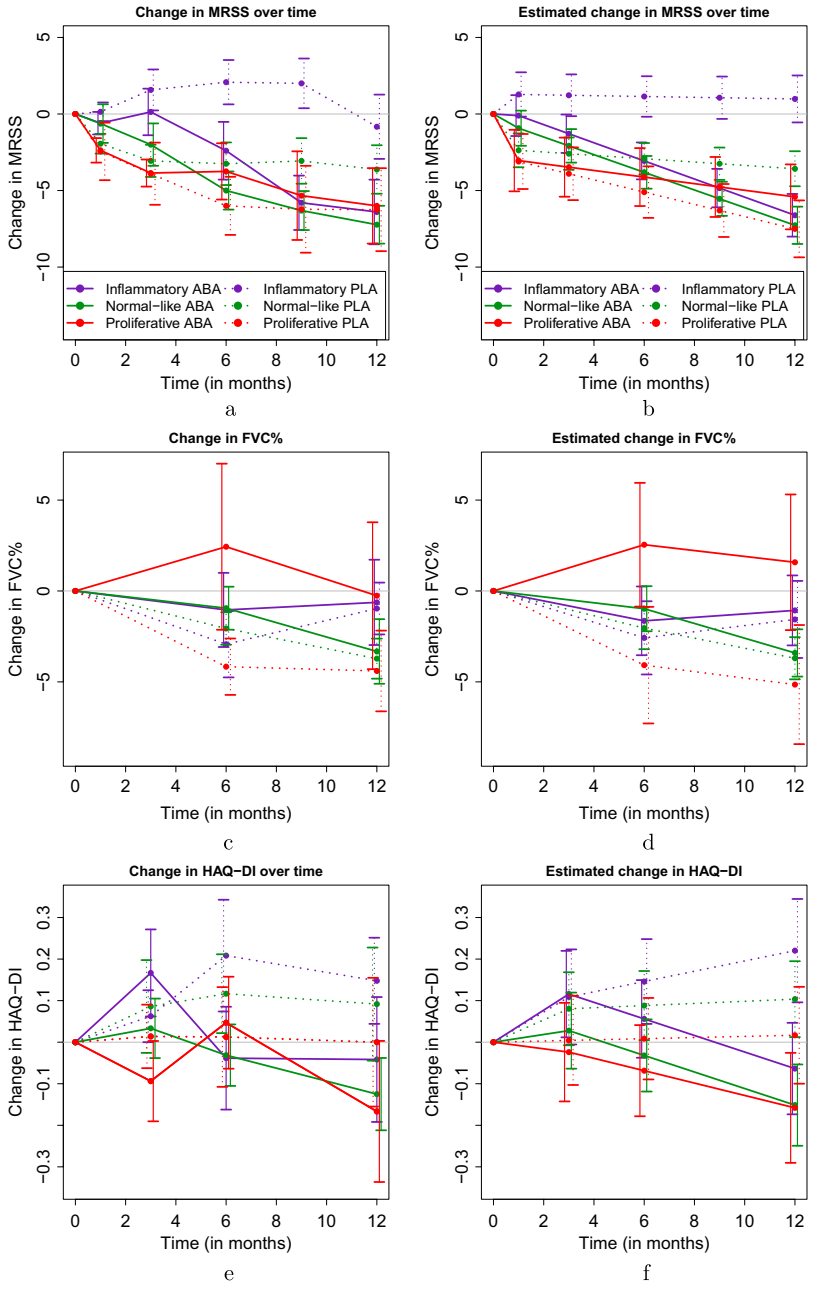

Figure 3. Observed average change from baseline in the modified Rodnan skin thickness score (MRSS) (**a**), forced vital capacity percent predicted (FVC %) (**c**), and Health Assessment Questionnaire disability index (HAQ DI) (**e**) and estimated average change from baseline in the MRSS (**b**), FVC % (**d**), and HAQ DI (**f**) in the placebo (PLA) and abatacept (ABA) groups and in the 3 intrinsic gene expression subsets (inflammatory, normal-like, and proliferative). Estimates were obtained from a linear mixed model fitted to the change from baseline in MRSS, FVC %, and HAQ DI, respectively, with the following predictors: MRSS, FVC %, and HAQ DI at baseline; month in the study; treatment group; interaction of treatment group and month; and a subject-specific random effect. Values are the mean ± 1 SEM.

(Table 3). In the placebo group, 27% of the patients experienced SAEs versus 20% in the abatacept group. These included more noninfectious SAEs in the placebo group compared to the abatacept group (23% versus 16%) and the same proportion of infectious SAEs in both groups (5%). Additionally, more patients in the placebo group withdrew from the study due to AEs (6 [14%]) compared to the abatacept group (5 [11%]). Renal crisis occurred in 3 patients in the abatacept group (days 11, 25, and 46 after initiation of study medication) versus 1 patient in the placebo group (day 56 after initiation of study medication). The number of patients with treatment-emergent AEs by severity grade was similarly distributed between the 2 treatment groups, with a total of 36 (82%) in the abatacept group and 40 (91%) in the placebo group experiencing an AE (Supplementary Table 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract). There were no cases of

Table 3. Adverse events among study patients*

	Placebo (n = 44)	Abatacept (n = 44)
Participants with ≥1 AE, no. (%)	40 (91)	35 (80)
Participants with ≥1 infectious AE, no. (%)	25 (57)	19 (43)
Withdrawal because of an AE, no. (%)	6 (14)	5 (11)
Participants with ≥1 SAE, no. (%)	12 (27)	9 (20)
Participants with specific SAEs		
Infections and infestations		
Cellulitis	–	1
Mastoiditis	–	1
Paronychia	1	–
Pneumonia	1	–
Cardiac disorders		
Atrial flutter with conduction defects	1	–
Cardiac arrest	1	–
Congestive heart failure	1	–
Myocardial infarction/acute coronary syndrome	1	1
Pulmonary arterial hypertension	1	1
Pericardial effusion	–	1
Gastrointestinal disorders		
Anemia	1	–
Cholecystitis	1	–
Dysphagia	1	1
Erosive esophagitis	1	–
Gastric antral vascular ectasia	1	–
Gastric antral vascular ectasia with anemia	1	–
Melena	–	1
Pseudoobstruction	–	1
Neoplasm disorders		
Basal cell skin carcinoma	1	–
Squamous cell skin carcinoma	–	1
Respiratory disorders		
Respiratory failure	–	1
Renal disorders		
Scleroderma renal crisis	1	3
Vascular disorders		
Digital ischemia	1	–
Mental disorders		
Depression with suicidal ideation	1	–

* Some patients experienced ≥1 serious adverse event (SAE) during the course of the study.

tuberculosis during the trial. No significant laboratory abnormalities were noted; 1 patient in each group had a hemoglobin decline of >2 gm/dl related to dcSSc (among patients with baseline values ≥8 gm/dl). There were 20 AEs of special interest in the abatacept group and 26 in the placebo group, including 1 injection site reaction in the abatacept group (Supplementary Table 7, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract).

Three deaths occurred in the study. One patient died due to cardiac arrest 310 days after starting the study medication (placebo); this death was not considered to be related to the study medication. Two patients in the abatacept group experienced scleroderma renal crisis leading to death; of these 2 patients, 1 died on day 11 after randomization due to renal crisis (which was considered to not be related to the study medication), leading to respiratory failure (which was considered to be related to the study medication). The second patient was admitted to the hospital due to gastrointestinal dysmotility and myositis on day 25 and then experienced renal crisis on day 46; both were considered to be not related to the study medication.

DISCUSSION

In this phase II trial, we showed that abatacept is well-tolerated in early dcSSc. Although a statistically significant treatment difference in the primary efficacy end point (change from baseline in the MRSS at 12 months) was not achieved, there were clinically meaningful and statistically significant differences in HAQ DI (a measure of function) and ACR CRISS results. In addition, a larger proportion of patients who received placebo needed immunomodulatory escape therapy compared to those who received abatacept, further supporting the favorable impact of abatacept. In addition, this is the first prospective trial showing that intrinsic gene expression subsets can predict clinical outcome measures with greater precision.

Skin involvement was chosen as the primary outcome measure as it is an important concern for patients due to its relationship to disability caused by small and large joint contractures, pruritus, and allodynia (17). Skin thickness, as assessed by the MRSS, is a feasible, reliable, valid outcome measure and is sensitive to change (12). In addition, the MRSS is utilized by scleroderma physicians to assess for worsening and improvement of skin involvement (1). In early disease, skin involvement is a surrogate for internal organ involvement and mortality (18,19). Because of this, the MRSS has been incorporated as the primary end point in early SSc trials (20). However, the absence of a statistically significant result in the current trial is similar to recently published and presented data from studies on anti–interleukin-6 receptor in the treatment of SSc (20,21). The current results occurred despite recruitment of a study population with early disease (mean disease duration 1.59 years); 60% of patients were recruited within 18 months of diagnosis, and only a small proportion received background immunosuppressive therapy. There was a significant heterogeneity in MRSS trajectory over the 12-month study period (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract) (22,23), which is likely driven by autoantibodies (24) and skin gene expression profile (25).

The HAQ DI, which improved significantly with abatacept treatment, is a validated measure of function in SSc (26), and numerical improvements in other patient-reported outcome measures were seen as well (although many did not achieve clinically meaningful thresholds). These changes are important, as they directly address the Food and Drug Administration (FDA) mandate on assessing how a patient feels, functions, and survives (FDA Code of Federal Regulations, Title 21). The efficacy of abatacept

is also suggested by the lower proportion of the abatacept group who needed escape therapy for worsening dcSSc relative to the placebo group (16% versus 36%). These data should be interpreted with caution as no adjustments for multiplicity were made.

In addition, there were statistically significant and clinically meaningful improvements in a new composite index, the ACR CRISS (15), that showed evidence in support of abatacept. The ACR CRISS was designed to capture the global or holistic evaluation of the likelihood of improvement in early SSc. It is based on a probability score of 0.0 to 1.0 (no improvement to marked improvement, respectively, with an improvement of ≥0.60 considered clinically meaningful) and includes 2 steps. Step 1 assesses for worsening or incident cases of cardiopulmonary-renal involvement and assigns a score of 0.0. For those who do not meet the criteria for step 1, a probability score is calculated that incorporates changes in 5 physical or functional areas: MRSS (assessment of skin), FVC % predicted (assessment of lungs), HAQ DI (measure of patient function), PtGA, and PhGA. The median change in the ACR-CRISS score was 0.72 (IQR 0.99) with abatacept versus 0.02 (IQR 0.75) with placebo ($P = 0.03$), with the proportion of patients who improved by ≥0.60 significantly higher in the abatacept group. These results are similar to recent data from a phase III trial of tocilizumab (21) and highlight the importance of global assessment in a multisystem heterogeneous disease.

Study patients who received placebo experienced a greater number of AEs, AEs leading to discontinuation, and SAEs, which highlights the safety of abatacept in SSc when compared to those who received abatacept and other immunomodulatory therapies. These data are supported by findings from studies on other rheumatic diseases in which abatacept has been used with immunosuppressive therapy (27,28).

There were 3 deaths in the trial: 2 in the abatacept group and 1 in the placebo group. Both deaths in the abatacept group were related to scleroderma renal crisis, a challenging complication in early SSc. There was 1 additional case of scleroderma renal crisis in the abatacept group that did not result in death. All 3 cases occurred early in the disease (11–46 days after randomization), while the 1 case in the placebo group occurred 56 days after randomization. Inhibition of Treg cell function prior to reduction in the numbers and activity of pathogenic effector T cells in abatacept-treated patients could account for early flares but could also lead to eventual reduction in disease activity in SSc (29,30), though data are needed to validate this hypothesis.

In a prior pilot study of abatacept in SSc with molecular gene expression data obtained from skin (9), 4 of 5 patients who showed improvement with abatacept (as determined by change in MRSS) were in the inflammatory subset, and the remaining patient who showed improvement was in the normal-like subset. Improvement was accompanied by a decrease in gene expression for immune pathways, including the CD28 and CTLA-4 receptors targeted by abatacept. In this trial, we were able to test and support our a priori hypothesis that patients in the inflammatory subset would show a significant decline in MRSS during abatacept therapy. The results are especially interesting and novel considering the likely mechanism of action of abatacept as a targeted immunomodulator. On this basis, it would be expected that patients showing the inflammatory gene signature would be the most likely to exhibit treatment effect in the skin (Figure 3). The most prominent difference in MRSS changes, as seen in both the actual and estimated plots in Figure 3, occurred among patients in the inflammatory subset. There was a marked (and statistically significant) divergence of trajectory of MRSS change among patients in the inflammatory subset compared to the other intrinsic subsets, and no apparent effect of abatacept on the fibroproliferative subgroup (Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41055/abstract).

In contrast, for FVC change, which may reflect lung fibrosis (31), only the fibroproliferative subset showed trends in support of abatacept. This provides evidence of differing potential molecular pathology between the skin and lung in SSc and is consistent with the impact of abatacept on different disease features at different sites. It is also notable that the MRSS is improved by abatacept, whereas for FVC the apparent impact in patients in the fibroproliferative subset is to prevent decline. These data are consistent with results from a pilot study of abatacept (9), and they extend these findings, for the first time, to a large placebo-controlled trial that shows intrinsic skin gene expression subsets may predict differential response to a targeted biologic therapy. This has implications for stratification of cases according to intrinsic gene expression subsets, which would in turn maximize the number of informative SSc cases in clinical trials as well as potentially for future clinical practice.

Our study has many strengths. First, it was conducted at centers with substantial experience in scleroderma, and we were able to recruit patients with early active disease. Second, despite a large proportion of patients who received escape therapy (26%), we made every effort to continue follow-up of these patients in the trial and capture actual data. Third, we continued to build a body of evidence on the potential utility of the ACR CRISS as a primary end point that can be used as an alternative to changes in skin thickness, given the number of SSc studies using MRSS as the primary end point that have yielded negative results. Use of the ACR CRISS is also supported by statistically significant results of the proof-of-concept trial on lenabasum, in which the ACR CRISS was the primary outcome measure (32) and post hoc and planned analyses performed using data from phase II and III trials on tocilizumab, in which study medication could not be differentiated from placebo when the MRSS was the primary outcome measure (21,33). Last, one of the novel aspects of this study was the ascertainment of intrinsic gene expression–based subsets (inflammatory, fibroproliferative, or normal-like) at baseline that could be integrated into a subgroup analysis for potential treatment effect.

Study limitations include the lack of trials in early dcSSc with positive results, which could have provided guidance for the sample size calculation, and missing data, which we addressed using mixed models and multiple imputation (both valid under the missing at random assumption). We did not adjust for multiple comparisons or control for Type I error with secondary and exploratory end points; thus, we cannot make definitive statements about these outcomes, which should be considered hypothesis-generating. In deriving conclusions for our study, we considered both the clinical importance of abatacept effects, the totality of the study data, and the literature on other biologics in SSc. We allowed background low-dose prednisone at study entry (as done universally in trials of early SSc), and 14% of study patients were taking low-dose prednisone at baseline visit. The impact of background prednisone on skin gene expression data is unknown and should be explored in future analyses. We have not reported data on autoantibodies and their relationship to outcome measures, but we plan to perform these analyses in a central laboratory in the near future. Finally, although the patients in our study are representative of other recent trials in early dcSSc, they may differ from patients seen in clinics (34).

In summary, abatacept was well-tolerated in the present study, but change in MRSS was not statistically significant. Secondary outcome measures showed some evidence in favor of abatacept. A phase III trial should be conducted before drawing definitive conclusions about the efficacy and safety of abatacept in dcSSc.

ACKNOWLEDGMENTS

We wish to thank the participants, study coordinators, statistical analysts (Haoyan Zhong and Richard McLain), and the Data Safety Monitoring Board (Donald Tashkin, MD, Chair, University of California at Los Angeles; Thomas Medsger, Jr., MD, University of Pittsburgh, Pittsburgh, Pennsylvania; and Robert Parker, ScD: Massachusetts General Hospital, Boston).

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. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Khanna, Spino, Chung, Whitfield, Denton, Mehta, Molitor, Kafaja, Mayes, Hant, Matucci-Cerinic, Fox, Furst.

Acquisition of data. Khanna, Spino, Johnson, Chung, Whitfield, Denton, Mehta, Molitor, Steen, Lafyatis, Simms, Gill, Kafaja, Frech, Hsu, Domsic, Pope, Gordon, Mayes, Schiopu, Young, Sandorfi, Park, Hant, Bernstein, Chatterjee, Castelino, Ajam, Wang, Wood, Matucci-Cerinic, Distler, Bush, Fox, Furst.

Analysis and interpretation of data. Khanna, Spino, Chung, Whitfield, Denton, Berrocal, Franks, Mehta, Lafyatis, Kafaja, Pope, Schiopu, Hant, Castelino, Wang, Allanore, Matucci-Cerinic, Distler, Singer, Bush, Fox, Furst.

ROLE OF THE STUDY SPONSOR

This was an investigator-initiated trial designed by Dinesh Khanna, MD, MSc, and the Steering Committee. The industry funder, Bristol-Myers Squibb, had no role in collecting, analyzing, and interpreting the data. Mechanistic studies, including analysis of gene expression in skin biopsies, was funded by the NIH/National Institute of Allergy and Infectious Diseases (NIAID) through the University of Michigan Clinical Autoimmunity Center of Excellence. The data were stored at the University of Michigan. The manuscript was drafted by Drs. Khanna and Spino with input from other coauthors and was reviewed by Bristol-Myers Squibb and NIH/NIAID before final submission. No medical writer was involved in the creation of the manuscript. Publication of this article was not contingent upon approval by Bristol-Myers Squibb.

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.
2. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.
3. Kalogerou A, Gelou E, Mountantonakis S, Settas L, Zafiriou E, Sakkas L. Early T cell activation in the skin from patients with systemic sclerosis. Ann Rheum Dis 2005;64:1233–5.
4. Roumm AD, Whiteside TL, Medsger TA Jr, Rodnan GP. Lymphocytes in the skin of patients with progressive systemic sclerosis: quantification, subtyping, and clinical correlations. Arthritis Rheum 1984;27:645–53.
5. Fleischmajer R, Perlish JS, Reeves JR. Cellular infiltrates in scleroderma skin. Arthritis Rheum 1977;20:975–84.
6. Assassi S, Khanna D, Hinchcliff M, Steen VD, Hant F, Gordon JK, et al. Cell type specific gene expression analysis of early systemic sclerosis skin shows a prominent activation pattern of innate and adaptive immune system in the Prospective Registry for Early Systemic Sclerosis (PRESS) cohort [abstract]. Arthritis Rheumatol 2017;69 Suppl 10. URL: https://acrabstracts.org/abstract/cell-type-specific-gene-expression-analysis-of-early-systemic-sclerosis-skin-shows-a-prominent-activation-pattern-of-innate-and-adaptive-immune-system-in-the-prospective-registry-for-early-system/.
7. Ponsoye M, Frantz C, Ruzehaji N, Nicco C, Elhai M, Ruiz B, et al. Treatment with abatacept prevents experimental dermal fibrosis and induces regression of established inflammation-driven fibrosis. Ann Rheum Dis 2016;75:2142–9.
8. Boleto G, Guignabert C, Pezet S, Cauvet A, Sadoine J, Tu L, et al. T-cell costimulation blockade is effective in experimental digestive and lung tissue fibrosis. Arthritis Res Ther 2018;20:197.
9. Chakravarty EF, Martyanov V, Fiorentino D, Wood TA, Haddon DJ, Jarrell JA, et al. Gene expression changes reflect clinical response in a placebo-controlled randomized trial of abatacept in patients with diffuse cutaneous systemic sclerosis. Arthritis Res Ther 2015;17:159.
10. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.
11. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573–6.
12. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2017;2:11–8.
13. Milano A, Pendergrass SA, Sargent JL, George LK, McCalmont TH, Connolly MK, et al. Molecular subsets in the gene expression signatures of scleroderma skin. PLoS One 2008;3:e2696.

14. Khanna D, Clements PJ, Furst DE, Korn JH, Ellman M, Rothfield N, et al, for the Relaxin Investigators and the Scleroderma Clinical Trials Consortium. Recombinant human relaxin in the treatment of systemic sclerosis with diffuse cutaneous involvement: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2009;60:1102–11.
15. Khanna D, Berrocal VJ, Giannini EH, Seibold JR, Merkel PA, Mayes MD, et al. The American College of Rheumatology provisional Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis. Arthritis Rheumatol 2016;68:299–311.
16. Khanna D, Clements PJ, Volkmann ER, Wilhalme H, Tseng CH, Furst DE, et al. Minimal clinically important differences for the modified Rodnan skin score: results from the Scleroderma Lung Studies (SLS-I and SLS-II). Arthritis Res Ther 2019;21:23.
17. Wiese AB, Berrocal VJ, Furst DE, Seibold JR, Merkel PA, Mayes MD, et al. Correlates and responsiveness to change of measures of skin and musculoskeletal disease in early diffuse systemic sclerosis. Arthritis Care Res (Hoboken) 2014;66:1731–9.
18. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum 2000;43:2445–54.
19. Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger TA Jr. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. Ann Rheum Dis 2011;70:104–9.
20. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–40.
21. Khanna D, Lin CJ, Kuwana M, Allanore Y, Batalov A, Butrimiene I, et al. Efficacy and safety of tocilizumab for the treatment of systemic sclerosis: results from a phase 3 randomized controlled trial. Arthritis Rheumatol 2018, 70 Suppl 10. URL: https://acrabstracts.org/abstract/efficacy-and-safety-of-tocilizumab-for-the-treatment-of-systemic-sclerosis-results-from-a-phase-3-randomized-controlled-trial/.
22. Amjadi S, Maranian P, Furst DE, Clements PJ, Wong WK, Postlethwaite AE, et al, for the Investigators of the D-Penicillamine, Human RecombinantRelaxin, and Oral Bovine Type I Collagen Clinical Trials. Course of the modified Rodnan skin thickness score in systemic sclerosis clinical trials: analysis of three large multicenter, double-blind, randomized controlled trials. Arthritis Rheum 2009;60:2490–8.
23. Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, et al. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis Rheum 2007;56:2422–31.
24. Herrick AL, Peytrignet S, Lunt M, Pan X, Hesselstrand R, Mouthon L, et al. Patterns and predictors of skin score change in early diffuse systemic sclerosis from the European Scleroderma Observational Study. Ann Rheum Dis 2018;77:563–70.
25. Stifano G, Sornasse T, Rice LM, Na L, Chen-Harris H, Khanna D, et al. Skin gene expression is prognostic for the trajectory of skin disease in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheumatol 2018;70:912–9.
26. Khanna D, Furst DE, Hays RD, Park GS, Wong WK, Seibold JR, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Ann Rheum Dis 2006;65:1325–9.
27. Langford CA, Monach PA, Specks U, Seo P, Cuthbertson D, McAlear CA, et al. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis 2014;73:1376–9.
28. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non–life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:3077–87.
29. Langdon K, Haleagrahara N. Regulatory T-cell dynamics with abatacept treatment in rheumatoid arthritis. Int Rev Immunol 2018;37:206–14.
30. Frantz C, Auffray C, Avouac J, Allanore Y. Regulatory T cells in systemic sclerosis. Front Immunol 2018;9:2356.
31. Sargent JL, Milano A, Bhattacharyya S, Varga J, Connolly MK, Chang HY, et al. A TGFβ-responsive gene signature is associated with a subset of diffuse scleroderma with increased disease severity. J Invest Dermatol 2010;130:694–705.
32. Spiera R, Hummers L, Chung L, Frech T, Domsic R, Hsu V, et al. Safety and efficacy of lenabasum (JBT-101) in diffuse cutaneous systemic sclerosis subjects treated for one year in an open-label extension of trial JBT101-SSc-001 [abstract]. Ann Rheum Dis 2018;Suppl 2:52.
33. Khanna D, Lin CJ, Spotswood H, Siegel J, Jahreis A, Denton CP, et al. Evaluation of American College of Rheumatology provisional Composite Response Index in Systemic Sclerosis (ACR CRISS) in a phase 3 randomized controlled trial [abstract]. Arthritis Rheumatol 2018;70 Suppl 10. URL: https://acrabstracts.org/abstract/evaluation-of-american-college-of-rheumatology-provisional-composite-response-index-in-systemic-sclerosis-acr-criss-in-a-phase-3-randomized-controlled-trial/.
34. Villela R, Yuen SY, Pope JE, Baron M, and the Canadian Scleroderma Research Group. Assessment of unmet needs and the lack of generalizability in the design of randomized controlled trials for scleroderma treatment. Arthritis Rheum 2008;59:706–13.