Safety and efficacy of abatacept in early diffuse cutaneous systemic sclerosis: Results from the open-label extension of a phase II investigator-initiated randomized controlled trial

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Include full study protocol/link to full study protocol

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Summary (300 words—currently 298)

Background

We recently reported that abatacept was well tolerated with potential efficacy for early diffuse cutaneous systemic sclerosis (dcSSc) in a phase II placebo-controlled randomized trial. We report here the results of the six-month open-label extension (OLE) period.

Methods

This was a double-blind, randomized controlled trial with OLE conducted at 22 centers in the US, Canada, and the UK (clinicaltrials.gov NCT 02161406). Participants with dcSSc of < 3 years duration from first non-Raynaud symptom were treated for six months with subcutaneous abatacept 125 mg weekly after completion of 12 months of abatacept or placebo during the double-blind period. Safety and exploratory efficacy endpoints, including modified Rodnan skin score (mRSS), were assessed over the 18-month period. Descriptive statistics were performed including all participants who completed the double-blind period and received at least one dose of open-label treatment.

Findings

Eighty-eight participants were randomized in the double-blind period between September 22, 2014 and March 15, 2017, and 32 in each group completed the six-month OLE. Infections occurred in nine (12 events, one serious) and 11 (14 events, one serious) participants in the placebo-abatacept and abatacept-abatacept groups, respectively. There were no deaths during the OLE. Abatacept resulted in a mean(SD) improvement in mRSS of -6·6(6·43) at month 12, with further improvement in the open-label period, resulting in a mean(SD) improvement of -9·8(8·14) from baseline to month 18. Participants who initially received placebo experienced a

mean(SD) improvement in mRSS of -3·7(7·58) at month 12 and a mean improvement of -6·3(9·27) from baseline to month 18.

Interpretation

The six-month OLE did not identify any new safety signals for abatacept in the treatment of early dcSSc. Clinically meaningful improvements in mRSS were observed in both the abatacept and placebo groups when transitioned to open label treatment. These data support further studies of abatacept in dcSSc.

Funding

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Research In Context

Evidence before this study

We searched PubMed with the terms systemic sclerosis or scleroderma and a combination of systemic sclerosis with any of the following terms: CTLA4, abatacept, modified Rodnan skin score, clinical trials, and interstitial lung disease.

Activated T cells are implicated in the pathogenesis of early systemic sclerosis, particularly with respect to cutaneous disease. Animal models that mimic the early inflammatory skin changes seen in systemic sclerosis demonstrate that abatacept can prevent and induce the regression of dermal fibrosis. In addition to decreasing T cell activation, abatacept may mediate its anti-fibrotic effects by preventing the differentiation of circulating fibrocytes into myofibroblasts/fibroblasts. One pilot trial and recent analysis from an observational cohort showed beneficial effects on skin, joints, and disability.

Added value of this study

This study is the open label extension of a well-controlled Phase II placebo-controlled trial in patients with early systemic sclerosis to show a clinically significant—albeit not statistically significant—improvement of skin sclerosis, and clinically relevant improvement in disability and a new composite index in patients treated with abatacept. The safety profile was consistent with complications of systemic sclerosis, and with the safety profile of abatacept.

Implications of all the available evidence

Given the lack of disease-modifying treatment options for patients with early systemic sclerosis, combined with the morbidity and mortality associated with this disease, data from our trial provide hope for a potential future treatment. These data should be further investigated in an adequate, randomized, well-controlled, phase 3 trial before definitive conclusions can

be made about its risks and benefits.

Introduction

Systemic sclerosis (SSc) is an immune-mediated connective tissue disease characterized by inflammation and fibrosis of the skin and internal organs.[1] Participants with diffuse cutaneous systemic sclerosis (dcSSc) have high mortality rates, particularly those who experience progressive skin fibrosis.[2] Autologous hematopoietic stem cell transplantation (HSCT) has survival benefits in early dcSSc, but can be associated with significant toxicities and costs, and is usually reserved for participants with worsening internal organ involvement.[3,4] Nintedanib was recently approved for the treatment of SSc-associated interstitial lung disease, but options remain limited for disease modifying therapies aimed at the treatment of overall disease, including skin involvement.[5,6]

Several studies implicate activated T cells in the pathogenesis of early dcSSc, particularly with respect to cutaneous disease.[7] Skin biopsies from patients with early dcSSc are enriched with an inflammatory infiltrate comprised of activated T cells and macrophages in perivascular regions.[8-10] Abatacept is a CTLA4 immunoglobulin fusion protein that blocks T cell co-stimulation. Animal models that mimic the early inflammatory skin changes seen in dcSSc demonstrate that abatacept can prevent and induce the regression of dermal fibrosis.[11] In addition to decreasing T cell activation, abatacept may mediate its anti-fibrotic effects by preventing the differentiation of circulating fibrocytes into myofibroblasts/fibroblasts.[12]

A pilot six-month placebo-controlled study of ten participants with dcSSc showed that abatacept was well-tolerated with potential utility in the treatment of skin tightening.[13] Given these pre-

clinical and clinical data, we conducted a Phase II double-blind placebo-controlled clinical trial of weekly subcutaneous abatacept over 12 months in participants with early dcSSc (≤36 months disease) that was recently published.[14] This study showed numeric, but not statistically significant improvement in mean change from baseline to month 12 in modified Rodnan Skin Score (mRSS, the primary endpoint) with abatacept. In addition, abatacept was found to be safe, and resulted in statistically significant and clinically meaningful changes in secondary outcome measures, including the Health Assessment Questionnaire disability index (HAQ-DI) and the composite index, the American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS).[14,15] At the completion of the double-blind phase, all participants were eligible to transition to open-label treatment with weekly subcutaneous abatacept for an additional six months. The aim of this report is to describe the safety and exploratory efficacy outcomes through month 18, including the six-month open-label extension period.

Methods

Study design

This clinical trial was an investigator-initiated Phase II double-blind, randomized controlled trial with an open-label extension phase conducted at 22 centers in the US, Canada, and the UK (clinicaltrials.gov NCT 02161406) comparing the safety and efficacy of subcutaneous abatacept to placebo in participants with early dcSSc. Each participating site obtained approval from their local institutional review board or ethics committee. The study design and participant inclusion and exclusion criteria have been previously published and the study protocol is available from the corresponding author.[14]

Participants

Participants were 18 years of age or older and fulfilled the 2013 American College of Rheumatology/European Union League Against Rheumatism classification criteria for SSc,[16] with diffuse cutaneous involvement as defined by LeRoy and Medsger.[17] Eligible participants had to have either 1) disease duration ≤18 months from the time of the first non-Raynaud phenomenon manifestation and mRSS ≥10 and ≤35 units at the time of screening; or 2) disease duration >18 to ≤36 months, mRSS of ≥15 to ≤45 units, as well as evidence of active disease at the screening visit compared to the participant's last visit in the prior six months. Active disease was defined as at least one of the following: 1) increase of ≥ three units on mRSS; 2) involvement of one new body area with increase of ≥ two mRSS units; 3) involvement of two new body areas with increase of ≥one mRSS unit, and/or 4) presence of one or more tendon friction rubs. All participants provided written informed consent prior to any study procedures. The study was conducted in accordance with the Declaration of Helsinki.

Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive either 125 mg SC abatacept weekly or matching placebo (provided by Bristol-Myers Squibb) for the first 12 months of the study. Randomization was stratified by duration of dcSSc (≤18 months vs. >18 to ≤36 months). Escape therapy with non-biologic immunomodulatory agents was permitted at month six for participants with worsening dcSSc. At month 12, all participants in the abatacept and placebo groups transitioned to open-label therapy with 125 mg SC abatacept weekly for up to six additional months. The Data Coordinating Center (DCC) at the University of Michigan prepared the

randomization schedule, using computer-generated block randomization with random block sizes of two and four (known only by the DCC). The study staff (including the research pharmacists, outcomes assessors and those analyzing the data) and participants were blinded with regard to the treatment assigned.

Procedures

Eligible participants were assessed for adverse events, physical examination, and mRSS at baseline and months one, three, six, nine, and 12 during the double-blind phase, then at months 14, 16, and 18 during the open-label phase. HAQ-DI (0-3), and patient and physician global assessments of overall disease by visual analogue scale (0-10, higher score denoting worse symptoms) were collected at baseline and months three, six, 12 and 18, while pulmonary function tests (PFT) were obtained at baseline and months six, 12, and 18.

Outcomes

The primary efficacy endpoint was change from baseline in mRSS at month 12 for the double-blind portion of the study as previously reported.[14] Exploratory efficacy endpoints included changes from baseline to month 18 in mRSS, percentage of participants with >five units improvement in mRSS (greater than the minimal clinical important difference (MCID),[18] %predicted forced vital capacity (FVC), HAQ-DI, patient and physician global assessments, and the American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS). Safety was assessed by the number of participants with at least one adverse event, infectious AE, AE leading to withdrawal, or serious adverse event (SAE). The number of SAEs were reported by system organ class.

Statistical Analysis

Descriptive statistics of safety and exploratory efficacy endpoints by original randomized treatment group are provided separately for the double-blind and open-label treatment periods. This approach, which includes all measures without censoring for escape therapy (the principle approach in the primary double-blind analyses), allows for more interpretable conclusions about the impact of continued abatacept in participants randomized to abatacept and the early abatacept experience in participants randomized to placebo. All randomized participants who received at least one dose of double-blind or open-label abatacept (modified intent-to-treat population) are included in the double-blind and open-label analyses, respectively. Summary statistics (e.g., means and standard deviations [SD]) of observed data (i.e., with no imputation for missing data) were calculated. SAS version 9·4 was used for all statistical analyses.

Role of the Funding Source

This was an investigator-initiated trial designed by corresponding author and the Steering Committee. The industry funder of the study, Bristol-Myers Squibb, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The data was stored at the University of Michigan. No medical writer was involved in the creation of the manuscript. It was reviewed by Bristol-Myers Squibb prior to final submission but publication of this article was not contingent upon approval by Bristol-Myers Squibb. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Eighty-eight participants were randomized in the double-blind period of the study between September 22, 2014 and March 15, 2017 (Figure 1). Forty-four participants were originally assigned to receive weekly subcutaneous placebo (PLB group) and 44 participants were originally assigned to receive weekly subcutaneous abatacept 125 mg (ABA group). At month 12, 34 (77%) participants in the PLB group and 33 (75%) participants in the ABA group transitioned to open-label treatment with 125 mg weekly subcutaneous abatacept. Thirty-two participants in each group completed the Month 18 assessments. During the open-label phase, three participants discontinued the study (two originally assigned to PLB and one originally assigned to abatacept). Escape therapy was received by 13 participants originally assigned to PLB (12 who started during the double-blind phase and one who started during the open-label extension) and six participants originally assigned to ABA (five who started during the double-blind phase and one who started during the open-label extension) (Figure 1).

Baseline characteristics were similar between participants who were randomly assigned in the double-blind period and those who transitioned to open-label treatment (Table 1).

Abatacept resulted in a mean (SD) improvement in mRSS of -6·6 (6·43) at month 12 during the double-blind period, with further improvement in the open-label period, resulting in a total mean (SD) improvement of -9·8 (8·14) from baseline to month 18 (Figure 2 and Table 2). Furthermore, the participants who received placebo during the double-blind period experienced a mean (SD) improvement in mRSS of -3·7 (7·58) at month 12 and additional benefits during the open-label period for a total mean improvement of -6·3 (9·27) from baseline to month 18. The

proportion of participants who experienced > five units improvement in mRSS was 36% in the ABA group at month 12 and increased to 72% after six months of open label treatment. Likewise, the percentage of participants achieving the MCID for mRSS was 27% in the placebo group at month 12 and increased to 65% at month 18.

Among the secondary outcome measures, the %predicted FVC declined in both groups during the double-blind period, with a mean (SD) decrease of -2·7 (5·48)% in the placebo group and -1·6 (7·95)% in the abatacept group at month 12. However, during the open-label period both treatment groups experienced improvements in %predicted FVC such that the mean change from baseline to month 18 was minimal (-0·3 (6·31)% in the placebo to abatacept group and 0·9 (9·9)% in the continuous abatacept group) (Figure 3A, Table 2). Participants treated with abatacept during the double-blind period experienced an improvement in mean HAQ-DI at month 12, while those treated with placebo had worsened disability; however, the HAQ-DI remained stable in both groups during the open-label phase (Figure 3B, Table 2). Patient global VAS scores initially worsened and then improved during the double-blind phase of the study, with maintenance of improvements during the open-label phase (Figure 3C). In contrast, the physician global VAS scores improved in the treatment arm during the double-blind phase with a mean (SD) decrease of -1·4 (1·52) in the abatacept group compared with -0·3 (1·89) in the placebo group (Table 2). The physician global VAS improved in both abatacept and placebo groups during the open label treatment period (Figure 3D). The median ACR CRISS score was significantly greater in the abatacept group compared with the placebo group at month 12 (0·72 (IQR 0·99) vs 0·02 (IQR 0·75)). Both groups experienced improvement in CRISS scores during

the open label treatment period, with median scores of 0·99 (IQR 0·94) in the continuous abatacept group and 0·35 (IQR 0·99) in the placebo to abatacept group at month 18.

Abatacept was well-tolerated with no new safety signals throughout the double-blind and open label portions of the study. In general, AEs, infectious AEs, AEs leading to withdrawal, and SAEs were more common in the placebo group compared with the abatacept group during the double-blind period, and occurred in smaller proportions of participants in both groups during the open-label period than the double-blind period (Table 3). During the open-label phase, treatment emergent adverse events (TEAE) that led to study drug discontinuation included one participant in the PLB-ABA group (SAE ventricular fibrillation/cardiac arrest), and two participants in the ABA-ABA group (tachycardia and URI/night sweats, both not SAEs). Infections occurred in nine (12 events) and 11 (14 events) participants in the PLB-ABA and ABA-ABA groups, respectively, and one event in each group was considered serious: one participant in the PLB-ABA group suffered from an infected Bartholin's cyst and one participant in the ABA-ABA group had cellulitis (Table 3). Other serious AEs included one participant in the PLB-ABA group who experienced ventricular fibrillation with cardiac arrest and three participants in the ABA-ABA group with gastric antral vascular ectasia related to underlying SSc, pancreatitis, and pregnancy, respectively. Regarding AEs of special interest during the open label phase, seven participants experienced a decrease in hemoglobin > 2 gm/dL, five in the PLB-ABA group, (two of whom had a drop that resulted in hemoglobin < 8gm/dL) and two in the ABA-ABA group. There were no deaths reported during the open label period.

Discussion

This open-label extension of this Phase II randomized controlled clinical trial showed that abatacept is safe in participants with early dcSSc for up to 18 months and suggested preliminary efficacy for various outcome measures. Infectious AEs were less common in participants initially treated with abatacept than placebo during the blinded phase of the study. In addition, lower rather than higher proportions of participants experienced infectious complications in both groups upon transitioning to open-label treatment. Although the primary endpoint of change in mRSS from baseline to month 12 was not statistically different in the abatacept compared with the placebo group, exploratory analyses suggest potential disease modifying effects of abatacept in participants with SSc.

The treatment of early dcSSc, including skin involvement remains a challenge. Current options include mycophenolate mofetil, methotrexate, and cyclophosphamide,[6] however none of them has been shown to be effective in randomized controlled trials. In addition, improvements in skin involvement is modest, and these therapies can be complicated by cytopenias, infections and gastrointestinal toxicities. HSCT also leads to improvements in skin fibrosis and prevention of pulmonary deterioration but has high associated risks and costs, and requires specialty, multi-disciplinary management.[3,4]

Similar to other recent clinical trials, mRSS showed numerical improvement in the abatacept group compared to the placebo group but with marked individual heterogeneity. This occurred despite enrichment strategies that were included in the trial design. In the double-blind portion of the ASSET trial, skin gene expression signature influenced change in outcome measures over 12

months, highlighting the molecular heterogeneity in early disease. There are additional data in the double-blind and open-label extension phases of the study that provide us more confidence in a disease modifying effect of abatacept in participants with early dcSSc. As an example, both groups experienced improvements in %predicted FVC during the open-label phase. %predicted FVC is an objective outcome measure and is now considered a surrogate measure for SSc-associated interstitial lung disease. In addition, the ACR CRISS score improved significantly more in the initial abatacept than placebo group at month 12, with further improvements in both groups at month 18. The HAQ-DI, patient and physician global assessments also improved in both groups during open-label treatment with abatacept, with the exception of physician global VAS, where the participants initially assigned to placebo experienced a much greater improvement once transitioned to open-label treatment than those initially assigned to abatacept.

Abatacept is well-tolerated in participants with early dcSSc with a safety profile that was better than placebo in this study. In particular, abatacept does not appear to increase the risk for infectious complications. The two deaths that occurred in the double-blind period in the abatacept group were related to scleroderma renal crisis, a severe complication that can affect up to 25% of participants with early dcSSc,[19] and no participants died during open label treatment with abatacept.

Many novel agents are currently being evaluated for the treatment of skin tightening in participants with early dcSSc.[20,21] Our results are similar to those from the Phase II faSScinate study (tocilizumab vs. placebo) in that clinically important but statistically insignificant improvements in mRSS were observed during the double-blind phase, followed by further

improvements in the open-label period.[22,23] Likewise, stabilization in %predicted FVC was observed comparing baseline values to the end of the open-label extension period in both clinical trials. However, infectious AEs were more common in those treated with tocilizumab than placebo in the faSScinate study, while they were less common in those treated with abatacept compared with placebo in our study. Other biologic therapies, such as belimumab, rituximab, and fresolimumab, have been evaluated for the treatment of early dcSSc in small, single-center studies, but larger studies are necessary for more definitive results.[24-27]

The present study had some limitations, particularly with respect to the open-label uncontrolled nature of the study. It is possible that survivor bias affected our study results, as participants who completed the 12 months of double-blind therapy and entered the open-label phase were likely more responsive to therapy or had less severe disease. In addition, the study was not powered for formal statistical comparison of the two treatment arms and all results from the open-label period must be considered exploratory. Third, missing data was unavoidable despite rigorous monitoring during the conduct of the clinical trial.

The strengths of this study include the sole participation of centers with substantial clinical trials experience in systemic sclerosis. Second, there was a low discontinuation rate during the open-label period, with only 3/67 (4%) of participants discontinuing the study. Third, we obtained further information on the sensitivity to change in the ACR CRISS score over an 18-month period of time. This is particularly useful as this outcome measure is now being used as the primary end point for several clinical trials in early dcSSc.

In summary, the results of this open-label study support those of the double-blind period in that abatacept appears to be very safe in participants with early dcSSc. Exploratory outcome measures during the open-label period, including the composite ACR CRISS score, indicate that abatacept may promote overall global improvement in these participants. A Phase III clinical trial is necessary to definitively assess the safety and efficacy of abatacept in this participant population.

Data Sharing Statement

Deidentified data is available from the corresponding author. The interested researchers are encouraged to complete a 1-page proposal highlighting the objectives, planned analyses, and the data elements that are required for proposed analysis. (The whole dictionary will be posted on the University of Michigan Scleroderma Program website). The proposal is reviewed by the steering committee and if approved, the data will be shared in the mutually agreed format. The study protocol is available from the corresponding author.

Contributors

Lorinda Chung: Contributed to study design, recruitment, and wrote the initial draft.

Cathie Spino: Contributed to study design, was PI for the Data Coordinating Center, and participated in the statistical analysis.

Richard McLain: participated in the statistical analysis

Sindhu R. Johnson: Recruitment, and provided input on the submitted draft.

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David A. Fox: Recruitment, and provided input on the submitted draft.

Daniel E. Furst: Recruitment, and provided input on the submitted draft.

Dinesh Khanna: Contributed to study design, PI of the project, recruitment, approved final draft and takes responsibility of data integrity.

Declaration of Interests

Lorinda Chung: Grant support: United Therapeutics, Boehringer Ingelheim; Consultant/Advisory Board: Boehringer Ingelheim, Mitsubishi Tanabe, Eicos Sciences, Inc; Data Safety Monitoring Board: Reata

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Table 1: Demographic and baseline disease characteristics

	Placebo (N=44)	Abatacept (N=44)	Pbo-Aba (N=34)	Aba-Aba (N=33)
Age, Years, mean (SD)	49 (13)	50 (12)	51 (12)	49 (12)
Female, N (%)	35 (80)	31 (70)	27 (79)	27 (82)
White, N (%)	37 (84)	35 (80)	30 (91)	27 (79)
Not Hispanic or Latino, N (%)	36 (82)	40 (91)	29 (88)	32 (94)
Disease Duration, Years[1], mean (SD)	1·52 (0·79)	1·66 (0·84)	1·50 (0·77)	1·70 (0·82)
Disease ≤18 Months, N (%)	27 (61)	26 (59)	22 (65)	18 (55)
mRSS, mean (SD)	21·6 (7·33)	23·3 (7·95)	21·1 (6·59)	23·4 (8·47)
FVC% Predicted, mean (SD)	86·5 (16·60)	84·2 (13·50)	88·5 (16·49)	85·9 (11·34)
DLCO%[2,3], mean (SD)	76·4 (18·44)	79·6 (18·12)	78·7 (19·23)	84·3 (16·09)
Patient Global Assessment[4], mean (SD)	4·3 (2·56)	3·9 (2·21)	4·1 (2·63)	3·4 (2·04)
HAQ-DI[5], mean (SD)	1·0 (0·70)	1·1 (0·72)	0·9 (0·69)	1·0 (0·69)
Physician Global Assessment[4], mean (SD)	4·8 (1·67)	4·8 (1·66)	4·7 (1·72)	4·6 (1·68)
TJC with any TJ, mean (SD), N (%)	5·4 (7·15), 21 (48)	3·6 (5·73), 28 (64)	4.1 (6·06), 19 (56)	4·2 (6·37), 15 (45)
SJC with any SJ, mean (SD), N (%)	39 (5·85), 21 (48)	3·6 (5·62), 21 (48)	3·9 (6·49), 13 (38)	3·0 (4·94), 14 (42)
Large Joint contractures, N (%)	32 (73)	31 (70)	26 (76)	24 (73)
Friction Rub, N (%)	13 (30)	19 (43)	12 (35)	14 (42)
ESR (mm/hr), mean (SD)	17·6 (15·84)	17·9 (15·20)	17·2 (16·50)	15·1 (11·24)
hsCRP, mean (SD)	1·03 (1·394)	1·09 (1·173)	0·94 (1·493)	0·89 (0·893)
Anti-Centromere Positive, N (%)	1 (2)	3 (7)	1 (3)	2 (6)
Anti-RNA polymerase-3 Positive, N (%)	17 (40)	22 (51)	13 (41)	19 (59)
Anti-topoisomerase, N (%)	7 (17)	9 (21)	4 (13)	6 (19)
Use of Prednisone, N (%)	5 (11)	7 (16)	2 (6)	7 (21)

[1] :Disease onset was defined as first non-Raynaud's sign or symptoms, [2]: Predicted, [3]: Corrected for hgb, [4]: Theoretical range 0-10, [5]:Theoretical range 0-3.
mRSS=modified Rodnan skin score, SD= Standard deviation, HAD-DI= Health assessment questionnaire- disability index, FVC=Forced vital capacity, DLCO=Diffusion capacity of carbon monoxide, TJC= Tender joint count, SJC= Swollen Joint count, ESR= Erythrocyte sedimentation rate , hsCRP= high sensitivity C-Reactive Protein

Table 2. Change from baseline to month 12 (double-blind period) or month 18 (including open-label period) in mRSS and exploratory end points (intent-to-treat population; observed data)

	Double-Blind Period, Month 12		Open-Label Period, Month 18	
Change from baseline	**Placebo n=44**	**Abatacept n=44**	**Placebo-Abatacept n=34**	**Abatacept-Abatacept n=33**
mRSS				
Mean (SD)	-3·7 (7·58)	-6·6 (6·43)	-6·3 (9·27)	-9·8 (8·14)
Decrease >5 units[1], n/N (%)	12/38 (27)	16/34 (36)	20/31 (65)	23/32 (72)
HAQ-DI, Mean (SD)	0·09 (0·432)	-0·09 (0·457)	0·04 (0·471)	-0·13 (0·427)
Clinician global VAS, Mean (SD)	-0·3 (1·89)	-1·4 (1·52)	-1·0 (1·96)	-1·3 (2·12)
Patient global VAS, Mean (SD)	-0·4 (3·30)	0·0 (2·24)	-0·6 (3·28)	-0·4 (2·08)
% FVC[2], Mean (SD)	-2·7 (5·48)	-1·6 (7·95)	-0·3 (6·31)	0·9 (9·90)
% DLCO[2,3], Mean (SD)	-2·1 (10·80)	0·7 (12·49)	-2·4 (11·67)	0·9 (11·94)
TJC mean change, Mean (SD)	-0·9 (6·52)	-1·1 (8·18)	-1·6 (3·91)	-2·5 (6·37)
SJC mean change, Mean (SD)	-1·5 (4·10)	-0·7 (3·92)	-1·5 (4·39)	-1·7 (4·17)
ACR CRISS, Median (IQR)	0·02 (0·75)	0·72 (0·99)	0·35 (0·99)	0·99 (0·94)

[1]: Indicates improvement; [2]: Predicted; [3]: Corrected for hgb; mRSS=modified Rodnan skin score, SD= Standard deviation, HAD-DI= Health assessment questionnaire- disability index, VAS=Visual analog scale, FVC=Forced vital capacity, DLCO=Diffusion capacity of carbon monoxide, TJC= Tender joint count, SJC= Swollen Joint count, ACR CRISS= American College of Rheumatology combined response index in systemic sclerosis, IQR= Interquartile range.

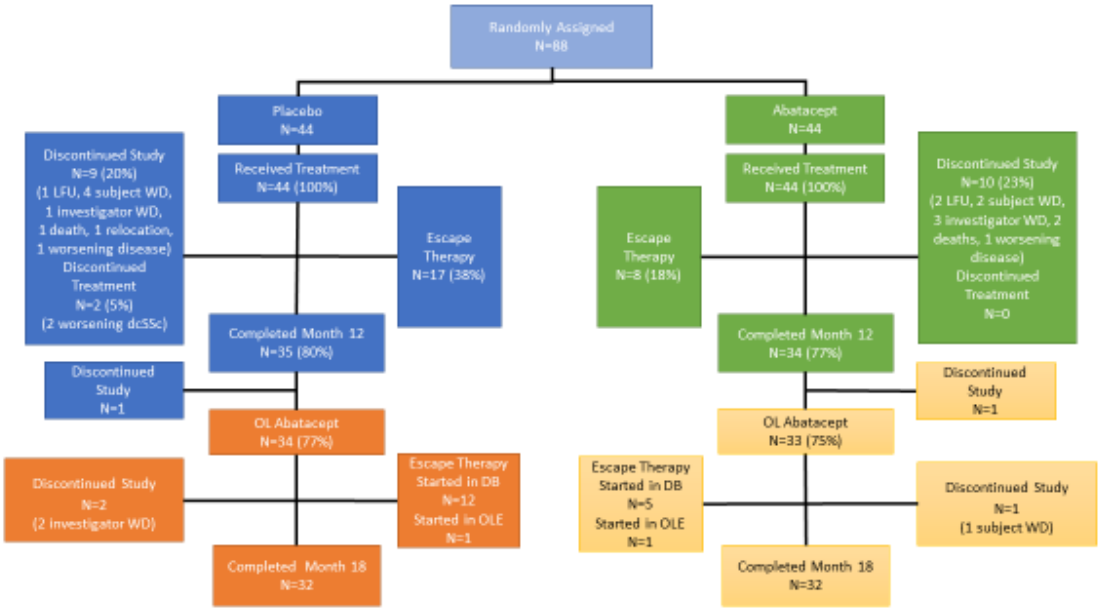
Table 3: Adverse events (safety population)

	Double-blind period		Open-label period	
	Placebo N=44	**Abatacept N=44**	**Placebo-Abatacept N=34**	**Abatacept-Abatacept N=33**
Participants with ≥ 1 AE, n (%)	**40 (91)**	**35 (80)**	**23 (68)**	**25 (76)**
Participants with ≥ 1 infectious AE, n (%)	**25 (57)**	**19 (43)**	**9 (26)**	**11 (33)**
Participants with AEs leading to withdrawal, n (%)	**6 (14)**	**5 (11)**	**1 (3)**	**2 (6)**
Participants with ≥ 1 SAE, n (%)	**12 (27)**	**9 (20)**	**2 (6)**	**4 (12)**
Infections and Infestations (# SAE/# Participants)	**2/2**	**2/2**	**1/1**	**1/1**
Cellulitis, n	..	1	..	1
Mastoiditis, n	..	1	..	..
Paronychia, n	1	..	..	..
Pneumonia, n	1	..	..	..
Infected Bartholin's cyst, n	..	..	1	..
Cardiac Disorders (# SAE/# Participants)	**6/3**	**2/2**	**1/1**	**0/0**
Atrial flutter with conduction defects, n	1	..	..	..
Cardiac arrest, n	1	..	..	..
Congestive heart failure, n	1	..	..	..
Myocardial infarction/acute coronary syndrome, n	1	1	..	..
Pulmonary arterial hypertension, n	1	1	..	..
Pericardial effusion, n	..	1	..	..
Worsening AV block, n	1	..	..	..
Ventricular fibrillation cardiac arrest, n	..	..	1	..
Gastrointestinal Disorders (# SAE/# Participants)	**6/6**	**3/2**	**0/0**	**2/2**
Anemia, n	1	..	..	..
Cholecystitis, n	1	..	..	..
Dysphagia, n	1	1	..	..
Erosive esophagitis, n	1	..	..	..
Gastric Antral Vascular Ectasia, n	1	..	..	1
Gastric Antral Vascular Ectasia with anemia, n	1	..	..	..
Melena, n	..	1	..	..
Pseudo-obstruction, n	..	1	..	..

Pancreatitis, n	..	..	..	1
Gynecological (# SAE/# Participants)	..	..	..	**1/1**
Pregnancy, n	..	..	..	1
Neoplasm Disorders (# SAE/# Participants)	**1/1**	**1/1**	**0/0**	**0/0**
Basal cell skin carcinoma, n	1	..	..	..
Squamous cell skin carcinoma, n	..	1	..	..
Respiratory Disorders (# SAE/# Participants)	**0/0**	**1/1**	**0/0**	**0/0**
Respiratory failure, n	..	1	..	..
Renal Disorders (# SAE/# Participants)	**1/1**	**3/3**	**0/0**	**0/0**
Scleroderma renal crisis, n	1	3	..	..
Vascular Disorders (# SAE/# Participants)	**1/1**	**0/0**	**0/0**	**0/0**
Digital ischemia, n	1	..	..	..
Mental Disorders (# SAE/# Participants)	**1/1**	**0/0**	**0/0**	**0/0**
Depression with suicidal ideation, n	1	..	..	..

AE= Adverse event; SAE= Serious adverse event

Figure 1. Flow chart showing the disposition of study participants



LFU = lost to follow-up, subject WD = subject withdrew, investigator WD = investigator withdrew subject, dcSSc = diffuse cutaneous scleroderma

Figure 2. Mean change (95% CI) in mRSS from baseline to month 18 (intent-to-treat population; observed data)

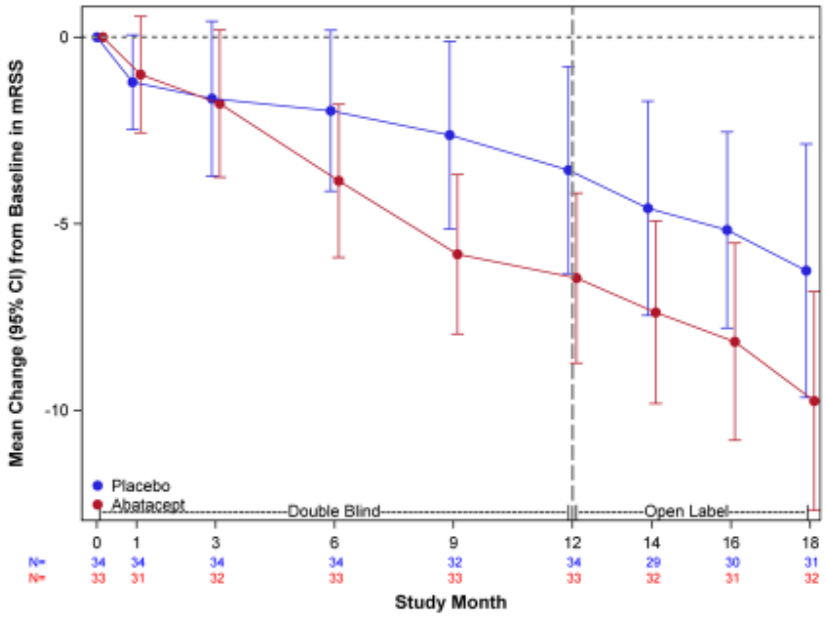


Figure 3. Mean change (95% CI) in exploratory endpoints from baseline to month 18 (intent-to-treat population; observed data)