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ADRCs for SSc Hand Function

Adipose-Derived Regenerative Cell Transplantation in Systemic Sclerosis: Scleroderma Treatment with Celution Processed Adipose Derived Regenerative Cells- a Randomized Clinical Trial

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Abstract

Objective: Hand dysfunction is common in systemic sclerosis (SSc). The objective of this study was to evaluate the capacity of autologous Adipose-Derived Regenerative Cells (ADRCs) to improve hand function in SSc patients.

Methods: The STAR Trial was a prospective, randomized, double-blind trial of ADRCs injected into each finger digit of subjects with SSc. The primary endpoint was change in hand function at 24 and 48 weeks assessed using the Cochin Hand Function Scale (CHFS). Secondary endpoint included the change in Health Assessment Questionnaire-Disability Index (HAQ-DI) at 48 weeks. Separate analysis of subjects with diffuse (dcSSc) and limited cutaneous SSc (lcSSc) was pre-specified.

Results: 88 subjects were randomized to ADRCs (n=48; 32 dSSc:16 lcSSc) or Placebo (n=40; 19 dcSSc: 21 lcSSc). The primary end point was numerically higher for the ADRC group but did not achieve statistical significance (8.9±10.5 vs. 11.0±12.5, p= 0.299). For subjects with dcSSc the between group difference for the CHFS at 48 weeks was 6.3 points (nominal p=0.069). The HAQ-DI secondary endpoint exhibited a difference of 0.17 points (nominal p=0.044) for dcSSc group. 52% of ADRC-treated subjects with dcSSc reported improvement greater than the minimal clinically important difference for both CHFS and HAQ-DI compared with 16% in the placebo group (nominal p=0.016). Small volume adipose harvest and ADRC-treatment was well-tolerated.

Conclusion: While the primary end point of this trial was not achieved, efficacy trends were observed in subjects with dcSSc. Adipose harvest and ADRC injection were demonstrated to be feasible. Further clinical trial of this intervention in dcSSc is warranted.

INTRODUCTION

Impairment of hand function is universal in patients with systemic sclerosis (SSc)[1]. While associated with less clinical morbidity than other complications of SSc[2], impaired hand function in SSc has a significant impact on quality of life, participation in the workforce, and activities of daily living[3, 4]. Despite the significance of hand dysfunction in SSc, there are few treatments with demonstrated effectiveness that specifically address this problem.

Human adipose tissue has been shown to be a rich source of cells with the potential to impact the inflammatory, vascular, and fibrotic sequelae of SSc[5, 6]. When isolated from adipose tissue using a standardized cell processing approach that meets standards for clinical use, this population is referred to as Adipose-Derived Regenerative Cells (ADRCs)[7]. Preclinical studies have shown that ADRCs promote increased vascularity and decreased fibrosis in a mouse model of SSc[5]. A 12 patient open label, single center trial has reported data obtained following injection of ADRCs into the subcutaneous interdigital webspace of the fingers of patients with moderate to severe hand dysfunction due to SSc[8-10]. This study reported substantial improvement in hand function as early as two months after treatment that was sustained for up to three years[10].

In order to address the limitations of a single-arm, open label trial, we executed the Scleroderma Treatment with Celution Processed Adipose Derived Regenerative Cells (STAR) clinical trial that enrolled 88 SSc subjects using a randomized, double blind, placebo-controlled design.

PATIENTS AND METHODS

Study Overview

The STAR trial (Clinicaltrials.gov NCT02396238) was a prospective, randomized, double-blind, placebo-controlled, multi-center device trial (RCT) to assess safety and efficacy of ADRCs delivered by subcutaneous injection for the treatment of impaired hand function due to SSc. The study enrolled male and female subjects aged ≥18 and ≤70 years with a diagnosis of SSc according to the 2013 ACR/ EULAR classification and sub-classified as diffuse cutaneous SSc (dcSSc) with duration >5 years or with limited cutaneous SSc (lcSSc) by the Leroy criteria from May 2015 to September 2017. Subjects also had to have moderate to severe hand dysfunction as evidenced by a Cochin Hand Function Scale[11, 12] (CHFS) score of ≥20 units. Full inclusion/exclusion criteria are provided in Supplemental Data. Subjects were permitted to continue use of systemic steroids and immunosuppressant medications provided dosing was stable and within pre-specified limits. This study was performed in compliance with the Helsinki Declaration. Institutional Review Board approval was obtained at each site and all subjects signed informed consent.

Randomization

Subjects were randomized via an interactive web response system into one of two parallel arms in a 1:1 ratio to receive either ADRCs or placebo. Subjects were assigned the next available number in a computer - generated randomization schedule and received the treatment that corresponded to their randomization number. Randomization occurred after written informed

consent had been obtained, all screening procedures had been completed, the subject's eligibility for the study had been confirmed, and just prior to the start of the liposuction procedure. A CONSORT flow chart showing subject enrollment and analysis is shown in Supplemental Figure 1.

Preparation and Injection of ADRCs

After screening and randomization subjects underwent a small volume (100mL-360mL) tumescent liposuction using manual aspiration under local anesthesia with or without conscious sedation. Tissue was then processed using the automated Celution® System (Paracrine Inc. San Diego, CA) according to the manufacturer's instructions. Briefly, tissue was injected into the processing chamber, washed, mixed with Celase® (a blended enzymatic reagent), and continuously mixed at ~37°C for 20 minutes. The ADRCs were then pumped to a centrifuge chamber where they were concentrated and washed. ADRCs were released for injection if they met cell viability and dose limits and had a negative gram stain. An aliquot of the cell and placebo product was sent for additional bacterial testing using the BacT system. Placebo comprised lactated Ringer's solution visually matched to the ADRCs (to ensure retention of blinding) by addition of 0.1-0.2mL of the subject's blood. Cell count and viability were determined using the NC-100™ NucleoCounter® automated cell counting system (Chemometec, Allerod, Denmark). In order to maintain blinding, an un-blinded technician not involved with patient enrollment, care, or outcome assessment prepared a placebo syringe containing lactated Ringer's solution visually-matched to the ADRCs by addition of 0.1-0.2mL of the subject's blood. With the sole exception of this technician, all Sponsor and study personnel and participating staff remained blinded to treatment group throughout the procedure and the full duration of the study.

ADRCs (four million cells per finger or placebo) were injected under conscious sedation, neuraleptanalgesia, or topical analgesia into the subcutaneous space along the neurovascular bundle on each side of each finger (0.5mL/injection) using a 25G needle.

Endpoints

The co-primary endpoint was change in CHFS at 24 and 48 weeks. The CHFS is a validated patient-reported outcome for assessment of hand function in SSc[11, 12]. The instrument assesses five domains rated from 0 (no problems performing the task) to five (impossible to perform) with a total score range from 0 to 90. Two secondary endpoints were pre-specified: change in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at 48 weeks and change in Raynaud's Condition Score (RCS) at 48 weeks. The HAQ-DI is a validated instrument for the assessment of disability[13, 14]. The final score ranged from zero to three; higher scores indicated greater disability. The Raynaud's Condition Score (RCS) is a diary-based tool in which subjects record a score (from 0-10) that best indicates the difficulty they had each day with their Raynaud's condition[15]. The RCS is the average score for the 14 days prior to the study visit. Exploratory endpoints included assessment of CHFS, RCS, and HAQ-DI at various time points. Other exploratory endpoints included the EQ-5D (for assessment of general health-related quality of life)[16], patient and physician global assessment of SSc (captured using a 0-10 Visual Acuity Scale (VAS) for activity, damage, and overall subject health), hand corner distances (1st corner is distance between the tips of the thumb and index finger at maximum hand extension; 2nd corner distance is the distance from the tips of the index and small fingers at maximum hand

extension), grip and pinch strength assessed using a dynamometer, a modified Rodnan Skin Score assessing only the hand (three sites/hand: the back of each hand and the first and second phalanges of most affected finger in each hand), hand volume[17], finger circumference, and digital ulcer counts. The statistical analysis plan pre-specified separate analysis of data from all subjects and subset analysis by disease subtype (dcSSc and lcSSc).

Safety was assessed throughout the study by capture of adverse events that were mapped into MedDRA, version 17.1, by system organ class and preferred terms.

Statistical analysis

In a pilot trial[9] in SSc, the change in the CHFS score from baseline to six months was 27.3±17.2 units (mean ± standard deviation). A power calculation showed that a sample size of 41 subjects per treatment group was needed to provide 90% power to detect a between-group difference of ≥13.7 points in the primary end point (alpha = 0.025; to adjust for assessment at both 24 and 48 weeks) assuming that 50% of the 27.3 point response on the CHFS observed in the pilot was attributable to the placebo effect.

Safety and efficacy endpoints were summarized by treatment group using descriptive statistics for quantitative variables and frequencies/percentages were used for categorical variables. Between-group comparisons were performed using analysis of covariance (ANCOVA) models with effects for the baseline value of the variable. Time to event analysis (time to formation of a new digital ulcer) was determined through Kaplan Meier analysis with log-rank testing and hazard ratio. *Post hoc* analyses of responder rates were performed using the Fishers Exact Test. Except where explicitly stated, no adjustments for multiple comparisons have been made to the p-values of secondary or exploratory endpoints. All data described herein are from the Intent-to-Treat (ITT) data set.

The minimal clinically important difference (MCID) for the CHFS instrument in subjects with significant hand dysfunction (baseline CHFS ≥20) and dcSSc was determined from the STAR population at baseline using the Distribution Method[18, 19]. The reliability of the CHFS in patients with SSc has been reported as 0.97[12]. A multiplier of 1.645 was applied to provide 90% confidence interval around the mean change score. As a sensitivity analysis, the MCID was also calculated using the Anchor Method with change in the HAQ-DI as an anchor[19, 20]. These two approaches derived MCID values of 9.5 and 9.9 respectively. Given the ordinal nature of the CHFS, subjects were considered as meeting the MCID threshold if the change from baseline was ≥10 points.

RESULTS

Baseline Characteristics

A total of 105 subjects were screened; 88 subjects were entered into the trial. Forty were randomized to the placebo arm (19 dcSSc, 21 lcSSc) and 48 to the ADRC arm (32 dcSSc, 16 lcSSc; Supplemental Figure 1). All subjects completed the 24-week follow-up with only 1 subject (ADRC group) not completing the 48-week final visit. The majority (85%) of subjects were women. Mean age was 53 years with an average duration of disease of 13 years (Table 1). Subject demographics are shown in Table 1 with additional data in Supplemental Table 1.

Except for the greater frequency of dcSSc in the ADRC-treated arm (67% vs. 48% for placebo), the two arms were well balanced.

Primary Endpoint

The primary end point of this trial was not met (Figure 1, Table 2). Specifically, while ADRC treatment was associated with improvement in the CHFS that was numerically greater than that evident in the placebo arm, this difference was not statistically significant at either 24 or 48 weeks for all subjects or for either pre-specified subset. The greatest numerical difference between the placebo group and the ADRC-treatment group at 48 weeks was evident for the pre-specified subgroup of subjects with dcSSc, which showed a between group difference of 6.3 points (95% confidence interval -0.5 to 13.1 points; nominal p=0.069; Table 2; Figure 1c). *Post hoc* analysis showed that 58% (18/31) of subjects with dcSSc who were treated with ADRCs exhibited improvement in CHFS at 48 weeks that was greater than the MCID compared to 26% (5/19) in the placebo arm (nominal p value = 0.042 for between-group difference).

Secondary Endpoints

While the trial did not meet the primary endpoint, further analysis was performed in order to provide insights that might guide future studies in this indication. These assessments should be deemed exploratory and the corresponding p-values (which have not been corrected for multiple comparisons) viewed as nominal.

The secondary end point (improvement from baseline in HAQ-DI at 48 weeks) was numerically greater for the ADRC-treated group than for the placebo group for the overall population (Table 3). This difference was most notable for the pre-specified subgroup with dcSSc (between group difference 0.17 points; 95% CI 0.04 to 0.38 points; nominal p=0.044; Table 3). This 0.17-point superiority in the ADRC treatment arm is greater than the MCID for the HAQ-DI instrument in SSc (0.14)[20]. *Post hoc* analysis showed that 63% of ADRC-treated subjects with dcSSc exhibited improvement in HAQ-DI at 48 weeks that was greater than the established MCID, compared to only 26% in the placebo-treated arm (nominal p value = 0.019). Similarly, 47% of ADRC-treated subjects with dcSSc showed improvement in HAQ-DI at 48 weeks that was greater than the threshold indicating at least moderate improvement (>0.25 points) compared with only 16% of such subjects in the placebo arm (p = 0.035).

There was considerable concordance between change in CHFS and change in HAQ-DI for subjects with dcSSc treated with ADRCs (Pearson correlation coefficient 0.72; $p<0.0001$). As shown in Figure 2a, 52% of ADRC-treated subjects with dcSSc exhibited improvement greater than the MCID for both the CHFS and HAQ-DI compared to 16% of subjects who received placebo (nominal p-value = 0.0163; Figure 2).

No relevant differences in the other secondary end point (improvement in RCS at 48 weeks) were observed for any subgroup (Table 3). Pre-specified exploratory analysis of RCS at other time points suggested greater improvement in the ADRC arm compared to the placebo arm at 12 weeks for all subjects (1.3±2.0 compared with 0.4±2.9; p=0.009); 1.7±1.7 compared with 0.9±1.8 (p=0.09) for subjects with dcSSc and 2.3±1.5 compared with 1.3±2.4 (p=0.022) for lcSSc.

Exploratory Endpoints

Assessment of the time course of change in CHFS for the dcSSc subset suggested an early separation between the ADRC and placebo treatment arms such that at 4 weeks following treatment there was a between group difference of 4.5 points (95% confidence interval -0.8 to 9.7 points; p=0.09; Figure 1c). At 12 weeks following treatment the mean between group difference approached the MCID (9.3 points; 95% confidence interval 2.6 to 16 points; p=0.008; Figure 1c). Numerically superior improvement in the ADRC-treatment arm at 48 weeks was evident in each of the CHFS domains (Kitchen, Dressing, Bathroom, Office, and Miscellaneous; Supplemental Figure 2a) and in HAQ-DI domains presumably related to the hand (Activities, Dressing, Eating, Grip, Hygiene, and Reach; Supplemental Figure 2).

EQ-5D instrument showed numerically superior improvement from baseline at 48 weeks for the ADRC group relative to the placebo group for all pre-specified subgroups (all subjects, lcSSc, and dcSSc groups; Table 3). The between group differences in EQ-5D subdomains were larger in the ADRC-treatment group for subdomains presumably more related to the hand (e.g.: Self-Care and Usual Activities) than for the Anxiety/Depression subdomain (Supplemental Figure 2c).

The changes in Patient and Physician Assessment of SSc Activity favored the ADRC-treatment group (Table 3) with differences more evident in patient assessments for all subjects overall (p=0.027) and for the subgroup of subjects with dcSSc (p=0.046). Further, 23% (7/31) of ADRC-treated subjects with dcSSc reported improvement in SSc activity of more than two-points at 48 weeks compared with 0% (0/19) in the placebo arm (p=0.035). There was a moderate correlation between improvement in CHFS and improvement in Patient Assessment of SSc Activity in subjects with dcSSc treated with ADRCs (Pearson coefficient 0.44; p=0.014). (Table 4).

The ability of the subject to fully open their hands was assessed from the sum of the distances from the tip of the thumb to the tip of the small finger at full extension (sum of the corner distances). Among subjects with dcSSc, between group differences favored the ADRC treatment arm such that at four weeks after treatment the sum of all corner distances for both hands decreased by approximately 5mm in the placebo arm compared to an average improvement of 15.7mm in the ADRC-treatment arm (nominal p=0.027; Figure 2b). The mean absolute improvement of approximately 15mm was sustained at 12 weeks (nominal p=0.012) and at the 48-week time point (14.1mm) though the difference from placebo at the later timepoint was no longer associated with a low nominal p-value. No consistent, relevant differences were evident for grip or pinch strength for any subgroup (data not shown).

Subjects with dcSSc exhibited a numerically higher incidence of digital ulceration at baseline than lcSSc (24% incidence; mean 3.25 ulcers per affected patient compared with 16% incidence and 2.0 ulcers/affected patient). ADRC treatment had no apparent effect on the healing of existing ulcers, but it was associated with reduction in the development of new ulcers in subjects with lcSSc: 18.8% (3/16) of ADRC-treated subjects with lcSSc developed new ulcers during the study compared with 52.4% (11/21) of lcSSc subjects in the placebo group.

Safety

Serious adverse events (SAEs) were reported in one subject (2.1%; two different SAEs) in the ADRC arm and in five subjects (12.5%; total eight different SAEs) in the placebo arm. The patient in the ADRC arm was hospitalized for respiratory symptoms with radiographic evidence of pneumonia, possibly due to aspiration, that was successfully treated with antibiotics. Given the use of conscious sedation, the event was deemed as possibly related to either the liposuction or the injection procedure. The same subject had another hospitalization for aspiration pneumonia 8 months later. SAEs in the placebo arm included anemia secondary to a vaginal bleed, hypotension, joint effusion, angina, and upper GI tract hemorrhage. All occurred more than 30 days after treatment and were not deemed related to study procedures. At least one adverse event was reported in 81.3% (39/48) of ADRC-treated subjects and in 82.5% (33/40) of placebo-treated subjects. Additional safety data are presented in Supplemental Tables 2-4.

AEs of any grade deemed potentially related to the liposuction proceudre were reported in three subjects (9%) in the ADRC arm and three subjects (16%) in the placebo arm. The only SAE in the ADRC group was the aspiration event discussed above. All other events were deemed "mild" and included anemia, elevated transaminases, and abdominal wall hardness and all resolved without sequelae within 21 days. AEs of any grade deemed potentially related to the injection of ADRCs or placebo were reported in subjects; six (19%) in the ADRC arm and two (11%) in the placebo arm. One subject in the ADRC arm reported moderate cellulitis in one finger. This resolved within eight days without sequelae. All other events were deemed "mild" and included injection site swelling/discomfort, numbness, and edema. All resolved within 36 days except one ongoing case of mild numbness in the left index finger in one subject in the ADRC group. Finally, AEs deemed potentially related to overall treatment were reported in subjects; six (19%) in the ADRC arm and one (5%) in the placebo arm. These included the injection-related events listed above and a subject in the ADRC arm who exhibited moderate grade of decreased hemoglobin that resolved by study day eight.

DISCUSSION

While notably a systemic disease[21], SSc has profound impacts on hand function leading to substantial reduction in the ability of patients to perform daily activities and on their quality of life[1]. Early data have been reported that suggest impaired hand function in SSc may be modified by direct application of autologous regenerative cells[5, 9, 10]. We conducted a double blind, RCT of intra-digital injection of autologous ADRCs to more rigorously assess the safety and efficacy of intra-digital injection with autologous ADRCs in SSc subjects with impaired hand function. Although the primary end point of this trial was not met, the data contain potentially important findings about the effects of ADRCs in subjects with SSc. Specifically, results showed that improvement from baseline to 24 or 48 weeks in the ADRC-treated group was not statistically significantly different than that in the placebo group for all subjects or for the pre-specified subgroups with lcSSc or dcSSc.

The data is informative for both dcSSc and lcSSc subsets. Hand dysfunction in long standing SSc (disease mean duration of 13 years in the current trial) is multifactorial with contributions in varying degrees from skin thickening and resulting tethering, associated tendon shortening leading to claw hand deformity, involvement of upper extremity with large joint contractures,

vascular complications such as Raynaud's disease and digital ulcers, calcinosis; and inflammatory arthritis. The efficacy and durability of the data is impressive for CHFS in dcSSc (mean improvement of 12.8 units vs. 8.0 units in placebo) and may be related to a beneficial effect on severe skin thickening and tethering of the skin and the associated tendon shortening seen in the dcSSc subset. Our hypothesis is supported by the ability of subjects to fully open their hands, a measure of hand dexterity, that favored the ADRC treatment arm in dcSSc with the mean absolute improvement of approximately 15mm that was seen at 12 weeks (nominal p=0.012) and at 48 weeks (14.1mm). In addition, there was a larger placebo change in lcSSc vs. ADRC group. This may be related to a milder skin thickening and tethering in this subset (a known feature of this subset) and a higher placebo response. There were no differences in the RCS and patient assessment of activity in dcSSc and lcSSc diseases to explain the differences. ADRC treatment was associated with reduction in development of new digital ulcers in subjects with dcSSc— 41% in ADRCs vs. 53% in placebo group and in lcSSc 19% in ADRC vs. 52% in the placebo group without a beneficial impact on CHFS.

Further analysis was performed to identify matters that might guide the design of future studies. *Post hoc* assessments showed that the percentage of ADRC-treated subjects with dcSSc exhibiting clinically meaningful improvement (improvement > MCID) at 48 weeks for both the CHFS and HAQ-DI instruments (each of which has been validated in SSc) was greater than in the corresponding placebo group (52% dual-response rate compared to 16% in the placebo arm, Figure 2). Further, analysis of individual domains within the CHFS, HAQ-DI, and EQ-5D instruments indicated greatest effects on those parameters more obviously pertinent to the hand (for example, self-care and usual activities) rather than those less directly related to hand function (eg: walking and anxiety/depression; Supplemental Figure 2). This improvement in subjective measures of hand function was associated with improvement in objective finger extension as evidenced by early and sustained improvements in the total distance between the fingers at maximum extension (sum of corner distances; Figure 2b). Data for other exploratory endpoints showed trends that generally favored the ADRC-treatment arm, although the differences should be considered imprecise and exploratory.

The time course for each of these improvements in hand function following treatment (Figure 1, Figure 2b) was consistent with Granel *et al*[9] with the maximum improvement evident by week 12. The durability of ADRC treatment was seen up to 3 years in Granel *et al*[9]. In the current trial, the beneficial effect in the dcSSc subset was maintained over 48 weeks. There was no longer term follow up in the trial to assess for continuing stability in the CHFS. The data provides us confidence in an effect that is attributable to ADRCs and if validated in another trial, will provide a durable treatment option in patients with dcSSc. An option for future studies is to repeat treatment at intervals of 12 or 24 weeks to see if this would lead to additional sustained improvements or initial improvement for those who didn't have a meaningful improvement earlier in the course. A notable discrepancy with the pilot study was the absence of a sustained effect on RCS. The reason for this difference with the pilot study may lie in the substantially lower baseline RCS score for subjects in the current study (4.2±2.4 on a 0-10 scale compared with 7.2±0.9 for the pilot study). Further, enrollment in the current study was commenced in late spring and completed by fall, thus most subjects were not subjected to the extremes of winter

during the study period, which may have impacted baseline symptoms and lead to a ceiling effect of the RCS. Another notable discrepancy from the prior open label study was the absolute improvement from baseline in the CHFS instrument. ADRC-treated subjects in the current trial exhibited improvement from baseline of approximately 12 points at one year. By contrast, the prior study reported improvement of 24.2 points at one year. The reason for this difference is not clear but may reflect the absence of a placebo arm in the pilot study, which might have inflated the subjects' perception of anticipated benefits, thereby increasing an underlying placebo effect. Additionally, there may be cultural differences that may add to treatment effect of an experimental agent. The open label trial was done in France and the double-blind trial was performed in US. Finally, there may be differences in the severity/damage associated with hand dysfunction and the impact of the single site vs. multicenter nature of the current trial. For example, baseline CHFS in the open label study was approximately 50 points compared to a baseline of approximately 40 points in the double-blind trial. As the current study was designed and statistical power calculated using this earlier work, this likely led to significant under-powering of the present study.

The mechanisms by which ADRC treatment could yield clinical benefit in SSc are not fully understood. SSc is characterized by endothelial injury with a distinctive set of morphologic capillary microarchitecture changes[22] and changes consistent with chronic endothelial activation at the molecular level[23, 24]. Granel et al[9] reported that ADRC-treatment in SSc was associated with reduction in avascular areas (Vascular Suppression Score) at the nailfolds[9]. Others have shown that delivery of adipose stromal vascular fraction (SVF; a research form of ADRCs) led to improved vascularity in an animal model of SSc[5]. These findings are consistent with several other preclinical studies showing improved blood vessel density and reduced inflammation with SVF/ADRCs[25-29]. They are also consistent with a report of improvement in hand function and reduced endothelial activation in a series of patients with SSc who received high dose immunosuppressive therapy and autologous hematopoietic cell transplant[24]. Given these reports, we hypothesize that ADRCs might act by elaboration of paracrine factors that lead to normalization of endothelial cell function with reduced capillary leakage, leukocyte infiltration, and improved angiogenesis. This hypothesis does not account for the absence of a treatment effect as assessed by the CHFS and HAQ-DI for patients with lcSSc in the current study.

The data from the current clinical trial (and from the single center, open label pilot) were obtained from a preparation of ADRCs that is very different from the population of cells obtained by simply centrifuging adipose tissue, which is performed at different centers. Centrifugation of aspirated adipose tissue separates morsels of adipose from other cells collected during aspiration. As reported by Yoshimura et al [30], flow cytometric characterization of these cells shows that the vast majority are simply cells from extravasated blood (CD45-positive white blood cells). This is expected, as liposuction does not break down the extracellular matrix that binds tissue and vascular cells together within the tissue morsels. By contrast, the process by which ADRCs are produced using the Celution System® starts with the removal of blood cells prior to digestion with Celase®. The cells concentrated by centrifugation of lipoaspirate are explicitly discarded during the production of ADRCs. Celase® enzymatically digests the extracellular matrix, releasing vascular cells (endothelial, vascular smooth muscle cells, and

pericytes), tissue macrophages, adipose tissue stromal (stem) cells, and blood cells trapped within vessels in the tissue morsels that may have a beneficial effect in SSc[31].

Consistent with the pilot study[9, 10], the current trial showed an acceptable safety profile; adverse events were mild or moderate in both study arms. Adipose tissue collection was well-tolerated with only the transient local pain and minor bruising expected from a small volume aspiration despite the generally lean nature of subjects with SSc and their susceptibility to cutaneous ulceration. This was likely due to the small volume of adipose tissue required and the use of manual aspiration performed by experienced plastic surgeons without use of general anesthesia or full sedation. Intra-digital ADRC injection was also well-tolerated with only one SAE in the hand and finger osteomyelitis in a subject in the placebo arm that occurred approximately 5 months after injection. This safety profile is likely due to the nature of the system used to prepare ADRCs. The Celution® System uses a sterile, functionally-closed fluid pathway and a sterile, pharmaceutical grade enzymatic reagent (Celase®) that is washed out to levels that fall below defined safety thresholds during processing.

There is an unmet need for treatments that improve hand function limited by chronic skin and soft tissue sclerosis in patients with established dcSSc. The current study is unique in that the mean duration of skin induration was approximately 13 years. Any therapy that could improve activities of daily living in this subset of established dcSSc would be a meaningful addition to rheumatologists' treatment armamentarium. The knowledge gained here can be used for other studies reporting positive results in those with orofacial dysfunction due to SSc[32].

In conclusion, the RCT demonstrated the feasibility and tolerability of small volume adipose tissue harvest and cell injection into each finger in subjects with SSc and hand dysfunction. While the pre-specified primary end point (change from baseline in the CHFS) was numerically higher in the ADRC group, the differences did not achieve statistical significance in the full cohort of either subgroup. The between group differences were most prominent in the dcSSc group. While certain end points were associated with improvements that exceeded established MCIDs, we recognize that the results of this trial should be interpreted as encouraging and not definitive. Importantly, the data from the STAR trial should help facilitate design and end point selection for an appropriately powered follow-up trial.

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Figure Legends

Figure 1. Change in the Cochin Hand Function Scale over 48 weeks in the A. overall group, B. limited cutaneous SSc, and C. diffuse cutaneous SSc between the ADRCs vs. placebo groups.

Figure 2. Change in Hand Function, as assessed by patient reported outcome measures and hand extension, in Subjects with diffuse cutaneous SSc; A: Change from Baseline in CHFS and HAQ-DI at 48 weeks. The Y axis is the change in HAQ-DI at 48 weeks and X axis in the change in CHFS at 48 weeks. B. Change in hand extension between ADRCs vs. placebo. Positive numbers on Y axis is improvement and negative numbers is worsening at 48 weeks. MCID= Minimal Clinically Important Difference.

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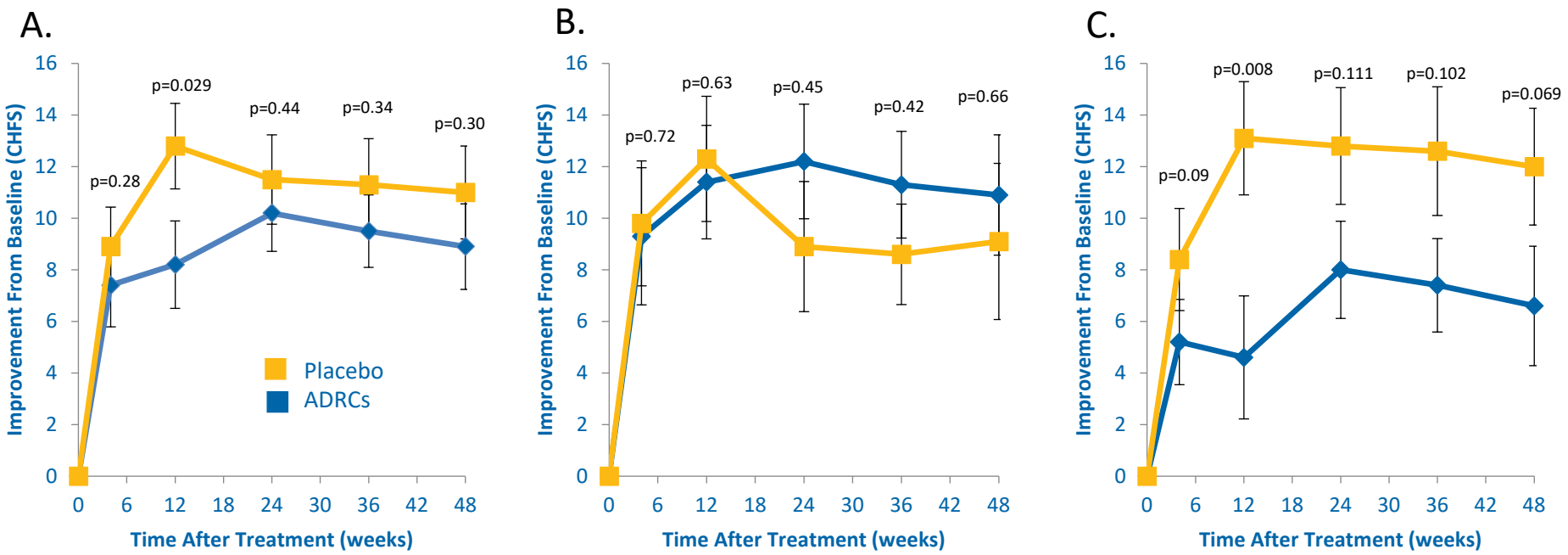

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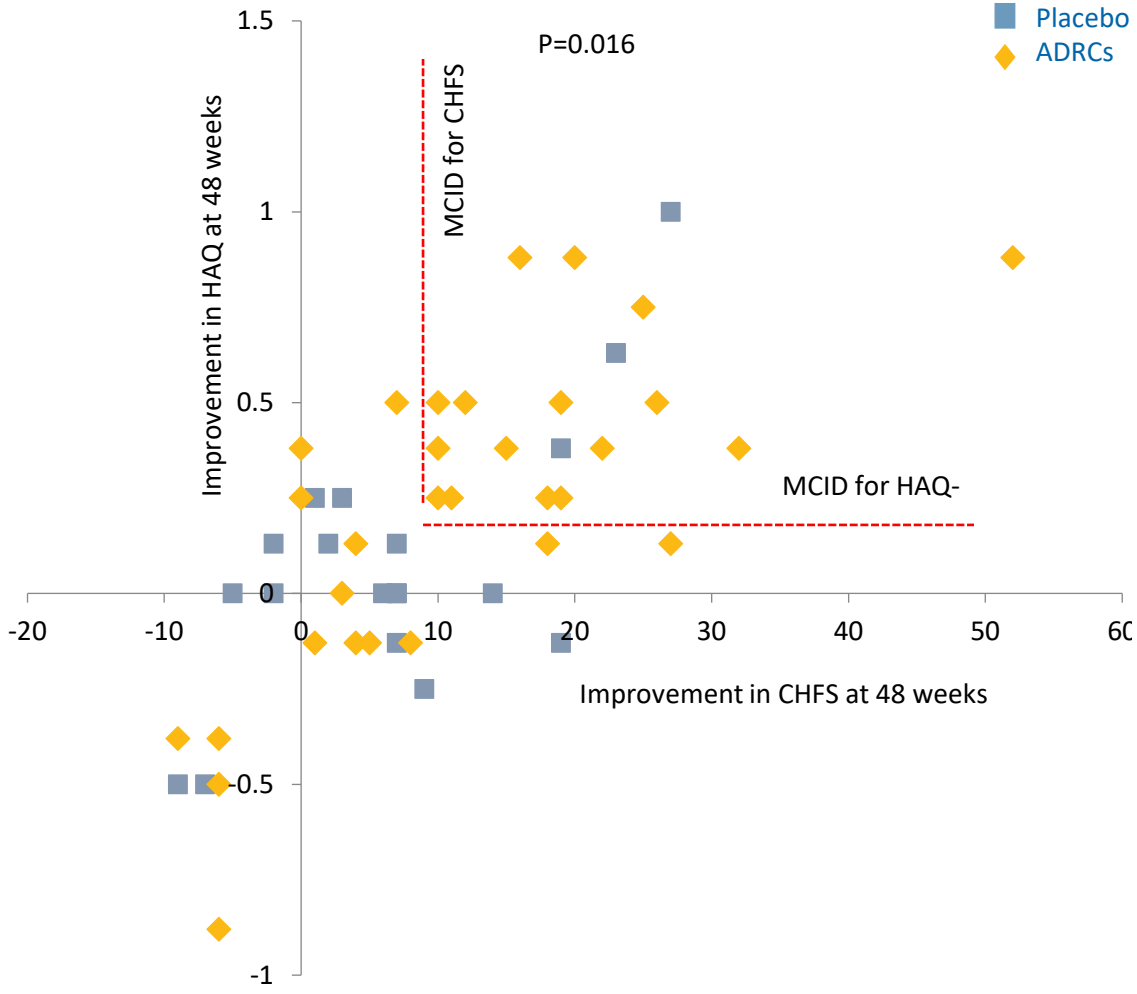

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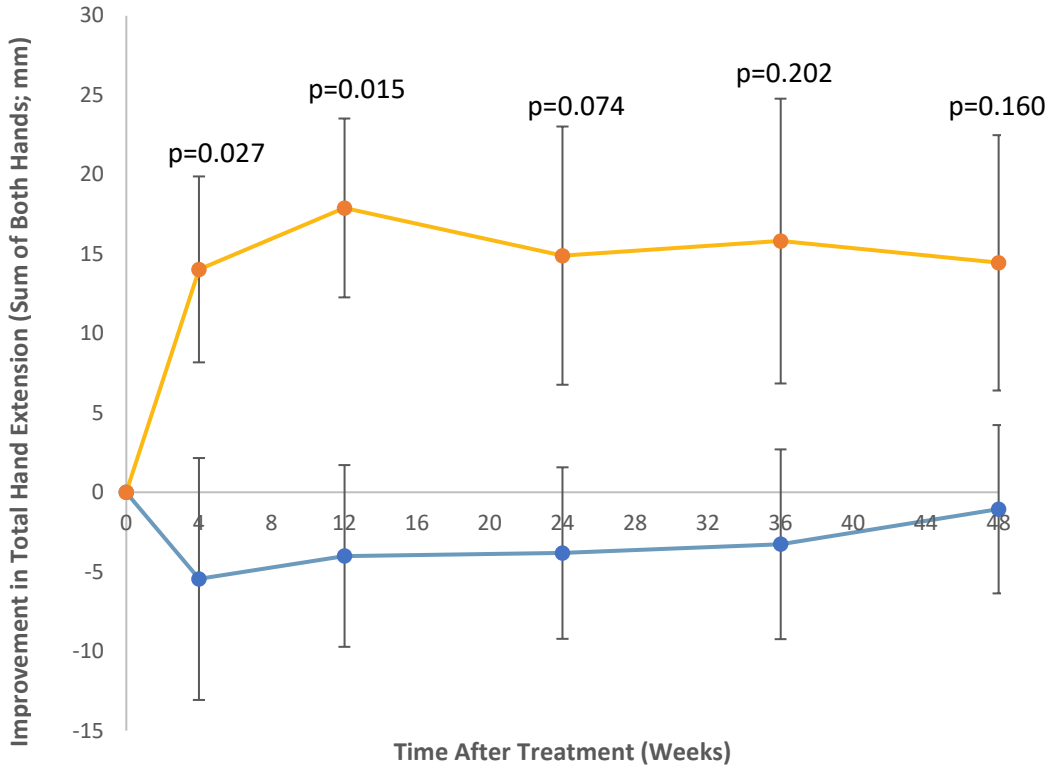

Table 1: Demographics of Subjects Enrolled in the STAR Trial

Variable	**Placebo**	**ADRCs**
Number of Subjects	40	48
Female Gender (n, (%))	35 (88%)	40 (85%)
Age (years; mean ±s.d.)	52 ± 12	54 ± 9
Disease Duration (SSc diagnosis) (years; mean ±s.d.)	13.3 ± 8.9	12.7 ±7.9
Duration Since Raynaud's Onset (years; mean ± s.d.))	15.4 ± 10.5	14.7 ± 9.5
Diffuse SSc Subtype (%)	19 (48%)	32 (67%)
Subjects with Digital Ulcers at Baseline (n, (%))	13 (33%)	17 (35%)
Ethnicity (n, (%))		
Asian	1 (3%)	0 (0%)
Black or African-American	4 (10%)	1 (2%)
White	34 (85%)	47 (98%)
Other	1 (3%)	0 (0%)
Prior Systemic Corticosteroids (n, (%))		
Prednisone	7 (18%)	4 (8%)
Autoantibodies (n, (%))		
Anti-Nuclear Antibodies		
Positive	23 (58%)	26 (54%)
Negative	7 (18%)	4 (8%)
Not Known	10 (25%)	18 (38%)
Anti-Topoisomerase Antibodies		
Positive	9 (23%)	9 (19%)
Negative	19 (48%)	20 (42%)
Not Known	12 (30%)	19 (40%)
Anti-Centromere Antibodies		
Positive	6 (15%)	2 (4%)
Negative	19 (48%)	22 (46%)
Not Known	15 (38%)	24 (50%)
Anti-RNA Polymerase III Antibodies		
Positive	4 (10%)	3 (6%)
Negative	8 (20%)	12 (25%)
Not Known	28 (70%)	33 (69%)

Table 2: Change from Baseline in CHFS

Group	Treat-ment	N	CHFS Score at Baseline	CHFS Score at 24 Weeks	Mean Improvement at 24 Weeks	Between-group difference in Improvement at 24w (95% CI; p value)	CHFS Score at 48 Weeks	Mean Improvement at 48 Weeks	Between-group difference in Improvement at 48w (95% CI; p value)
All Subjects	Placebo	40	42.1 ± 11.4	31.9 ± 14.9	10.2 ± 9.4	1.80 (-2.8 to 6.5; p=0.442)	33.2 ± 15.8	8.9 ± 10.5	2.62 (-2.4 to 7.6; p=0.299)
	ADRCs	48*	39.3 ± 10.5	27.8 ± 13.4	11.5 ± 12.0		28.1 ± 13.8	11.0 ± 12.5	
lcSSc	Placebo	21	40.7 ± 11.4	28.5 ± 14.3	12.2 ± 10.2	2.61 (-9.6 to 4.4; p=0.453)	29.8 ± 16.4	10.9 ± 10.7	-1.72 (-9.6 to 6.2; p=0.660)
	ADRCs	16	34.6 ± 12.3	27.5 ± 13.9	8.9 ± 10.1		27.3 ± 16.0	9.1 ± 12.1	
dcSSc	Placebo	19	43.6 ± 11.5	35.6 ± 15.0	8.0 ± 8.2	5.35 (-1.3 to 12.0; p=0.111)	36.9 ± 14.6	6.6 ± 10.1	6.3 (-0.5 to 13.1; p=0.069)
	ADRCs	32*	40.7 ± 9.4	27.9 ± 13.4	12.8 ± 12.8		28.6 ± 12.8	12.0 ± 12.8	

p-values are from an analysis of covariance (ANCOVA) model with treatment as the main effect and the baseline CHFS score as the covariate. Means±SD and 95% confidence intervals (CI) shown. P-values are not corrected for multiple comparisons.

*One subject with dcSSc in the ADRC-treated group did not complete the 48 week visit reducing sample size (n) for that visit to 47 overall and 31 for the dcSSc subgroup.

Table 3: Secondary and Exploratory Endpoints

End Point	Placebo		ADRCs		Between-group difference in Improvement at 48w (95% CI; p value)
	Baseline	48 Weeks	Baseline	48 Weeks	
HAQ-DI					
All Subjects	1.33 ± 0.56	1.22 ± 0.59	1.26 ± 0.47	1.04 ± 0.52	0.11 (-0.15 to 0.37; p=0.105)
lcSSc	1.21 ± 0.55	1.04 ± 0.59	1.23 ± 0.41	0.98 ± 0.49	0.07 (-0.33 to 0.47; p=0.587)
dcSSc	1.45 ± 0.56	1.41 ± 0.54	1.28 ± 0.50	1.07 ± 0.54	*0.17 (0.04 to 0.38; p=0.044)*
Raynaud's Condition Score					
All Subjects	4.3 ± 2.4	3.7 ± 3.0	3.4 ± 2.1	2.5 ± 2.6	0.305
lcSSc	4.7 ± 2.3	3.7 ± 2.8	3.3 ± 2.1	2.2 ± 3.0	0.404
dcSSc	3.9 ± 2.5	3.6 ± 3.3	3.4 ± 2.2	2.7 ± 2.4	0.430
Health-Related Quality of Life (EQ-5D 3L)					
EQ-5D (All)	0.70 ± 0.15	0.64 ± 0.19	0.73 ± 0.17	0.77 ± 0.14	*0.104 (0.050 to 0.154; p=0.0002)*
EQ-5D (lcSSc)	0.68 ± 0.17	0.64 + 0.17	0.70 ± 0.17	0.77 ± 0.11	*0.091 (0.005 to 0.177; p=0.033)*
EQ-5D (dcSSc)	0.71 ± 0.13	0.64 ± 0.22	0.74 ± 0.17	0.79 ± 0.15	*0.116 (0.077 to 0.163; p=0.005)*
Assessment of SSc Activity					
Patient Assessment, 0-10 (All)	5.6 ± 2.5	5.5 ± 3.0	4.6 + 2.3	3.6 ± 2.7	*0.76 (0.04 to 1.48; p=0.027)*
Patient Assessment, 0-10 (lcSSc)	5.8 ± 2.6	5.3 ± 2.7	4.3 ± 2.1	3.5 ± 2.9	0.27 (-1.06 to 1.60; p=0.220)
Patient Assessment, 0-10 (dcSSc)	5.5 ± 2.5	5.6 ± 3.3	4.7 ± 2.4	3.6 ± 2.6	*1.19 (0.06 to 2.32; p=0.046)*
Phys. Assessment, 0-10 (All)	4.0 ± 2.2	3.7 ± 2.3	3.5 ± 1.6	2.8 ± 1.7	0.38 (-0.18 to 0.94; p=0.122)
Phys. Assessment, 0-10 (lcSSc)	4.5 + 2.1	3.8 ± 1.7	3.5 ± 1.5	2.7 ± 2.1	0.21 (-1.18 to 1.60; p=0.262)
Phys. Assessment, 0-10 (dcSSc)	3.4 ± 2.2	3.5 ± 2.8	3.5 ± 1.7	2.9 ± 1.6	0.67 (-0.62 to 1.96; p=0.165

p-values are from an analysis of covariance (ANCOVA) model with treatment as the main effect and the baseline score as the covariate. p-values are not corrected for multiple comparisons. Means±SD with 95% confidence intervals presented. Differences associated with uncorrected p-value of less than 0.05 are shown in italics.95% confidence intervals not reported for RCS data as no pre-specified subgroup was associated with an uncorrected p-value of less than 0.05 for this end point.Scales: HAQ-DI: 0-3; RCS: 0-10; EQ-5D -0.109 to 1.000; Patient and Physician Assessments (0-10). Means ± S.D. presented. Differences associated with uncorrected p-value of less than 0.05 are shown in italics.