Anti-CTGF Oligonucleotide Reduces Severity of Postsurgical Hypertrophic Scars in a Randomized, Double-Blind, Within-Subject, Placebo-Controlled Study

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Background: Connective tissue growth factor (CTGF) levels are up-regulated in wounded skin and are thought to play a major role in scar formation. An antisense oligonucleotide targeting CTGF was evaluated in adult patients undergoing hypertrophic scar revision surgery, to determine effects on reducing the severity of subsequent scars.
Methods: In a randomized, double-blind, within-subject, placebo-controlled study, 23 female subjects (aged 28 to 55 years) with bilateral, symmetric, hypertrophic surgical scars of the breast underwent scar revision surgery. The resulting breast incisions were randomized to receive EXC 001 (5 mg/cm) or placebo injected intradermally at postsurgery weeks 2, 5, 8, and 11. Scar severity assessments were performed at weeks 12 and 24 by an expert panel using blinded photographs, and by physicians and subjects using a scar scoring scale, the Patient and Observer Scar Assessment Scale. An assumption of the design is that within-subject variance would be small and that whatever within-subject variance there was would be controlled through the randomization process.
Results: EXC 001 significantly reduced scar severity at both 12 and 24 weeks after scar revision surgery in all three measures (expert panel and physician Patient and Observer Scar Assessment Scale, $p < 0.001$; Patient and Observer Scar Assessment Scale, $p < 0.003$).
Conclusions: This study provided positive preliminary data that intradermal injection of EXC 001 produced a significant reduction in severity of postsurgical skin scars, as measured by physicians, subjects, and an expert panel. This study provided evidence that suppression of CTGF could be a viable strategy for hypertrophic scar reduction therapy and that further study of the antisense oligonucleotide EXC 001 was indicated. (*Plast. Reconstr. Surg.* 142: 192e, 2018.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

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THERAPEUTIC

Following skin injury, the healing process includes collagen production, macrophage recruitment, fibroblast proliferation, and neovascularization.[1] Skin wounds, including surgical incisions, in adults are repaired by a complex healing process that can sometimes result in the formation of a fibrous, hypertrophic scar or keloid scar.[2] Skin scarring can cause aesthetic, functional, and psychological effects and is often associated with substantial emotional and financial impact.[3]

Connective tissue growth factor (CTGF) is a matricellular protein that is known to regulate

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aspects of cell proliferation, migration, differentiation, angiogenesis, extracellular matrix production, and adhesion.[4] Overexpression of CTGF mRNA and protein has been observed in chronic fibrotic disorders affecting multiple organ systems, including the skin. CTGF is expressed at low levels in normal skin but becomes elevated following dermal injury, with levels of both CTGF mRNA and protein persistently overexpressed in cells isolated from hypertrophic or keloid scars.[5] In addition, cells cultured from hypertrophic scars elaborate more CTGF in response to stimulation with transforming growth factor-β, a known mediator of fibrosis.[6]

An antisense oligonucleotide (EXC 001) was developed to inhibit CTGF production, with the objective of reducing the CTGF-driven process of collagen deposition and scar formation. EXC 001 was selected from among hundreds of synthesized oligonucleotides directed against all regions of the CTGF mRNA based on screening in human vascular endothelial cells for inhibition of the expression of CTGF. The mechanism of action of EXC 001 is to bind to CTGF mRNA and inhibit expression of CTGF protein (Fig. 1). In a preclinical model, an animal-active analogue of EXC 001 has been demonstrated to reduce hypertrophic scarring in the rabbit ear.[7] This study, along with similar animal experiments, demonstrates the breadth of antifibrotic activity obtained from antisense inhibition of CTGF, and suggests that EXC 001 may have therapeutic benefit in the treatment of human diseases characterized by scarring or excessive fibrosis.

Before undertaking this phase 2 study, animal pharmacology and toxicology studies and phase 1 human safety studies were completed. Unpublished animal pharmacology and toxicology studies have also demonstrated that EXC 001 both suppresses CTGF expression and exhibits a well-tolerated safety profile.

Few pharmacologic interventions to reduce scar severity have been evaluated in controlled clinical trials. In this trial, we evaluated the impact of using EXC 001 to inhibit expression of CTGF on human scar formation following surgical revision of preexisting hypertrophic scars. The primary objective of this phase 2, proof-of-principle clinical trial was to assess the efficacy of EXC 001 in reducing skin scar severity in subjects undergoing surgical revision of hypertrophic scars from prior breast surgery. The secondary objective was to assess the safety of EXC 001 in subjects treated with EXC 001.

PATIENTS AND METHODS

Trial Design and Population

This study was conducted at Jewell Plastic Surgery Center, Eugene, Oregon; Connall Cosmetic Surgery, Tualatin, Oregon; the Division of Plastic Surgery, Northwestern University; Miller Cosmetic Surgery Center, La Jolla, California; Northwestern University, Chicago, Illinois; and Body Aesthetic Research Center, St. Louis, Missouri. This study was a randomized, double-blind, within-subject, placebo-controlled study in subjects who had previously undergone breast surgery that resulted in unacceptable bilateral scars and had chosen to have those scars revised. Its purpose was to obtain proof-of-principle data on both safety and efficacy, to determine whether further larger studies were justified.

Twenty-five women aged 28 to 65 years participated in the study; two withdrew before surgery, and two did not complete study treatment, for a total of

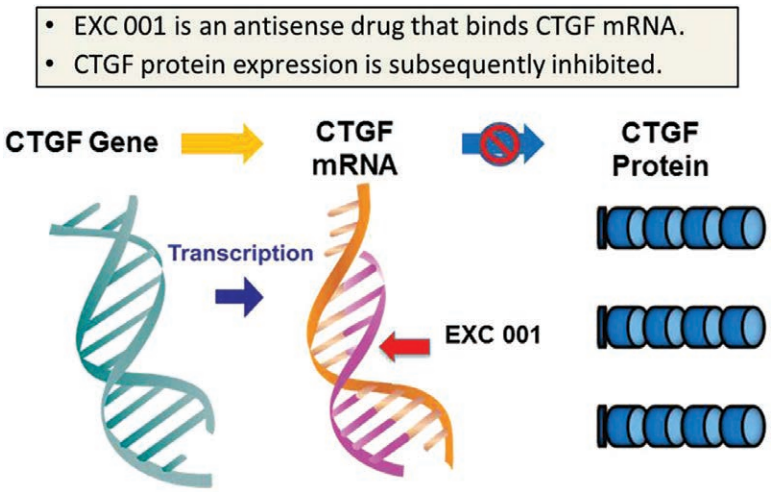

Fig. 1. Mechanism of action.

Table 1. Subject Demographics and Baseline Characteristics among Those Who Completed the Study

Variable	Value (%)
Total	21
Female sex	21 (100)
Race	
White	13 (61.9)
Black, African American, or of African heritage	6 (28.6)
Asian	2 (9.5)
Ethnicity	
Hispanic or Latino (were included in white race above)	2 (9.5)
Non-Hispanic or Latino	19 (90.5)
Mean age ± SD, yr	42.5 ± 9.07
Mean weight ± SD, lb	172.88 ± 34.375
Mean BMI ± SD, kg/m^2	29.01 ± 6.096

BMI, body mass index.

21 completing the study as shown in Table 1. Subjects were required to have undergone previous breast surgery (i.e., reduction, mastopexy, augmentation, or mastectomy) between 6 months and 6 years before study entry that resulted in hypertrophic, discolored, symmetric, bilateral scars of at least 6 cm in length. To avoid pregnancy during the trial, subjects were required to use two effective methods of birth control. Exclusion criteria included use of (1) medications that interfere with wound healing and (2) nicotine products. After obtaining informed consent, subjects entered a screening process that involved medical and surgical history, physical examination, 12-lead electrocardiography, and laboratory safety tests. These took place within 21 days before administration. The protocol and consent forms for this study were approved by a local institutional review board (Northwestern University) and a central institutional review board (Western Institutional Review Board). This study was conducted in accordance with (1) the Code of Federal Regulations (U.S. Food and Drug Administration); (2) the International Conference on Harmonization: Harmonized Guidelines for Good Clinical Practice; and (3) the Declaration of Helsinki, revised version of Somerset West, Republic of South Africa, October of 1996.

Randomization occurred after scar revision surgery and determined the treatments assigned to the right and left surgical incisions for each subject. Dosing kits containing the study drug and placebo with the assigned randomization number were provided for each subject. Investigators and subjects were blinded as to which surgical incision was to receive EXC 001 or placebo. PRA International (Charlottesville, Va.) generated randomization lists that assigned dosing kits sequentially as they were enrolled into the study.

Symmetrical 6-cm segments of the preexisting breast scars at least 3 cm apart were marked with a sterile marking pen, local anesthesia was administered, and the areas were prepared with povidone-iodine. The outlined scar segments were excised in a lenticular fashion and wounds were closed in layers with 3-0 and 4-0 Monocryl (Ethicon, Inc., Somerville, N.J.) sutures. After closure, the incisions were photographed in a standardized fashion using equipment and methods from Canfield Scientific, Inc. (Fairfield, N.J.). Standardized sterile dressings were applied to the incisions. The two surgical incisions were randomized to receive four treatments of either EXC 001 or placebo at postsurgery weeks 2, 5, 8, and 11. The skin immediately adjacent to both sides of each incision was injected intradermally with 5 mg of EXC 001, sterile solution for injection, along a 6-cm length of the incision perimeter divided equally between the two sides of each scar at a concentration of 25 mg/ml and an injection volume of 100 μl/cm. An identical volume of placebo and sterile saline (0.9%) containing a negligible amount of riboflavin to achieve desired color matching was injected intradermally along the contralateral incision using identical methodology (Fig. 2). The area of the injection was marked and measurements recorded to ensure that the injections were consistently administered to the same area of the incision at each dosing. Follow-up visits occurred on postsurgery days 2 or 3 and weeks 1, 2, 5, 8, 11, 12, 16, and 24. Visits included taking of vital signs, wound assessments, and review of concomitant medications. Any adverse events were reviewed and documented.

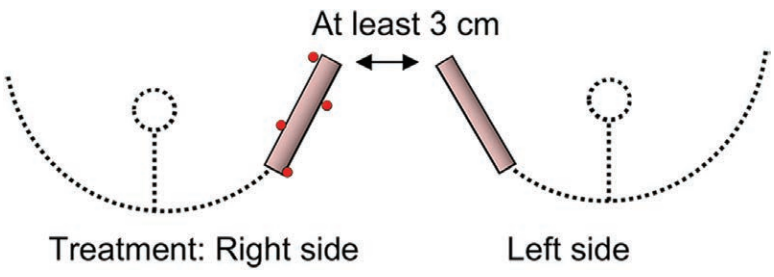

Fig. 2. Injection area.

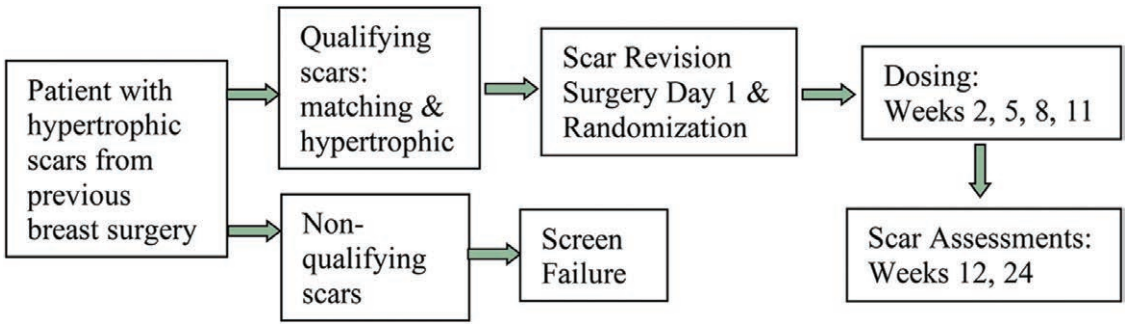

Fig. 3. Flow chart.

Table 2. Summary of Visual Analogue Scale Scar Assessment Scores among Those Who Completed the Study*

Visit Statistic	Scar Assessment Score*	EXC 001 Raw Score	Placebo Raw Score
Week 12			
No.	21	21	21
Mean ± SD	−14.7 ± 14.41	36.6 ± 12.68	51.4 ± 14.54
Median	−14.9	35.6	51.5
Range	−46–5	15–62	30–80
95% CI	−21.3 to −8.1	30.9–42.4	44.7–58.0
p†	<0.001		
Week 24			
No.	21	21	21
Mean ± SD	−26.0 ± 18.20	30.7 ± 13.55	56.7 ± 22.56
Median	−23.3	28.1	55.0
Range	−74–4	9–57	17–92
95% CI	−34.3 to −17.7	24.5–36.8	46.4–66.9
p†	<0.001		

*The scar assessment score is the differences in the ratings by an expert panel assessment of blinded photographs taken at weeks 8,12, and 24 of the two scars using two 100-mm visual analogue scales, where a score of 0 = best possible scar and a score of 100 = worst possible scar. A negative score indicates a better score for EXC 001–treated scars.
†The *p* value is from a two-sided paired *t* test.

Photographs of the incisions were taken on weeks 12 and 24, and laboratory evaluations were conducted at weeks 1, 2, 5, 8, 11, and 12.

Safety Assessments

Safety assessments included physical examinations, standard 12-lead electrocardiography, clinical laboratory tests (chemistry, hematology, and urinalysis), documentation of adverse events, and scar evaluations for skin reactions to intradermal injections of either EXC 001 or placebo. Safety parameters were assessed before surgery and on postsurgery days 2 or 3 and weeks 1, 2, 5, 8, 11, 12, 16, and 24.

Scar Assessments

Assessments for each scar were performed by an expert panel viewing blinded photographs of the scars. Subjects and the treating physician at the investigative site rated scar severity using the Patient and Observer Scar Assessment Scale[8] at postsurgery weeks 12 and 24. The Patient and Observer Scar Assessment Scale is a 10-point rating scale ranging from 1 = normal skin to 10 = very different from normal skin (patient rating) or 10 = worst imaginable scar (physician rating). The expert panel consisted of two plastic surgeons, two oculoplastic surgeons, and one dermatologist.[9] The standardized photographs taken at postsurgery weeks 12 and 24 were uploaded by the sites to Canfield together with the subject and physician study number. Canfield randomized the images for viewing by the expert panel in a blinded fashion. The scar pairs for each subject were rated using Canfield's electronic (eVAS) 100-mm visual analogue scale. The visual analogue scale ranged from 0 = best possible scar to 100 = worst possible scar. For each pair of scars, a visual analogue scale score was assigned to the "worst" scar followed by the "best" scar. The scar photographs were randomly presented and the difference scored three times by each rater specifically for the purpose of investigating within-rater reliability. These three scores were averaged to create a single score for each subject and rater, and the five rater's scores were averaged for an overall treatment effect for each subject.

Statistical Analyses

Efficacy was determined by the difference between the scores for EXC 001 and placebo-treated scars in each subject. This study was not powered for formal hypothesis testing of the treatment comparison of efficacy. Measures included the expert panel visual analogue scale score ratings of blinded scar photographs by an expert panel at postsurgery weeks 12 and 24, and physician and patient scar assessment scales at postsurgery weeks 12 and 24. Statistics were calculated using SAS version 9.1.3 (SAS Institute, Inc., Cary, N.C.). All *p* values presented are calculated using a paired *t* test.

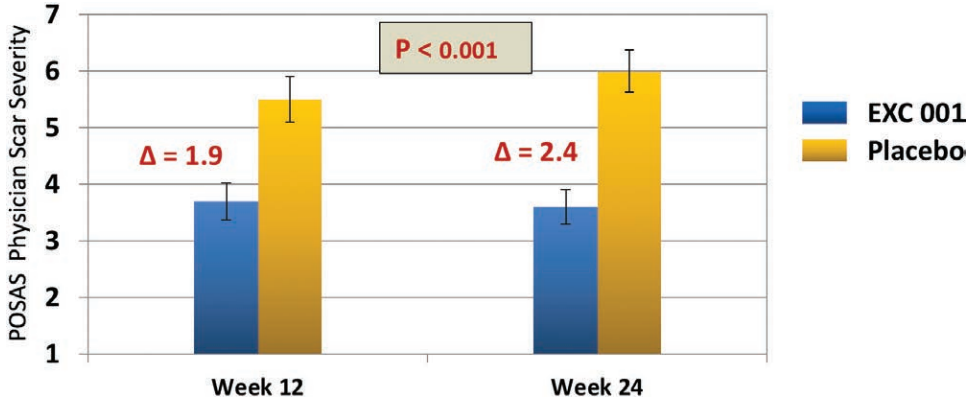

Fig. 4. Physician-rated scar assessment. *POSAS*, Patient and Observer Scar Assessment Scale.

RESULTS

Study participant flow is shown in Figure 3. Twenty-five subjects were enrolled (two were withdrawn before surgery for positive pregnancy or nicotine tests). Twenty-three were randomized and underwent breast scar revision surgery. One randomized subject withdrew after surgery and before dosing with EXC 001. Another subject missed two of the four scheduled doses and so was not included in the completed population according to the statistical analysis plan. The completed analysis population consisted of 21 subjects. Demographic variables for the 21 subjects who completed the analysis are shown in Table 1, and are similar to data recorded for the original 25 subjects enrolled and the 23 randomized subjects.

The results of the expert panel visual analogue scale scores for the EXC 001–treated and placebo-treated incisions favored treatment with EXC 001 (Table 2). Administration of EXC 001 at a dose of 5 mg per linear centimeter of scar significantly improved the visual analogue scale scores at week 12 by 14.7 mm (100-mm scale) compared with the placebo-treated scars ($p < 0.001$). By week 24, the difference in visual analogue scale scores increased to 26 mm in favor of EXC 001 ($p < 0.001$), with 90 percent of EXC 001–treated scars rated as less severe than placebo-treated scars.

The results of the physician-rated scar assessments at weeks 12 and 24 demonstrate that EXC 001–treated scars were significantly less severe overall ($p < 0.001$) than placebo-treated scars in 86 percent of the subjects (Fig. 4). In addition, individual scar characteristics at week 24 all favored EXC 001–treated scars as less severe (vascularity, $p < 0.001$; pigmentation, $p < 0.001$; thickness, $p < 0.001$; relief, $p < 0.001$; pliability, $p < 0.005$; and surface area, $p < 0.001$). See Table 3 for week-24 summary statistics.

Table 3. Summary of Week-24 Physician Observer Scar Assessment Scores among Those Who Completed the Study*

Assessment Category Statistic	Scar Assessment Score*	EXC 001 Raw Score	Placebo Raw Score
Vascularity			
No.	21	21	21
Mean ± SD	−2.3 ± 2.03	3.5 ± 1.29	5.8 ± 1.95
95% CI	−3.2 to −1.4	2.9–4.1	4.9–6.6
p†	<0.001		
Pigmentation			
No.	21	21	21
Mean ± SD	−1.9 ± 2.21	3.5 ± 1.21	5.4 ± 1.86
95% CI	−2.9 to −0.9	2.9–4.0	4.5–6.2
p†	<0.001		
Thickness			
No.	21	21	21
Mean ± SD	−1.8 ± 2.20	4.0 ± 1.82	5.8 ± 1.83
95% CI	−2.8 to −0.8	3.2–4.8	5.0–6.6
p†	0.001		
Relief			
No.	21	21	21
Mean ± SD	−2.4 ± 2.48	3.2 ± 1.78	5.6 ± 2.29
95% CI	−3.6 to −1.3	2.4–4.0	4.6–6.7
p†	<.001		
Pliability			
No .	21	21	21
Mean ± SD	−2.0 ± 2.84	3.2 ± 1.73	5.2 ± 2.34
95% CI	−3.2 to −0.7	2.5–4.0	4.1–6.3
p†	0.005		
Surface area			
No.	21	21	21
Mean ± SD	−2.2 ± 2.09	3.7 ± 1.71	5.9 ± 1.80
95% CI	−3.1 to −1.2	2.9–4.4	5.0–6.7
p†	<.001		
Overall opinion			
No.	21	21	21
Mean ± SD	−2.4 ± 2.01	3.6 ± 1.43	6.0 ± 1.70
95% CI	−3.3 to −1.5	2.9–4.2	5.2–6.8
p†	<0.001		

*The score is defined as the within-subject difference between EXC 001 and placebo scores. Each score is on a 10-point scale, where 1 = normal skin and 10 = worst scar imaginable. A negative score indicates a better score for EXC 001–treated scars.
†The *p* value is from a two-sided paired *t* test.

Study subjects rated their EXC 001–treated scars at week 12 as less severe overall ($p < 0.045$) than their placebo-treated scars (Fig. 5). By week

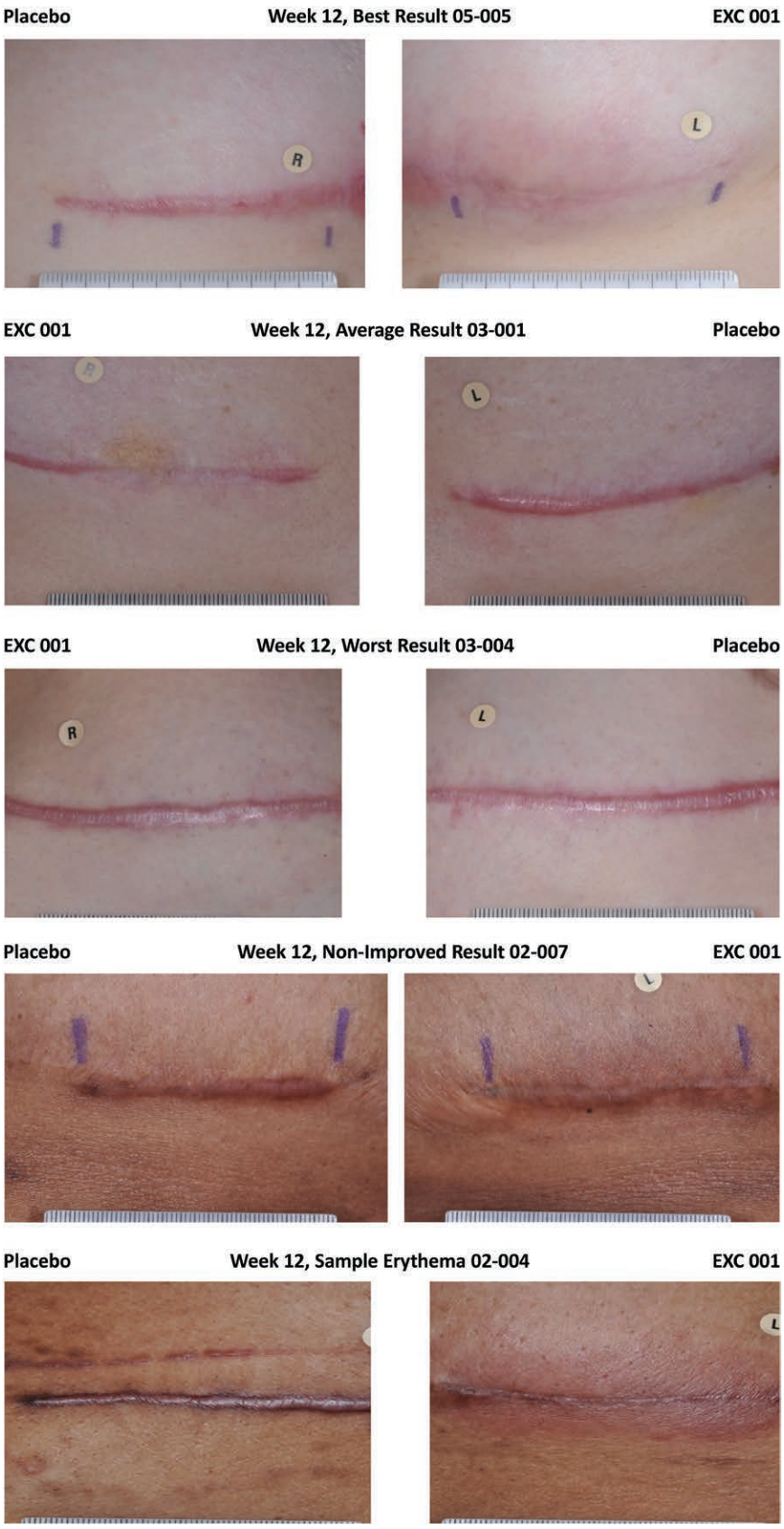

Fig. 5. Study subjects rated their EXC 001–treated scars at week 12 as less severe overall ($p = 0.045$) than their placebo-treated scars.

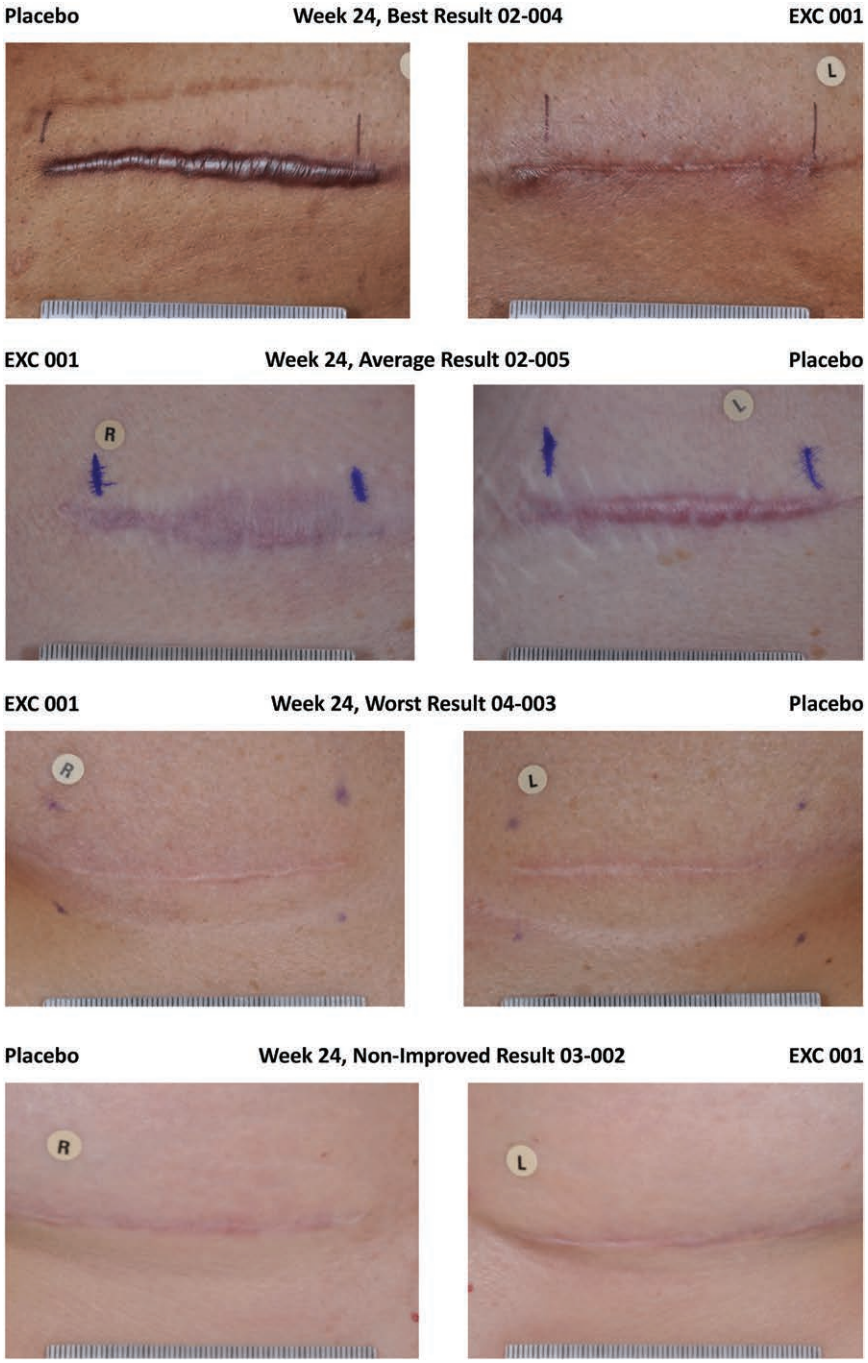

Fig. 6. By week 24, subjects perceived improvement of their scars treated with EXC 001 compared to placebo, and rated them less severe overall ($p = 0.003$).

24, subjects perceived improvement in their scars treated with EXC 001 when compared to placebo, and rated them less severe overall ($p = 0.003$), as shown in Figure 6. In addition, subjects rated their EXC 001–treated scars as having significantly improved color ($p = 0.010$), stiffness ($p = 0.003$), thickness ($p = 0.005$), and irregularity ($p = 0.032$) compared with their placebo-treated scars. Treatment with EXC 001 did not produce significant decreases in scar pain or itching ($p = 0.079$ and $p = 0.158$, respectively). See Table 4 for week 24 summary statistics (Fig. 7).

EXC 001 was well tolerated, with no serious adverse effects and no changes in laboratory parameters considered related to the study drug. One serious adverse event was reported: bronchitis and exacerbation of preexisting asthma that was considered by the investigator to be unrelated

Table 4. Week 24 Summary of Subject Observer Scar Assessment Scores among Those Who Completed the Study*

Assessment Category Statistic	Scar Assessment Score*	EXC 001 Raw Score	Placebo Raw Score
Has the scar been painful?			
No.	21	21	21
Mean ± SD	−1.0 ± 2.36	1.5 ± 1.08	2.4 ± 2.36
95% CI	−2.0–0.1	1.0–2.0	1.4–3.5
p†	0.079		
Has the scar been itching?			
No.	21	21	21
Mean ± SD	−0.6 ± 1.94	1.9 ± 2.00	2.5 ± 2.32
95% CI	−1.5–0.3	1.0–2.8	1.5–3.6
p†	0.158		
Is the color of the scar different from your normal skin?			
No.	21	21	21
Mean ± SD	−1.8 ± 2.83	5.2 ± 3.14	7.0 ± 2.77
95% CI	−3.0 to −0.5	3.8–6.7	5.7–8.3
p†	0.010		
Is the stiffness of the scar different from your normal skin?			
No.	21	21	21
Mean ± SD	−2.1 ± 2.95	3.6 ± 2.62	5.8 ± 3.33
95% CI	−3.5 to −0.8	2.4–4.8	4.2–7.3
p†	0.003		
Is the thickness of the scar different from your normal skin?			
No.	21	21	21
Mean ± SD	−2.4 ± 3.54	3.6 ± 2.48	6.0 ± 3.26
95% CI	−4.0 to −0.8	2.4–4.7	4.5–7.5
p†	0.005		
Is the scar more irregular than your normal skin?			
No.	21	21	21
Mean ± SD	−1.9 ± 3.69	4.3 ± 2.49	6.1 ± 3.20
95% CI	−3.5 to −0.2	3.2–5.4	4.7–7.6
p†	0.032		
What is your overall opinion of the scar compared to normal skin?			
No.	21	21	21
Mean ± SD	−2.3 ± 3.18	4.1 ± 2.48	6.5 ± 2.93
95% CI	−3.8 to −0.9	3.0–5.3	5.1–7.8
p†	0.003		

*The score is defined as the within-subject difference between EXC 001 and placebo scores. Each score is on a 10-point scale. For most scores, 1 = no (same as normal skin) and 10 = yes (very different). For pain and itching scores, 1 = no (not at all) and 10 = yes (worst imaginable). A negative score indicates a better score for EXC 001–treated scars.
†The *p* value is from a two-sided paired *t* test.

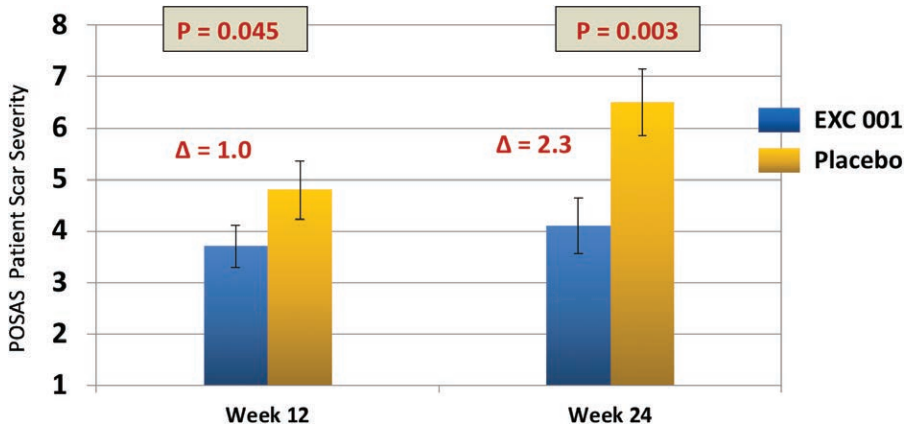

Fig. 7. Subject-rated scar assessment. *POSAS*, Patient and Observer Scar Assessment Scale.

to the study drug. Mild adverse events were reported by 16 patients (73 percent) during the treatment period, four of which were considered possibly drug-related (incision-site erythema, urinary tract infection, and keloid scar). The most common unrelated adverse events were headache and anxiety; each occurred in three patients. Mild, transient, local erythema around the drug administration site was observed in 12 percent of the patients. There were no adverse event–related discontinuations, and there were no deaths.

DISCUSSION

Hypertrophic scars following surgery remain a significant problem in terms of cosmetic appearance, impact on patient psychology, and functional symptoms. Surgical revision is one option, but recurrence of hypertrophic scarring is a common outcome.[10] Other scar therapies include noninvasive options such as compression therapy, silicone sheeting, and various lotions and creams. Invasive options include surgical excision and resuture, laser therapy, and cryosurgery. However, none of these approaches are particularly effective, and many patients continue to suffer from excessive and unwanted skin scarring.[2] Similarly, steroids such as triamcinolone are used to treat keloids and have a beneficial impact on itching; however, published clinical trial literature on the efficacy of steroids on scar prevention and scar morphology remains limited and contradictory.[11]

In this randomized, double-blind, placebo-controlled, proof-of-principle study, significant reductions in scar severity following treatment with EXC 001 were demonstrated by all three scar assessments at week 12 and more significantly at week 24 after surgery (expert panel, $p < 0.001$; physician, $p < 0.001$; subject, $p = 0.003$). Categorical analysis showed a high rate of response: EXC 001–treated scars were rated less severe by the expert panel 90 percent of the time (19 of 21) and by the treating physicians 86 percent of the time (18 of 21).

At week 24, subject, physician, and expert panel ratings were of similar magnitude, favoring EXC 001 by 2.3 and 2.4 (respectively) on the 10-point Patient and Observer Scar Assessment Scale and 26 points on the 100-point expert panel visual analogue scale. EXC 001 was well tolerated, with the only potential drug-related adverse event reported as mild erythema at the injection sites. The multiple intradermal injections were well tolerated; there were no withdrawals because of adverse events, and there was no evidence of hypersensitivity.

This study used a randomized, double-blind, within-subject design. The advantage of the within-subject control design is that it reduces variability that occurs between subjects. As a result, this design, assuming within-subject variance is low, has high statistical power to detect differences in treatment effects and can therefore generate statistically significant data with relatively few patients. Its primary drawback is that it makes assessment of systemic safety more difficult because every subject is exposed to investigational drug.

Because this was a preliminary proof-of-principle study in a relatively small number of patients, it used only one dosage regimen. It was encouraging that this dosage reduced scarring, but it is not known whether this is an optimal regimen for both safety and effectiveness.

SUMMARY

This study provided positive preliminary data that intradermal injection of EXC 001 produced a significant reduction in severity of skin scarring after surgery, as measured by physicians, subjects, and an expert panel. This study provided evidence that suppression of CTGF could be a viable strategy for hypertrophic scar reduction therapy and that further study of the antisense oligonucleotide EXC 001 was indicated.

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