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# Safety and Efficacy of a Scar Cream Consisting of Highly Selective Growth Factors Within a Silicone Cream Matrix: A Double-Blinded, Randomized, Multicenter Study

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## Abstract

**Background:** Several growth factors and hyaluronic acid are implicated in fetal scarless healing. Whether these factors can be applied to an adult scar to improve scar characteristics is unknown.

**Objective:** This study compared the efficacy and safety of SKN2017B, a proprietary topical cream consisting of selective synthetic recombinant human growth factors and hyaluronic acid in a silicone base containing a specifically formulated silicone cream for postsurgical scar treatment.

**Methods:** In this prospective, randomized, controlled, double-blinded study, unilateral or bilateral facial or truncal scars in adult surgical patients were randomly treated with SKN2017B or silicone cream. Study investigators, study patients, and 2 independent reviewers assessed improvement in scar characteristics after 4 and 12 weeks of treatment.

**Results:** Forty-nine bilateral and 12 unilateral scars in 45 patients were treated with SKN2017B or silicone. At 12 weeks, investigators rated 74% of scars treated with SKN2017B as showing overall improvement vs 54% of silicone-treated scars, a 73% relative improvement with SKN2017B ($P < 0.0001$). Patients rated a moderate-to-significant improvement in 85% of SKN2017B-treated scars vs 51% of silicone-treated scars, a 67% relative improvement with SKN2017B ($P < 0.001$). Independent reviewers rated 87% of scars treated with SKN2017B to be better overall vs 1% of scars treated with silicone ($P < 0.0001$). There were no tolerability issues or adverse reactions with either cream.

**Conclusion:** SKN2017B consists of highly selective growth factors within a silicone cream matrix and is well tolerated and effective for surgical scar management.

**Level of Evidence: 1**


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Scars represent the clinical endpoint of the wound healing process that ensues after a cutaneous insult. Wound healing proceeds via a series of highly regulated stages that when properly executed results in a scar that is minimally visible. A compromised healing process, on the other hand, may result in a visible unaesthetic scar. From a patient

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perspective, however, all scars are unaesthetic, prompting treatment to lessen their visibility, especially when they occur in exposed areas such as the face.

Various nonprescription topical products are available for treatment and mitigation of scars. These products contain a wide variety of ingredients, many of which lack data to support their efficacy. Clinically, silicone gel (either as a topical cream or a sheet) is the recommended topical therapy for scar management,[1] because robust clinical evidence supports its use.[2,3] But since the introduction of silicone cream in the early 1990s,[4] there has been a lack of progress in topical scar treatments.

It is well established that fetal wounds heal without scarring.[5–7] Fetal wound healing is distinguished from postnatal wound healing by an extracellular matrix rich in type III collagen and hyaluronic acid (HA), an antiinflammatory cytokine profile, a distinct growth factor profile, and attenuated biomechanical stress.[6] Therapies to minimize postnatal scarring have attempted to introduce individual or multiple aspects of fetal wound healing, with variable clinical success.[8–11]

The lead author has developed a proprietary cream, SKN2017B, consisting of synthetic recombinant human transforming growth factor beta-3 (TGF-β3) and HA as the key ingredients in a silicone matrix. Both TGF-β3 and HA are implicated in fetal scarless healing.[6,12,13] The cream also contains several other synthetic recombinant human growth factors as well as *Aloe vera* extract, vitamin C, and *Centella asiatica* extract, all of which have been individually shown to positively influence wound healing and/or scarring.[14–17] In this prospective, randomized, double-blinded study, the efficacy and safety of this topical cream is evaluated and compared with a specifically formulated silicone cream.

# METHODS

## Study Design and Population

This multi-centered, prospective, randomized, controlled, double-blinded study, conducted between May and December 2017, was approved by Solutions IRB (Little Rock, AR). All tenets of the Declaration of Helsinki for the protection of human patients in medical research were strictly observed, and informed consent was obtained from all patients before enrollment. Study patients were adult surgical patients (aged > 18 years) with unilateral or bilateral scars on their face or trunk that were more than 3 weeks but less than 12 months old. Patients who received previous treatments for the same scar, including intralesional injection of wound modulatory agents (i.e., triamcinolone or 5-fluorouracil), laser resurfacing, microneedling, or other topical treatments; had a known history of diabetes mellitus; were using tobacco products; or underwent or were undergoing surgery for removal of cancerous tissue were excluded. Additionally, female patients who were pregnant, planning to be pregnant, or breast feeding were also excluded from the study.

## Treatments

All enrolled patients applied both SKN2017B and the silicone cream twice daily to their scars, which were randomized by means of a computer-generated randomization sequence. For bilateral scars nearly symmetric in size, such as upper eyelid, facial, or breast incisions, each cream was randomly assigned to one of the scars. For unilateral scars, such as transabdominal incisions, each cream was randomly assigned to half of the same scar. Scar treatment with the assigned cream was intended for up to 3 months.

SKN2017B is a silicone cream matrix containing a proprietary scar cream that consists of synthetic recombinant TGF-β3, HA, *Aloe vera* extract, *Centella asiatica* extract, oil-soluble vitamin C, and several other synthetic recombinant human growth factors that are implicated in the fetal healing process. The silicone portion of both creams consists of dimethicione 10%. The creams have a similar texture, color, and adherence properties and lack fragrance. SKN2017B and silicone are manufactured by MD Medical Designs (Los Angeles, CA).

## Assessments

We assessed scars with a modified Vancouver Scar Scale at baseline (before treatment) and at weeks 4 and 12 after treatment initiation (Table 1). Scar parameters assessed included vascularity, height, pigmentation, and pliability. Vascularity and height of scars were assessed on a 4-point scale, whereas scar pigmentation and pliability were assessed on a 6-point scale. In each case, a higher score denoted a worse outcome.

Patients utilized a 4-point scale to self-assess the improvement from baseline in the overall appearance, texture, redness, and softness of the scar at week 12 as well as of their tolerability to the scar creams (Table 2). For each of the variables, except tolerability, a higher score denoted a favorable outcome. In the case of tolerability, a higher score denoted a worse outcome.

Patients were photographed at baseline and week 12 using a standardized Canfield Vectra 3D imaging system (Canfield Scientific Inc., Parsippany, NJ). Two independent reviewers (a dermatologist and a reconstructive surgeon), blinded to study treatment, assessed the images and graded the vascularity, pigmentation, and height of the scars with the modified Vancouver Scar Scale criteria (see Supplementary Figures 1–14 for independent reviewer grading scale). Pliability of scars was not assessed, because pliability is a

**Table 1.** Modified Vancouver Scar Scale

| Assessment | Score | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| Vascularity | Normal | Pink | Red | Purple | — | — |
| Pigmentation | Normal | Hypo | Mixed | Hyper (mild) | Hyper (moderate) | Hyper (severe) |
| Pliability | Normal | Supple | Yielding | Firm | Ropes | Contracture |
| Height | Flat | Minimal | Moderate | Extreme | — | — |

**Table 2.** Patient Self-Assessment Scale

| Assessment | Score | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Overall appearance | No change | Mild improvement | Moderate improvement | Significant improvement |
| Texture | No change | Mild improvement | Moderate improvement | Significant improvement |
| Redness | No change | Mild improvement | Moderate improvement | Significant improvement |
| Softness | No change | Mild improvement | Moderate improvement | Significant improvement |
| Tolerability of cream | No issues | Mild issues | Moderate issues | Severe issues |

clinical finding. Independent reviewers also performed a qualitative comparative assessment of scars or sides treated with each cream and noted the "better overall" scar or side.

## Statistical Analyses

### *Modified Vancouver Scar Scale*

Improvement or worsening of each of the scar parameters (vascularity, pigmentation, pliability, and height) at weeks 4 and 12 from baseline was computed and combined to compute overall improvement or worsening of scars. Margin of error (95% CI) was obtained from the binomial distribution. Statistical difference in improvement or worsening of scars between the 2 creams was determined using a Two-Proportions Z-Test.

### *Patient Self-Assessment Scale*

Scores reported by patients at week 12 were categorized into 3 thresholds: a threshold of 1 (scores ≥1), representing at least a mild improvement; a threshold of 2 (scores ≥2), representing a moderate-to-significant improvement; and a threshold of 3 (score of 3), representing a significant improvement from baseline. The proportion of scars within each threshold was averaged across the parameters that related to the scar appearance (overall appearance, texture, redness, and softness) to determine the proportion of scars demonstrating an overall improvement with each cream. The difference in overall improvement between the creams was determined, and 95% CI were derived from the binomial distribution. Statistical significance of the difference was assessed using a Two-Proportions Z-Test. Tolerability was excluded from this analysis, because it is not a scar parameter but rather denotes patient tolerability of the allocated cream.

### *Independent Reviewer Assessment*

The proportion of scars rated as "better overall" for each cream was computed and the margin of error derived from the 95% CI. Statistical significance in the difference between the proportions was determined using the Two-Proportions Z-Test.

## RESULTS

Forty-five patients (43 females and 2 males) met the inclusion criteria and were enrolled in this study. Mean age of patients was 42.2 (±12.9) years (range: 24-69 years). Forty-nine bilateral and 12 unilateral scars were treated with SKN2017B or silicone. Treatments were initiated at a mean of 5.3 (±5.4) weeks after surgery. Eleven of the 45 patients electively dropped out of the study at week 4 or week 8 because they noted that one of the sides was performing better. Ten of the 11 patients noted that the scar/side being treated with SKN2017B was better and 1 patient noted that silicone-treated scar/side was better.

## Investigator Assessment

At 4 and 12 weeks after treatment initiation, a greater proportion of scars treated with SKN2017B showed improvements from baseline across all parameters

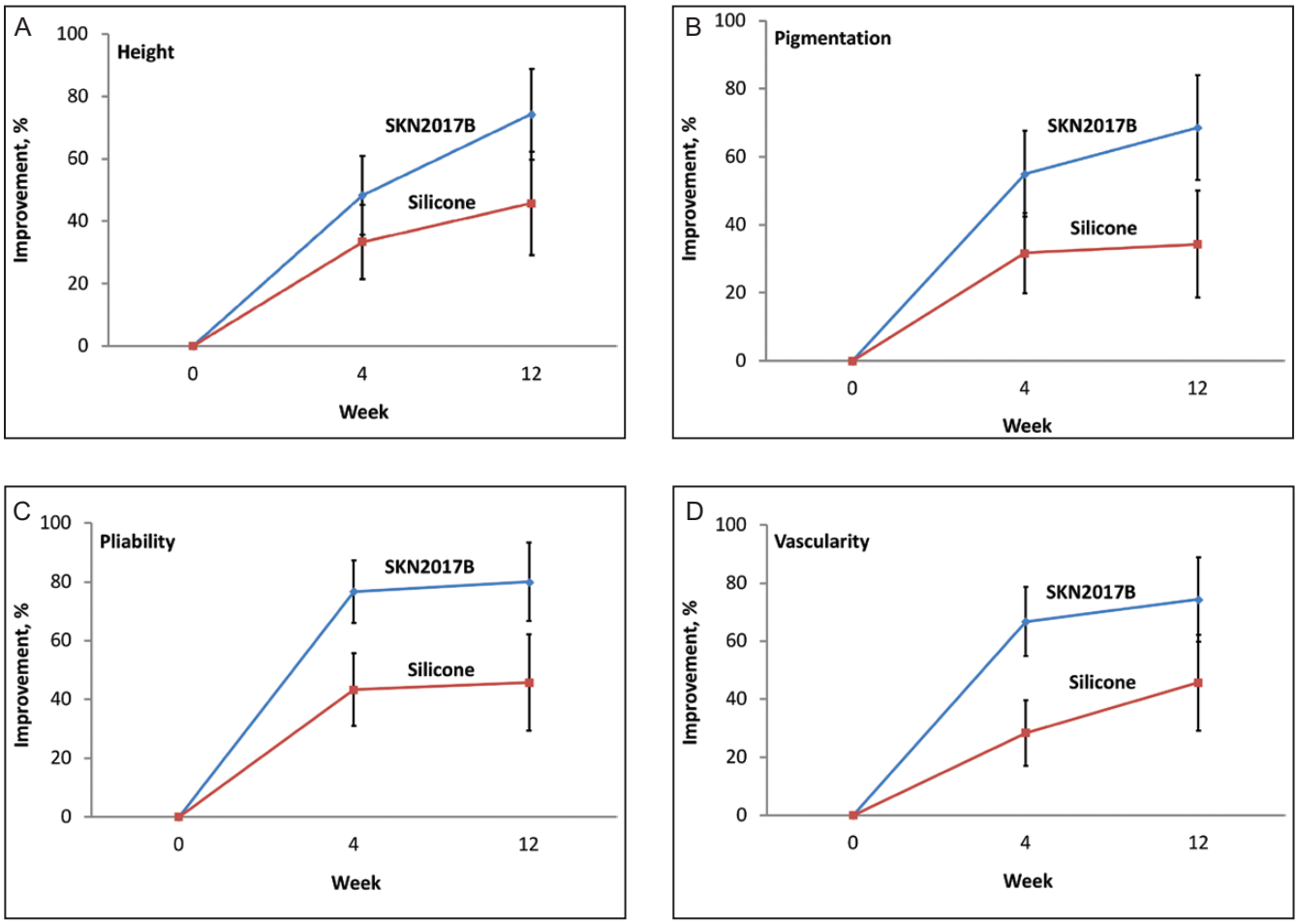


**Figure 1.** Modified Vancouver Scar Scale. Improvement in scar parameters: (A) height, (B) pigmentation, (C) pliability, and (D) vascularity.

(vascularity, pigmentation, pliability, and height) of the modified Vancouver Scar Scale compared with silicone cream alone (Figure 1). When all scar parameters were combined for each treatment, an overall improvement from baseline was seen in 62% and 74% of scars treated with SKN2017B at weeks 4 and 12, respectively (Figure 2). Among silicone-treated scars, an overall improvement from baseline was seen in 34% and 43% of scars at weeks 4 and 12, respectively. The difference in improvement rates between SKN2017B and silicone was statistically significant at both time points ($P < 0.0001$). Compared with silicone, SKN2017B treatment for 12 weeks resulted in a relative overall improvement in 73% of scars.

A small proportion of scars worsened with treatment (Figure 3). Worsening was more frequently observed with silicone than with SKN2017B. Overall, 15% and 19% of scars treated with silicone worsened at weeks 4 and 12, respectively, while approximately 4% and 1% worsened with SKN2017B treatment at weeks 4 and 12, respectively (Figure 4).

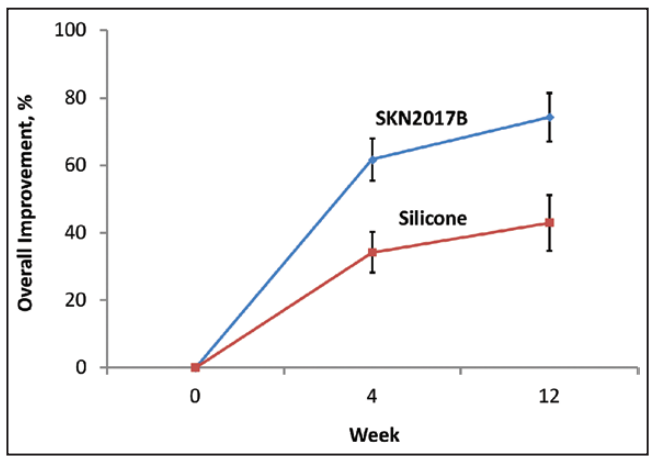


**Figure 2.** Modified Vancouver Scar Scale. Overall improvement of scars.

## Patient Self-Assessment

At week 4, patients reported a moderate-to-significant improvement from baseline (threshold 2) in 71% of scars

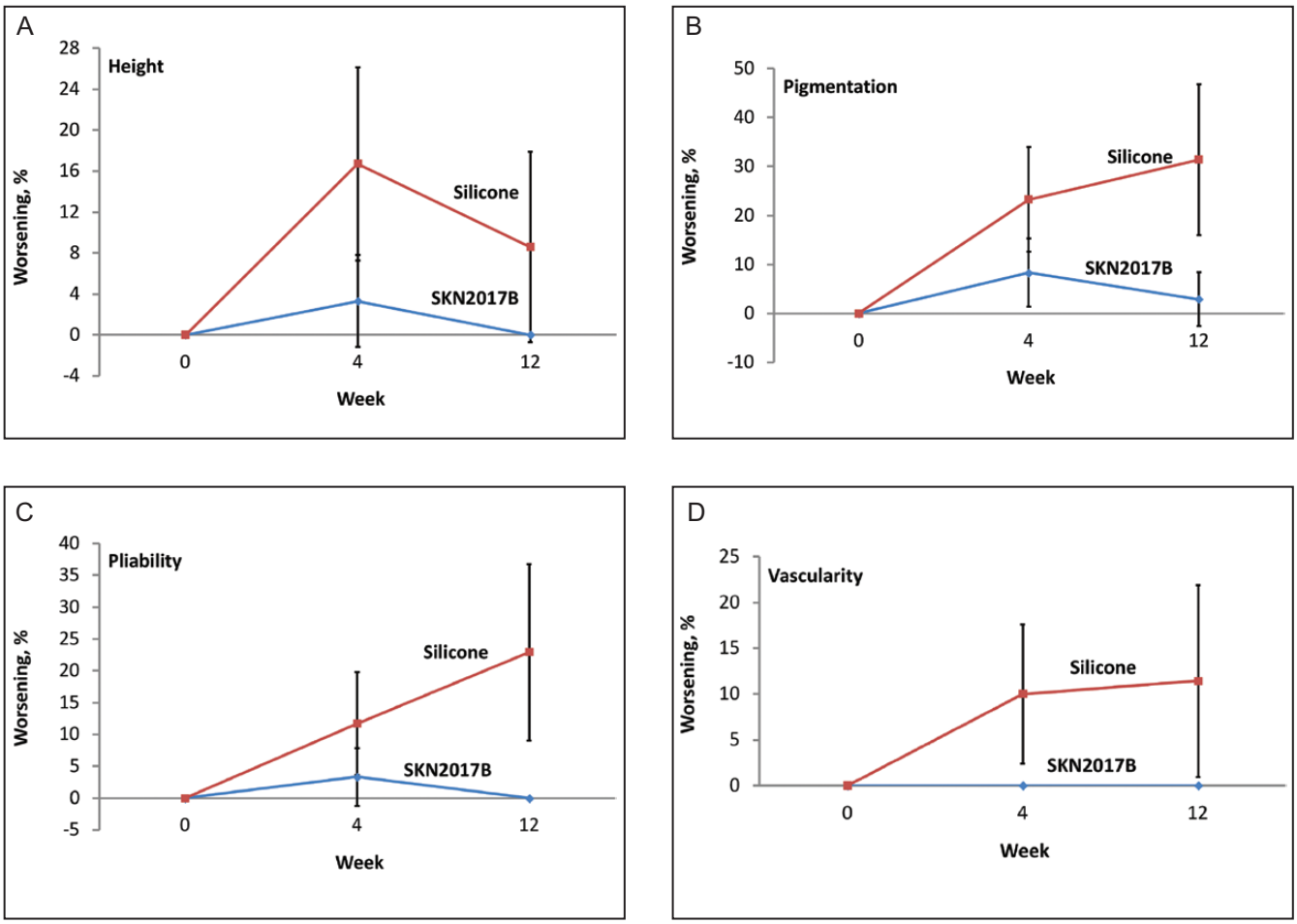


**Figure 3.** Modified Vancouver Scar Scale. Worsening of scar parameters: (A) height, (B) pigmentation, (C) pliability, and (D) vascularity.

treated with SKN2017B and 44% of scars treated with silicone, a 61% relative improvement with SKN2017B, which is statistically significant ($P < 0.001$) (Figure 5). Significant improvement from baseline (threshold 3) was reported in 28% vs 13% of SKN2017B- and silicone-treated scars, respectively, representing a relative improvement of 115% with SKN2017B ($P < 0.001$).

At week 12, a moderate-to-significant improvement from baseline was reported in 85% of scars treated with SKN2017B and 51% of scars treated with silicone, a 67% relative improvement with SKN2017B, which is statistically significant ($P < 0.001$) (Figure 5). Significant improvement was reported in 44% vs 22% of SKN2017B- and silicone-treated scars, respectively, representing a relative improvement of 100% with SKN2017B ($P < 0.001$).

Data for "at least a mild improvement" (threshold 1) did not differ between the creams because this was an all-inclusive threshold and are therefore not shown. All patients tolerated the topical products and displayed no adverse reactions while enrolled in the study (data not shown). No complications were reported.

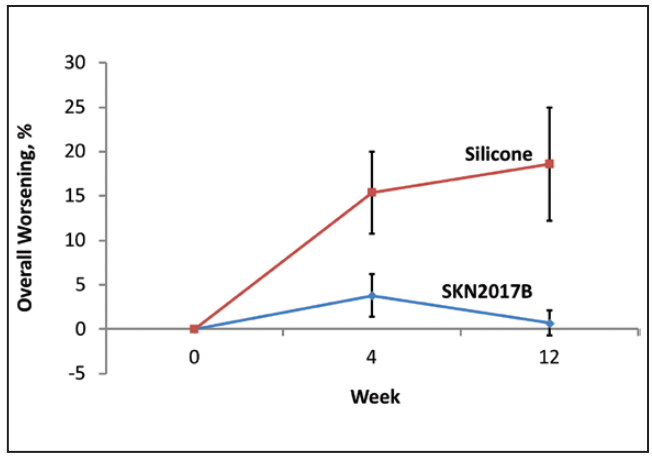


**Figure 4.** Modified Vancouver Scar Scale. Overall worsening of scars.

## Independent Reviewer Assessment

Reviewers rated 87% of scars treated with SKN2017B to be better overall as opposed to 1% of scars treated with

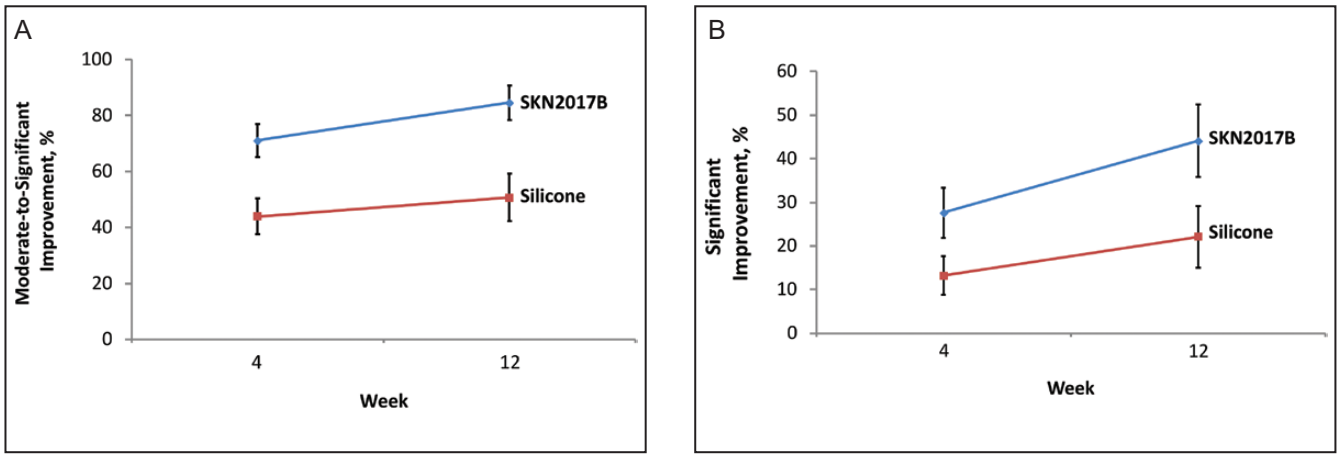


**Figure 5.** Patient Self-Assessment Scale: overall improvement from baseline. (A) Moderate-to-significant improvement. (B) Significant improvement.

silicone (Figure 6), which was statistically significant ($P < 0.0001$).

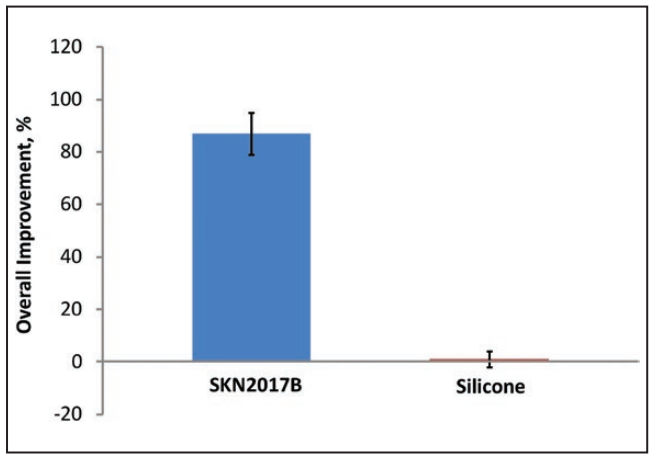


**Figure 6.** Independent-reviewer assessment: better overall improvement from baseline.

## DISCUSSION

An estimated 100 million individuals develop surgical scars annually in the developed world.[18] Approximately 15% of these individuals develop excessive or unaesthetic scarring. Unaesthetic scarring is a major cause of patient discontent with any procedure. Prevention and management of scars is thus an integral part of postsurgical patient care. Although many topical scar creams are available in the market, few have demonstrated efficacy in scar reduction. Besides silicone, many of the ingredients used in current scar creams lack efficacy data. Hence, SKN2017B was formulated using ingredients that have a scientific basis for scar reduction or improvement of scar appearance.

The results demonstrate that SKN2017B is more effective than silicone cream in improving scar appearance after 12 weeks of treatment. Assessment of scars before and after treatment by study investigators, study patients, and independent physician reviewers, all blinded to study treatment, indicated that SKN2017B-treated scars exhibited significantly greater overall improvement compared with silicone-treated scars. That 3 separate groups of assessors arrived at the same conclusion not only strengthens but also mutually validates the findings, resulting in a robust study. There were no safety concerns with SKN2017B; patients reported no tolerability issues (Figures 7–10).

Although the study did not investigate how SKN2017B works to improve scar appearance, the authors hypothesize that the individual ingredients in the cream may have worked synergistically to facilitate healing of the dermal layer. Each of the ingredients individually has a scientific and/or clinical basis to support its use as a scar treatment. Silicone, which is used as the foundational matrix in SKN2017B, has a long track record as a scar-reducing treatment.[1] In clinical trials, silicone has demonstrated effectiveness in preventing hypertrophic or keloid scarring in patients with newly healed wounds.[19] Topical silicone gel is currently the recommended first-line therapy for scar management.[1]

Wound healing is a complex process that requires a coordinated production of growth factors and various other cell types to allow the wound to heal as normally as possible. Nevertheless, some wounds heal abnormally, resulting in excessive thickening, redness, and/or pigmentation of the scar. Each of the ingredients in SKN2017B was selected considering the evidence for their contributory role in decreasing redness, pigmentation, and improving the collagen structure of scars as well as their role in fetal cutaneous wound repair.

Several growth factors have been implicated in fetal scarless healing. For instance, TGF-β3, together with TGF-β1 and TGF-β2, are involved in all steps of the

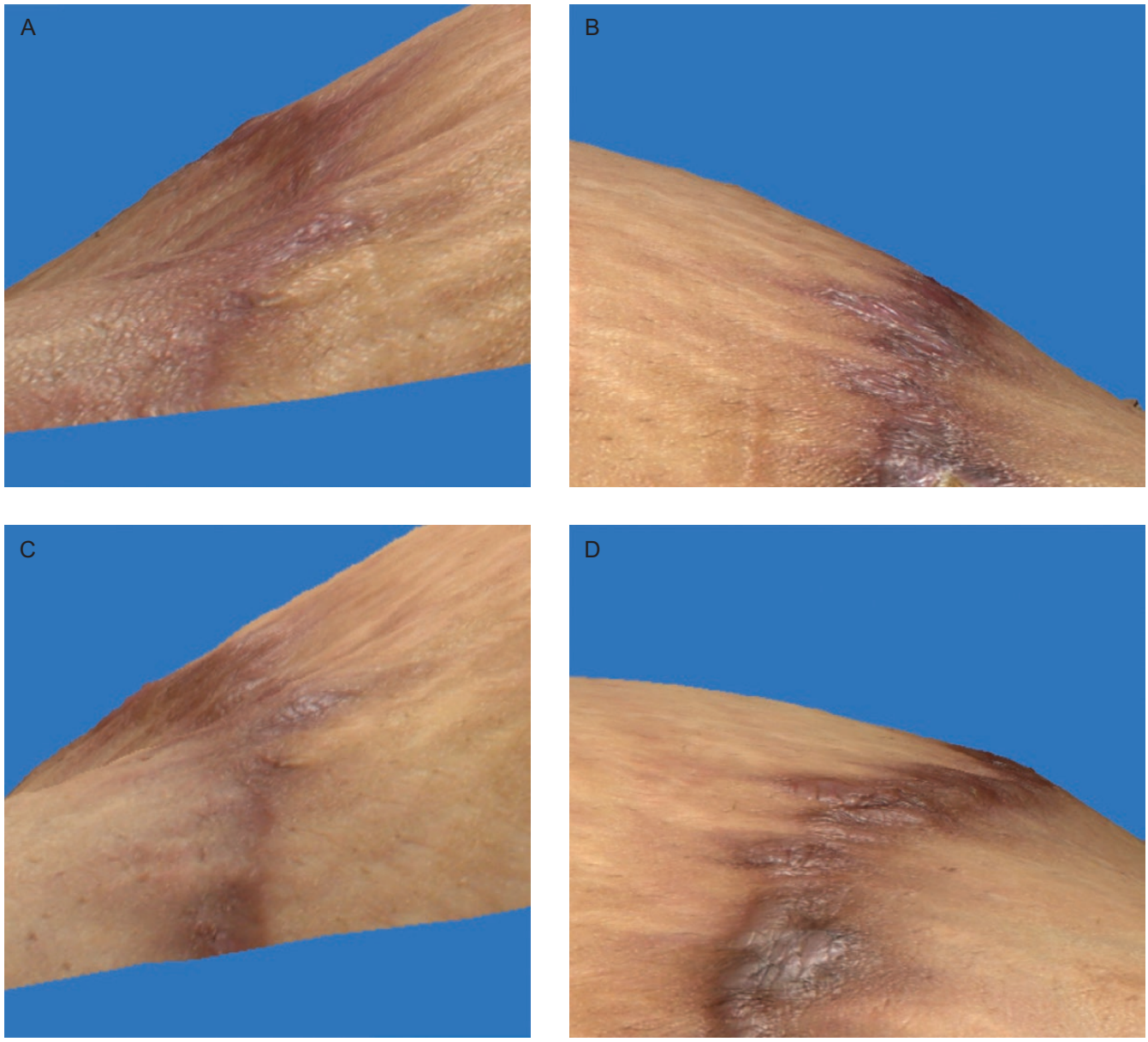


**Figure 7.** Three-dimensional photographic comparison of a unilateral abdominoplasty scar before and 12 weeks after twice-daily application of SKN2017B on one side (A) and silicone cream on the other side (B) in this 45-year-old, African American woman. There is noticeable improvement in pigmentation, vascularity, pliability, and height of the side treated with SKN2017B (C). In contrast, the side treated with silicone cream shows a worsening in pigmentation and height of the scar (D).

wound-healing process, but their expression differs in fetal and adult wounds. In fetal wounds, TGF-β3 is over-expressed, whereas the expression of TGF-β1 and TGF-β2 remain unchanged. Conversely, in adult wounds, TGF-β1 and TGF-β2 expression is increased whereas TGF-β3 expression is decreased.[20] Treatment of cutaneous wounds in adult rats with exogenous TGF-β3 or with neutralizing antibodies to TGF-β1 and TGF-β2 reduces scarring,[21] indicating that TGF-β1 and TGF-β2 promote whereas TGF-β3 prevents scar formation. Therapeutic use of TGF-β3, however, has produced mixed results. In phase I/II clinical trials, intradermal injections of a recombinant human TGF-β3 (avotermin) to full-thickness skin incisions were found to significantly improve scar appearance vs placebo.[10,11] However, a phase III trial of avotermin failed to meet its primary endpoint and halted its clinical development.

Basic fibroblast growth factor (bFGF; also known as FGF2) is expressed at higher levels in fetal skin than in adult skin.[12] A potent mitogen and chemoattractant for endothelial cells and fibroblasts, bFGF stimulates

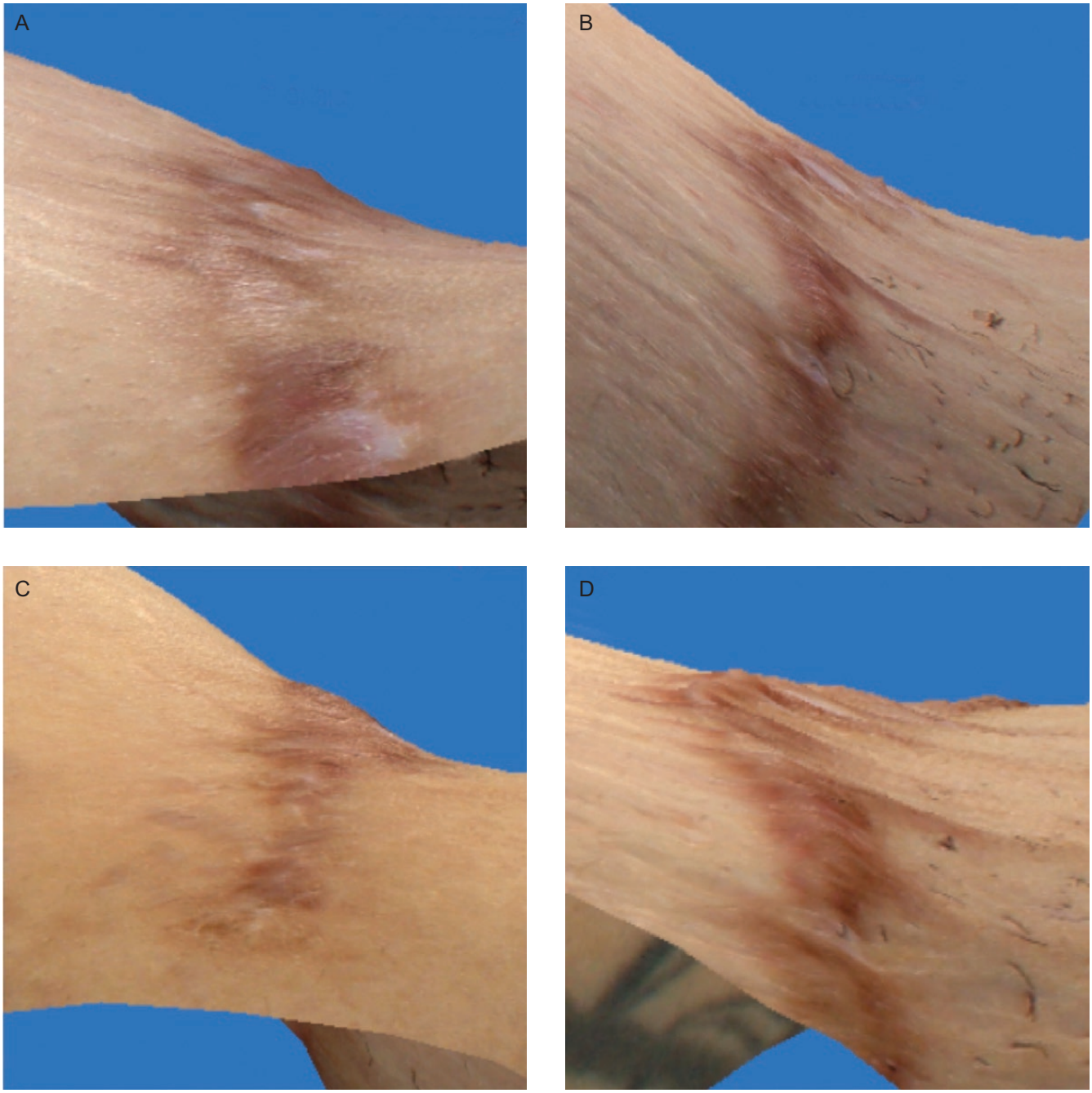


**Figure 8.** Three-dimensional photographic comparison of a unilateral abdominal scar before and 12 weeks after twice-daily application of SKN2017B on one side (A) and silicone cream on the other side (B) in this 52-year-old, Hispanic woman. The side of the scar treated with SKN2017B shows noticeable improvement in pigmentation, vascularity, pliability, and height (C) compared with the side treated with silicone cream (D).

metabolism, extracellular matrix growth, and movement of mesodermally derived cells.[22] In animal studies, bFGF administration to incisional wounds increases matrix metalloproteinase-1 expression, increases collagen degradation, decreases collagen deposition, and suppresses granulation tissue formation by promoting apoptosis.[22,23] Effective regulation of granulation tissue formation and collagen degradation/deposition help accelerate wound healing and improve scar quality, thus alleviating scarring.

Epidermal growth factor (EGF) is another growth factor that is implicated in scarless healing. Upregulation of EGF is seen in early stages of fetal healing, whereas there is downregulation of EGF in scar-forming tissue.[24] In an animal model, the application of a topical recombinant human EGF

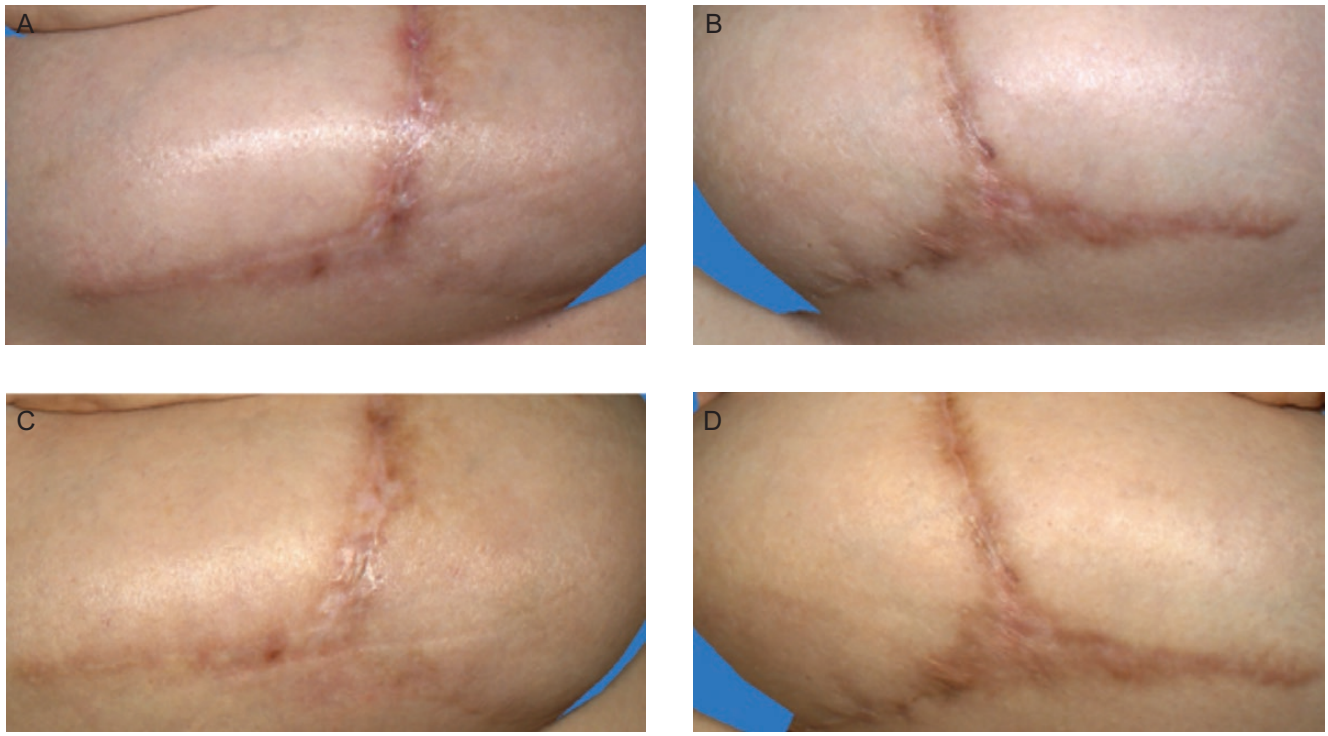


**Figure 9.** Three-dimensional photographic comparison of bilateral breast scars before and 12 weeks after twice-daily application of SKN2017B (A) or silicone cream (B) in this 36-year-old, Caucasian woman. The SKN2017B-treated scar shows noticeable improvement in pigmentation, vascularity, pliability, and height (C), whereas the silicone-treated scar shows worsening of pigmentation, pliability, and height (D).

(rhEGF) decreased TGF-β 1 expression, thereby reducing collagen deposition and cutaneous scarring.[25] Furthermore, in a pilot clinical study, significant improvements in scar severity were reported following 12 weeks of twice-daily application of rhEGF serum on Grade II-IV atrophic acne scars.[26] EGF is also implicated in chronic wounds. Its upregulation significantly accelerates reepithelialization and increases the tensile strength of wounds; conversely, downregulation of EGF prevents reepithelialization, resulting in chronic wounds. In clinical trials of chronic wounds (skin graft donor-healing sites, venous ulcers, and diabetic foot ulcers), the application of topical rhEGF shortened healing time by increasing reepithelialization.[27–29]

The attenuated antiinflammatory response of the fetal scarless phenotype is characterized by a reduced expression of the proinflammatory cytokines, interleukin (IL)-6 and IL-8, and an elevated expression of antiinflammatory cytokine IL-10.[6,30] Nevertheless, IL-6 has a prominent role in wound healing, initiating the healing response.[30] It is produced by neutrophils and monocytes, and its expression is increased after the onset of a wound and tends to persist in older wounds. IL-6 plays a significant role in initiating the inflammatory response and in reepithelialization and has a mitogenic and proliferative effect on keratinocytes and angiogenesis.[31] IL-10 suppresses the production of the proinflammatory cytokines as well as deactivates macrophages and neutrophils. In animal models, overexpression of IL-10 has recapitulated fetal scarless healing in postnatal wounds.[32,33] Phase II studies of a recombinant human IL-10 are promising. Skin incisions treated with the recombinant cytokine demonstrated better scar appearance and less redness than placebo or standard of care.[34]

HA is also implicated in fetal scarless healing. In fetal wounds, there is a prolonged elevation of high-molecular-weight HA, whereas in adult wounds there is transient elevation of low-molecular-weight HA.[6] Furthermore, HA-receptor expression is elevated 2- to 4-fold in fetal fibroblasts, suggesting HA helps facilitate rapid fibroblast migration. HA also upregulates TGF-β3 and type III collagen levels in the extracellular matrix. Globally, HA serves to create an environment that promotes regenerative healing. Various formulations of HA (dermal filler, film, and topical serum) are available for scar treatment.[35–37] HA is also widely used in grafts and dressings for wound care[38,39] as well as in topical creams and lotions to rejuvenate the skin.

*Aloe vera* has a long history of use in traditional medicine as a "healing plant".[40] Animal and clinical studies have shown that treatment with whole *Aloe vera* gel or extracts leads to accelerated wound healing.[14,15,40–42] Aloe brings about its effect by promoting inflammatory cell infiltration, angiogenesis, extracellular matrix deposition, and epithelialization.[40]

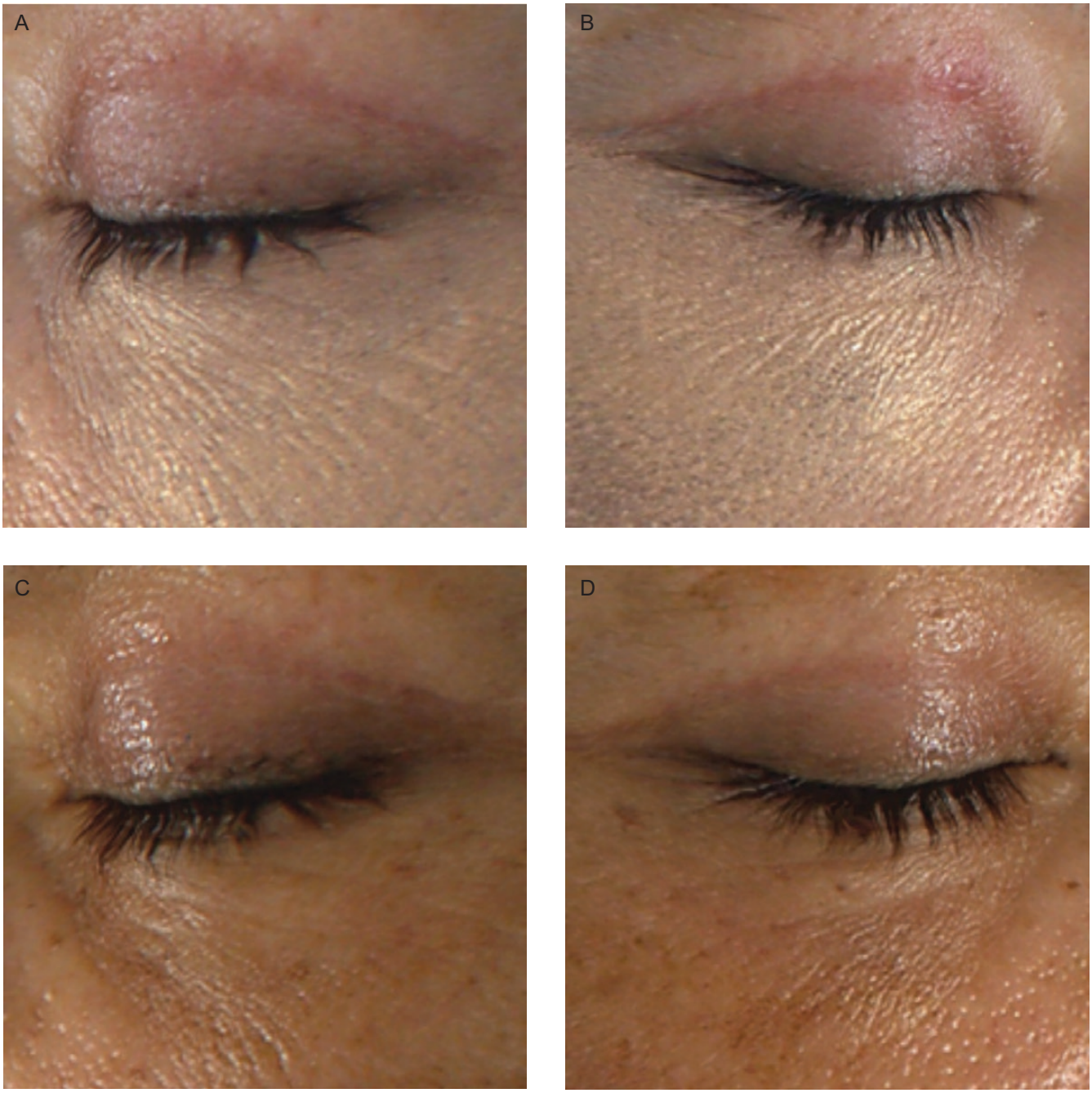


**Figure 10.** Three-dimensional photographic comparison of bilateral eyelid scars before and 12 weeks after twice-daily application of SKN2017B (A) or silicone cream (B) in this 52-year-old, Hispanic woman. SKN2017B-treated scar (C) shows a noticeable improvement in vascularity and height of the scar compared w the side treated with silicone cream (D).

Vitamin C is an antioxidant utilized extensively in topical cosmeceuticals and moisturizers to prevent UV damage and improve skin quality.[16] As a cofactor of collagenase, vitamin C also stimulates collagen synthesis, which promotes wound healing. Topical application of vitamin C, in combination with silicone or with HA, has been shown to improve scar appearance.[9,43]

*C. asiatica* is used in traditional medicine as a treatment for wounds and scars.[44] When applied to wounds, the extract increases cellular hyperplasia, collagen production, epithelization, and angiogenesis, which accelerate collagen cross-linking, reepithelialization, wound maturation, and wound contraction, thus shortening the wound-healing process.[17] Asiaticoside, an active ingredient of *C. asiatica*

extract, suppresses fibroblast proliferation, type I and type III collagen and mRNA expression, and TGF-βRI and TGF-βRII expression and increases Smad7 protein expression, which collectively suppress excessive scarring.

The current study is limited by a short follow-up of 12 weeks. However, substantial changes were noted between SKN2017B- and silicone-treated scars within 12 weeks. From a safety standpoint, long-term data are necessary to ensure that there are no untoward consequences. Importantly, the use of growth factors (human-based, synthetic, and/or plant-based) in topical skin cream formulations is not a novel concept. Growth factor-containing topical formulations have been available for consumer use for nearly 2 decades and have been used extensively in antiaging formulations with no known sequelae with long-term use.[45–47] However, the role of growth factors and their efficacy remain controversial, as some argue that growth factors are essentially "dead" polypeptides with little penetration past the stratum corneum. It may be true that high-molecular-weight compounds may have limited ability to penetrate an intact skin, but disrupted skin may facilitate their penetration. Also, very small amounts of growth factors and cytokines are needed to activate their receptors.[45,48] The individual contribution of each of the factors to the efficacy of SKN2017B was not assessed, which is another limitation of the study. Whether growth factors and HA in SKN2017B actually penetrate the skin and which of the growth factor(s) in SKN2017B is the true active ingredient will be evaluated in future studies.

## CONCLUSIONS

SKN2017B, a scar cream consisting of highly selective growth factors within a silicone cream matrix, is well tolerated and effective for surgical scar management. Significant improvement in scar appearance was seen after 12 weeks of treatment.

### Supplementary Material

This article contains supplementary material located online at www.aestheticsurgeryjournal.com.

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### Disclosures

Dr Zoumalan is a consultant for Allergan (Irvine, CA) and owns stock in and is the scientific advisor for MD Medical Designs, Inc. (Los Angeles, CA), manufacturer of the scar creams studied in this trial. Dr Rossi is on the advisory board of Allergan, has received honoraria from Cutera, Inc. (Brisbane, CA), and is a consultant for Canfield Scientific, Inc. (Parsippany, NJ). Dr Gabriel is a consultant for Allergan. Dr Roostaeian and Ms Tadayon declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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