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ORIGINAL CONTRIBUTION

# A single-center blinded randomized clinical trial to evaluate the anti-aging effects of a novel HSF™-based skin care formulation

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## Abstract

**Background:** Similar to chronic wounds, skin aging is characterized by dysfunction of key cellular regulatory pathways. The hypoxia-inducible factor-1 alpha (HIF-1α) pathway was linked to both conditions. Recent evidence suggests that modulating this pathway can rejuvenate aged fibroblasts and improve skin regeneration. Here, we describe the application of a novel HIF stimulating factor (HSF™)-based formulation for skin rejuvenation.

**Methods:** Over a period of 6 weeks using a split-face study design, the effects on skin surface profile, skin moisture, and transepidermal water loss were determined in 32 female subjects (mean age 54, range 32-67 years) by Fast Optical in vivo Topometry of Human Skin ($FOITS_{HD}$), Corneometer, and Tewameter measurements. In addition, a photo documentation was performed for assessment by an expert panel and a survey regarding subject satisfaction was conducted.

**Results:** No negative skin reactions of dermatological relevance were documented for the test product. A significant reduction in skin roughness could be demonstrated. The clinical evaluation of the images using a validated method confirmed significant improvement of wrinkles, in particular of fine wrinkles, lip wrinkles, and crow's feet. A significant skin moisturizing effect was detected while skin barrier function was preserved. The HSF™-based skin care formulation resulted in a self-reported 94% satisfaction rate.

**Conclusion:** With no negative skin reactions and highly significant effects on skin roughness, wrinkles, and moisturization, the HSF™-based skin care formulation achieved very satisfying outcomes in this clinical trial. Given the favorable results, this approach represents a promising innovation in aesthetic and regenerative medicine.

KEYWORDS

anti-aging, cosmetics, regenerative medicine, skin care, HIF stimulating factor (HSF™), hypoxia-inducible factor-1 alpha (HIF-1α)

## 1 | INTRODUCTION

Despite intensive research efforts currently focused on developing agents capable of mitigating or reversing the signs of cutaneous aging, no single approach has been identified that can address the various underlying factors, including structural and physiological components, epidermal and dermal atrophy, and loss of connective tissue structure and vascularity.[1] Most rejuvenation products, with the exception of retinoids, only provide adequate skin hydration; they lack the ability to actively support the biological processes known to be diminished in the aged population.[2,3]

Recent studies suggest that the mechanisms that hinder the physiologic healing response in chronic wounds, dysfunction of various cellular signaling pathways, are also responsible for impaired tissue homeostasis and regeneration in aged skin.[4-9] In particular, the hypoxia-inducible factor-1 alpha (HIF-1α) pathway has been identified as playing a key role in both settings.[4,9-11] Its activation leads to production of extracellular matrix including collagen, glycosaminoglycans, and nutritive blood vessels.[12,13] Modulating this pathway has been shown to significantly enhance tissue regeneration,[5,6,14-17] including in the setting of advanced age, which, similarly to diabetes and other degenerative skin diseases, correlates with attenuated HIF-1α function.[4-9]

In aging, increased activity of the prolyl hydroxylases (PHD)[4,9] causes destabilization of HIF-1α, resulting in impaired release of growth factors, reduced neovascularization, inadequate tissue regeneration, and poor tissue quality. Modulating this pathway holds great promise for rejuvenation. We have recently demonstrated that in vitro activation of HIF-1α in aged fibroblasts with deferiprone reduces cellular stress and enhances cell metabolism, proliferation, survival, and viability. In addition, we have shown that deferiprone is able to penetrate through human skin in relevant concentrations to activate dermal fibroblasts.[18] Based on these findings, we developed a HIF stimulating factor (HSF™)-based formulation for skin rejuvenation. Here, we assess its performance in a single-center blinded randomized clinical trial.

## 2 | MATERIAL AND METHODS

Study conduct and data analysis were based on the Quality Management System DIN EN ISO 9001:2015 as well as principles of GCP implemented at Institute Dr Schrader (Holzminden, Germany) and were in line with the Declaration of Helsinki. Women in overall good health, between the ages of 30 and 70 years, with Fitzpatrick skin types I-IV qualified for inclusion. Pregnant or lactating women and women with allergies to skin care products or those who received treatment with botulinum toxin, injectable fillers, microdermabrasion, platelet-rich plasma, chemical peelings, laser treatments, or other skin tightening treatments within 6 months of the study start date were excluded. After informed consent, 32 female subjects were included in this study (mean age 54, range 32-67 years) (Figure 1).

A split-face, randomized, blinded test design was chosen for this study to compare the effects of HSF™ product on skin physiology parameters (skin roughness, moisture, and transepidermal water loss) employing objective measurements. Each half of patients' faces was randomized to receive either the anti-aging regimen (HSF™ Skin Care, Tomorrowlabs) or control regime twice daily (morning and evening) over a period of 6 weeks (Figure 1). Patients and research and clinical staff were blinded to which treatment was administered. The first product application was done under the supervision of a technician. Test subjects were instructed to utilize a standardized application procedure including a cleansing step with water only. Subjects were evaluated for study eligibility at visit 1 (screening) and clinical evaluations were conducted at visit 2 (baseline, $t(0)$), and visit 3 (week 6, $t(6)$). From the screening appointment onwards, study subjects were asked to stop their regular skin care regime. No other skin care or cleaning products where allowed during the study period. Photo documentation was performed for assessment by an expert panel and a survey was conducted.

During the course of the study, overall changes in temperature of 20°C were recorded, fluctuating between −5°C and 15°C, while relative humidity was constantly above 60% due to the late autumn season. To minimize climatic influences on study outcomes, all measurements and evaluations were made in a special air-conditioned laboratory guaranteeing a constant room temperature and


**FIGURE 1** Clinical study design. After informed consent, 32 female subjects were included in the study (mean age 54, range 32-67 y). The anti-aging regimen (HSF™ Skin Care, Tomorrowlabs) was applied to half of the face twice daily (morning and evening) over a study period of 6 wk. The effects on skin surface profile, skin moisture, and transepidermal water loss were determined by FOITS$_{HD}$, Corneometer, and Tewameter measurements in the periorbital region. Furthermore, a photo documentation of the faces was performed by VISIA CR followed by an expert evaluation and a survey regarding satisfaction

**TABLE 1** Dermatological assessment

| | | | (+) | + | ++ | +++ | Number | Reaction Points |
|---|---|---|---|---|---|---|---|---|
| Assessment of Dermatologist - before Application | Control | No Reaction | | | | | 26 | |
| | | Reddening | 4 | 0 | 0 | 0 | 4 | 2 |
| | | Flaking | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dryness | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Others | 1 | 0 | 0 | 0 | 1 | 0.5 |
| | HSF Skincare | No Reaction | | | | | 26 | |
| | | Reddening | 3 | 0 | 0 | 0 | 3 | 1.5 |
| | | Flaking | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dryness | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Others | 2 | 0 | 0 | 0 | 2 | 1 |
| Assessment of Dermatologist - after 6 Weeks of Application | Control | No Reaction | | | | | 27 | |
| | | Reddening | 4 | 0 | 0 | 0 | 4 | 2 |
| | | Flaking | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dryness | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Others | 0 | 0 | 0 | 0 | 0 | 0 |
| | HSF Skincare | No Reaction | | | | | 28 | |
| | | Reddening | 3 | 0 | 0 | 0 | 3 | 1.5 |
| | | Flaking | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Dryness | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Others | 0 | 0 | 0 | 0 | 0 | 0 |

*Note:* HSF™ product's biocompatibility was evaluated by a board-certified dermatologist. Before and after the given application phase, the test areas were examined under constant light conditions. Skin reactions (reddening, scaling, dryness, and others) were graded according to a predefined scoring scale: Negative reaction (0 reaction points); Doubtful reaction (0.5 reaction points); Weak positive reaction (1 reaction points); Strong positive reaction (2 reaction points); and Extreme positive reaction (3 reaction points). The irritation scores were reported by means of reaction points showing every subject's score to each treatment area. The overall results were summarized in cumulative irritation scores, the total number of skin reactions, and total reactions points. After an application phase of 6 wk, no negative skin reactions of dermatological relevance were documented for the test product. Diagnostic findings in regard to compatibility parameters (Reaction: –: none; (+): doubtful; +: weak; ++: strong; +++: extremes).

humidity (22°C and 50% relative humidity). An acclimatization period of 45 minutes occurred before measurements were taken.

## 2.1 | Dermatological assessment

Demographic data, skin status/type/sensitivity, and medical history were collected during an initial screening by a board-certified dermatologist. HSF™'s biocompatibility was evaluated by a board-certified dermatologist. Before and after application, test areas were examined under constant light conditions. Skin reactions (reddening, scaling, dryness, and others) were graded according to a predefined scoring scale: Negative reaction (0 reaction points); Doubtful reaction (0.5 reaction points); Weak positive reaction (1 reaction points); Strong positive reaction (2 reaction points); and Extreme positive reaction (3 reaction points). The overall results were summarized in cumulative irritation scores, the total number of skin reactions, and total reaction points.

## 2.2 | Fast Optical in vivo Topometry of Human Skin ($FOITS_{HD}$)

$FOITS_{HD}$ scans were taken at baseline and at 6 weeks. FOITS uses an established optical procedure for noncontact measurements of

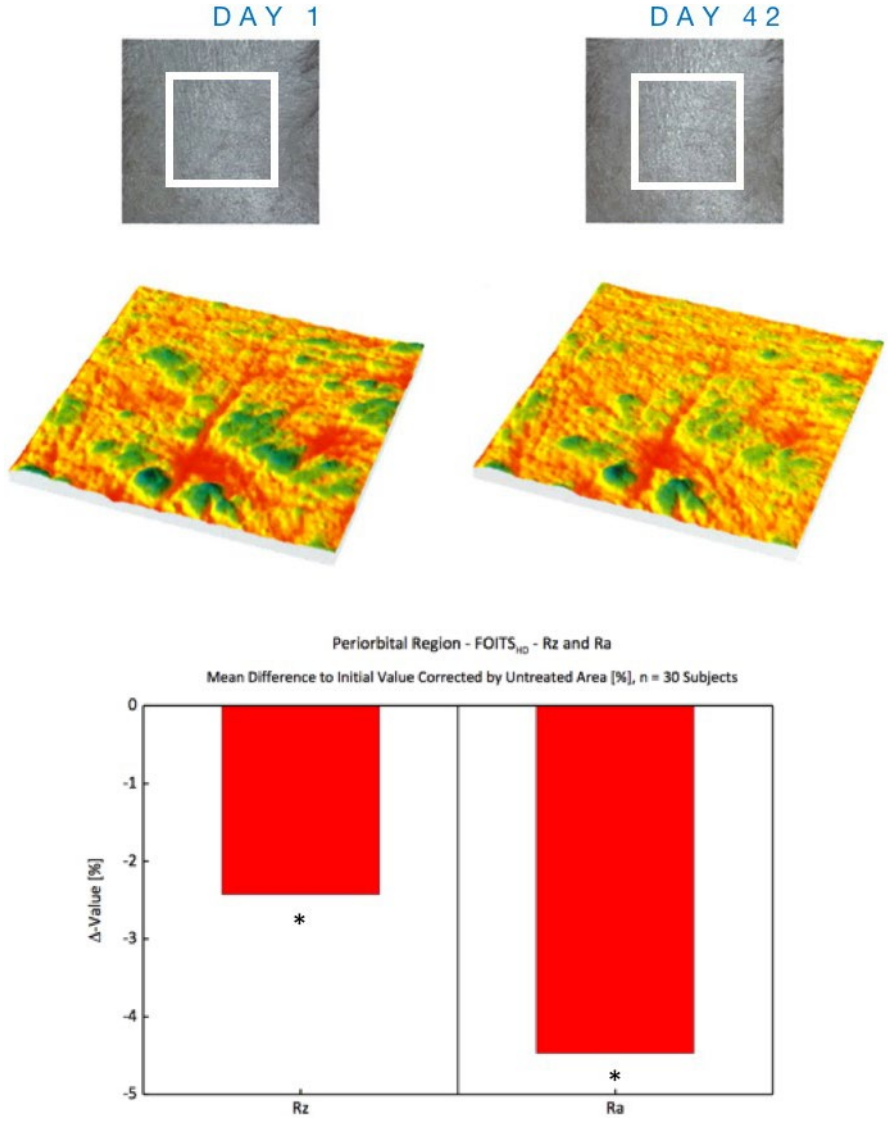
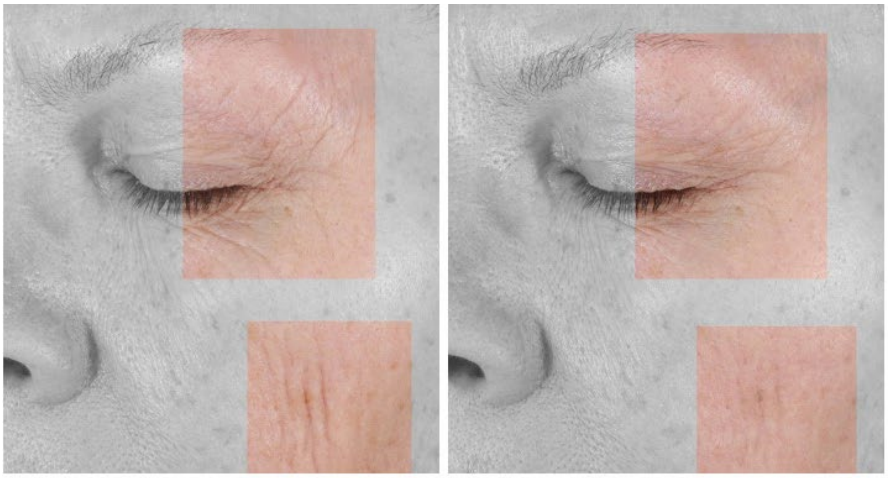



**FIGURE 2** Fast Optical in vivo Topometry of Human Skin (FOITS$_{HD}$). The basis parameters in order to describe the skin surface profile are the averaged depth of roughness (Rz) and the arithmetic mean roughness (Ra). The results of FOITSHD measurements in the periorbital region show a significant decrease in roughness parameters Rz and Ra after 6 wk of regular treatment with test product compared with untreated area

skin topography based on a combination of a gray-code and phase-shift techniques, producing a three-dimensional analysis of the microstructures of the skin.[19,20] Based on surface roughness standards, FOITS employs computer-assisted strip analysis to process information gathered from high-speed, noncontact scanning.[21]

In addition, FOITS$_{HD}$ enables the accurate measurement of absolute space coordinates of all object points in the selected image area in less than one second. The FOITS$_{HD}$ measurement system consists of a projection unit and two 5-Megapixel CCD cameras which are fixed at a triangulation angle. Concerning the gray-code method, grids with different numbers and width of lines are projected. The number of lines is doubled at each new projection up to a maximum of 128 lines. This gives a clearly defined hierarchy of lines for each image point. Regarding the phase-shift technique, only one grid with a sinus-like intensity distribution is projected several times with different phase positions. By using a stereo camera system, an increase in signal quality is achieved. An advantage of this combined imaging technique is that in addition to the brightness image of the inspected area for each image point the hierarchy, phase, and line value of the projected line pattern is calculated. The FOITS$_{HD}$ technique provides the opportunity of an excellent XY resolution of about 20 µm in combination with a field of view of approximately 17 cm$^2$. The FOITS$_{HD}$ technique is able to realize a depth of sharpness of 20 mm on an inspection area of 48 × 36 mm$^2$. The resolution in the vertical Z-direction is about 1 µm. The resolution in Z-direction is not limited to 256 gray steps of the high resolution CCD camera. The high resolution in the vertical direction is achieved by analyzing intensity and phase displacement of the projected grids. The surface structure of the analyzed area causes a deviation of the intensity and phase information of the projected grid structures from the theoretical model structure of a plane surface. With corresponding mathematical algorithms, the absolute 3D coordinates of the inspected area are calculated from these deviations. The current computer capacities enable an image sequence with corresponding analysis of coordinates in a few hundred milliseconds.

Baseline and 6 week images of the area of analysis are precisely overlaid by the software using mathematical algorithms, guaranteeing that initial and final evaluations are done on identical skin areas. In order to adapt to the morphological structure of the periorbital



| PARAMETERS | t=0 | t=1 | IMPROVEMENT (%) |
|---|---|---|---|
| FINE WRINKLES | 2.94 | 2.26 | 23%* |
| LIP WRINKLES | 1.76 | 1.28 | 27%* |
| CROW'S FEET | 2.74 | 2.14 | 22%* |
| FOREHEAD WRINKLES | 2.63 | 2.21 | 16% |
| GLABELLA FOLD | 2.18 | 1.79 | 18% |
| NASOLABIAL FOLD | 3.14 | 2.61 | 17% |
| MENTOLABIAL FOLD | 2.13 | 1.73 | 19% |

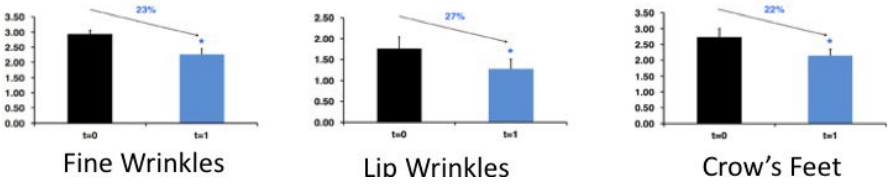



**FIGURE 3** Expert evaluation of standardized photographs. The grading of standardized images was conducted by means of a validated evaluation method. The objective measurement of signs and extent of dermal aging showed a significant improvement of the wrinkles in the facial area, in particular a significant reduction of fine wrinkles, lip wrinkles, and crow's feet after 6 wk of treatment with the HSF™-based skin care formulation

area in the analysis of wrinkles, the roughness parameters Rz and Ra (according to DIN)[22] are determined perpendicular to the main wrinkle direction for an evaluation area of 20 × 20 $mm^2$ using separate lines. Starting close to the eye, 50 separate lines with a distance of 400 µm are analyzed. The resulting roughness score is shown as a function of the number of lines. Ten successive lines each are averaged resulting in five areas of evaluation.

## 2.3 | Photo documentation by VISIA CR

Digital photos (right side, left side, and front of the face) were taken of each volunteer at baseline *t*(0) and after 6 weeks *t*(6) using the VISIA CR photo-station (Canfield Imaging Systems) with a Canon EOS 6D, 20-Megapixel DSLR camera (Canon Incorporated) under standardized lighting conditions. The imaging process is completely software controlled. All shooting parameters are encrypted in the image so that follow-up pictures are automatically adjusted, ensuring permanent quality control over the whole imaging process. A direct line between camera and computer allows the software to control all camera settings for standardized images. An integrated color standard (MacBeth reference color chip) is present for all images. A live video preview (ghost view) along with built-in positioning aids (adjustable headrest and chincup) ensure reproducible subject positioning between all time points. The volunteer's eyes are closed and their face is relaxed as much as possible during photography.

## 2.4 | Expert evaluation of standardized photographs

A blinded expert evaluation (6 independent dermatologists and plastic surgeons) of the standardized photographs was conducted based

on validated assessment scales.[23-25] Briefly, examiners compared photographs to a 5-point photonumeric rating scale based on morphed images to objectively quantify the severity of facial wrinkles.

### 2.5 | Corneometer

A quantitative evaluation of changes to the water content of the skin can be achieved by means of capacity measurements using a Corneometer. These capacity changes are registered by the measuring head capacitor and the data are processed automatically. There is no conductive (galvanic) connection between the object measured and the measuring equipment, eliminating the impact of ionic conductivity and polarization effects on measurement. A Corneometer probe CM 825 with MDD4 (Multi Display Device, Courage + Khazaka electronic GmbH) was used to measure the water content. Ten Corneometer values measured per test area and evaluation time are averaged out for every subject.

### 2.6 | Transepidermal water loss (TEWL)

A Tewameter probe TM 300 with MDD4 (Multi Display Device, Courage + Khazaka electronic GmbH) is used for measuring the transepidermal water loss, which is a reliable indicator for the integrity of the skin barrier. The Tewameter probe consists of a cylindrical tube with two capacitive moisture sensors that measure the moisture of the air at two defined distances above the surface. Three TEWL values measured per test area and evaluation time are averaged out for every subject.

### 2.7 | Survey

We performed a survey at the last follow-up appointment. A 6-item Likert scale[26] was employed to assess participant satisfaction with the HSF™ treatment. The questionnaire results were analyzed by means of descriptive statistics.

### 2.8 | Statistical analysis

Since $FOITS_{HD}$ data are log-normally distributed, we employed analysis of variance (ANOVA). The general *F*-test of ANOVA was used to determine significance. Paired *t* test was used for the remaining data points. Results were considered significant at $P \leq .05$.

## 3 | RESULTS

### 3.1 | Dermatological assessment

After an application phase of 6 weeks, no negative skin reactions of dermatological relevance were documented for the test product (Table 1). One subject (no. 1) discontinued the study due to personal reasons. The data of subject no. 2 were not taken into consideration for $FOITS_{HD}$ evaluation due to a pimple formation in the analysis area at t6w. Thus, results are based on 30 subjects for skin's surface profile measurements and on 31 subjects for all other analyses.

### 3.2 | Fast Optical in vivo Topometry of Human Skin (FOITSHD)

The results of $FOITS_{HD}$ measurements in the periorbital region show a significant decrease in Rz (depth of roughness) and Ra (arithmetic mean roughness) after 6 weeks of regular treatment with the test product (Figure 2). $FOITS_{HD}$ data show a significant skin smoothing effect for the HSF™-based skin care formulation ($P < .05$).

### 3.3 | Expert evaluation of standardized photographs

Objective measurement of dermal aging showed a significant improvement of facial wrinkles ($P < .05$), in particular a significant reduction of fine wrinkles, lip wrinkles, and crow's feet after 6 weeks of treatment with the HSF™-based skin care formulation (Figure 3).

### 3.4 | Corneometer

Skin moisture detection is an essential part of the examination of cosmetic care products. Corneometer measurements demonstrated a significant increase in skin moisture after 6 weeks of regular

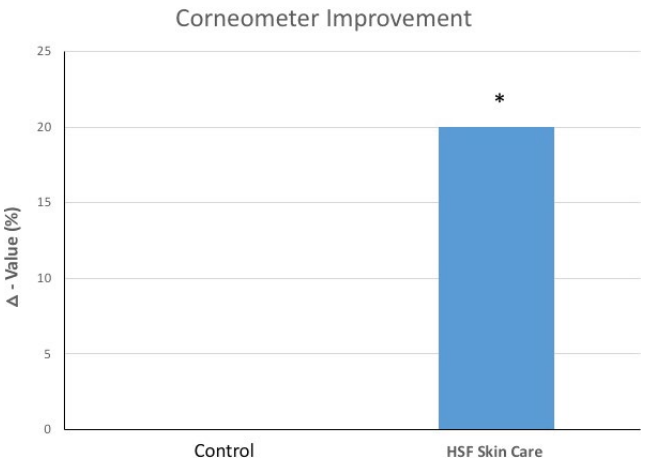



**FIGURE 4** Skin moisture detection. According to the results of Corneometer measurements, a significant increase in skin moisture is documented for the test product after 6 wk of regular application. The statistical comparison to untreated area shows a 20% difference of skin moisture in favor of the test product

application of the HSF™-based skin care formulation (20% greater; $P < .05$) (Figure 4).

### 3.5 | Transepidermal water loss (TEWL)

Tewameter measurements demonstrated no significant differences in TEWL after 6 weeks of treatment with the HSF™-based skin care formulation in comparison with baseline (data not shown), suggesting preservation of skin barrier function.

### 3.6 | Patient-reported outcome

Ninety-four percent of study participants were satisfied or very satisfied with their individual outcomes after 6 weeks of regular use of the HSF™-based skin care formulation (Figure 5).

## 4 | DISCUSSION

### 4.1 | Mechanisms of skin aging

At a cellular and molecular level, aging is characterized by the progressive accumulation of damage to DNA via oxidation, resulting in diminished physiological integrity and impaired functionality. Researchers are only just beginning to understand the biological basis of aging, relying extensively on relatively simple and short-lived organisms such as yeast.[27] Aging is often attributed to the natural result of entropy on cells, tissues, and organs.[28] However, accumulating evidence suggests a role for genetic regulation and that age-related breakdown of cellular processes represent a programmatic decision by the cell to either pursue or abandon maintenance procedures.[29] Regarding the skin, it is widely accepted that advanced age brings changes to all components of the integumentary system with consequent signs of deterioration in the epidermis, dermis, and hypodermis.

In general, age-related skin changes are triggered by a combination of intrinsic and extrinsic factors (eg, ultraviolet/infrared light exposure and smoking). Intrinsic or innate aging is a degenerative process involving a loss of function[30] characterized by a decreased capacity to respond to exogenous and endogenous stress,[31] including telomere loss, oxidative stress, and DNA damage.[2,3,32] Several studies indicate that telomere length modulates the pace of aging and onset of age-associated diseases.[33,34] Additionally, emerging evidence shows that lifestyle factors (obesity, smoking, and alcohol) may influence the health and lifespan of an individual by directly affecting telomere length,[35] demonstrating the strong interplay between the various proposed mechanisms of aging. Extrinsic aging is the result of skin exposure to external factors, most importantly ultraviolet radiation,[31] which weakens both the strength and elasticity of skin[36,37] causing "solar elastosis," a progressive accumulation of elastic fibers in the upper and mid-layers of the dermis.[38] Collectively, aging leads to degradation of collagen fibers, microtextural impairments, and loss of connective tissue structures.[39]

Both cytoplasmic and extracellular regenerative machinery are profoundly impaired in aged skin.[40,41] Aged and senescent cutaneous

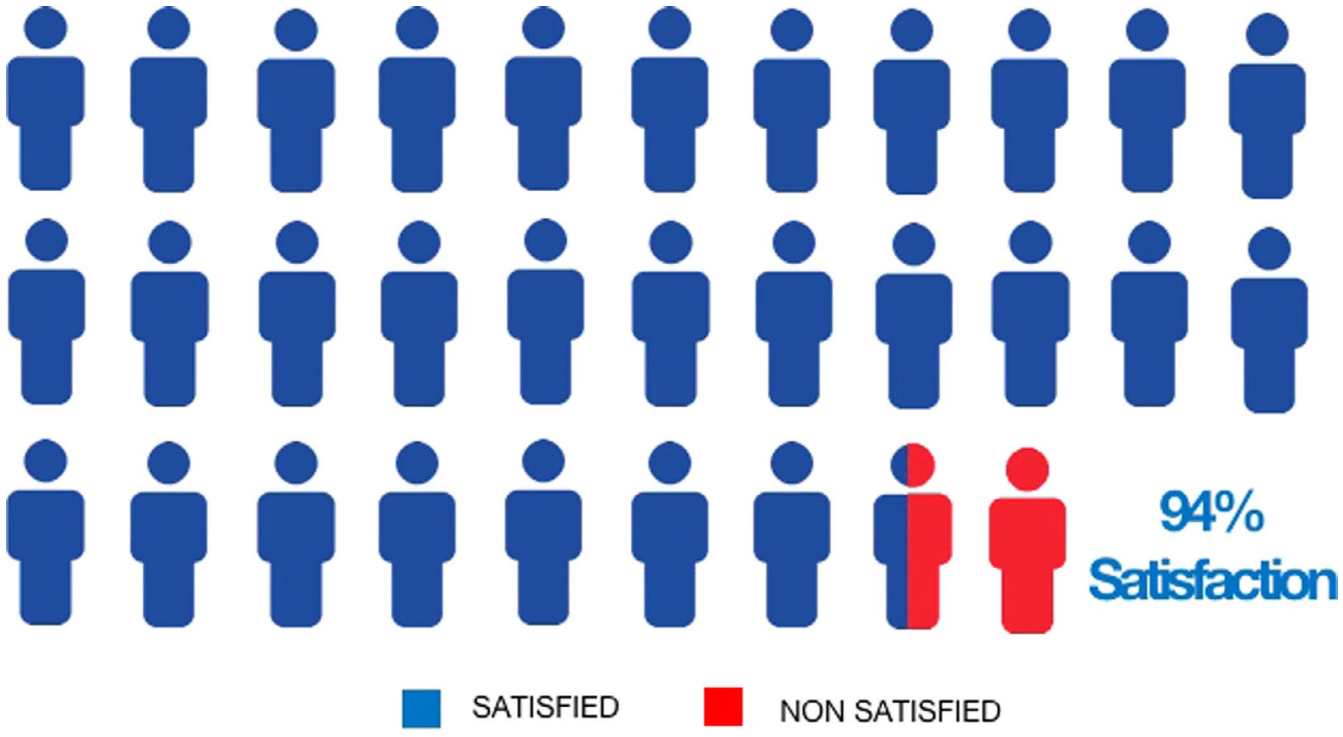



**FIGURE 5** Survey results. Being asked for their satisfaction with the results after 6 wk of regular use of HSF™-based skin care formulation, 94% of study participants were satisfied or very satisfied with their individual outcomes

cells demonstrate markedly lower rates of collagen biosynthesis than what is observed in infant or fetal tissue.[42,43] Similarly, the rate of elastin gene expression is markedly reduced after the fourth decade of life.[44] An imbalance between biosynthesis and degradation of elastin fibers clinically manifests as atrophy and loss of pliability in aged skin. Recent evidence also identifies matrix metalloproteinases (MMPs) as important mediators of this degeneration.[45] By destroying the endogenous collagen network, proteoglycans, fibronectin, and other components of the dermis, these enzymes result in a rapid, though not irreversible, cutaneous aging effect.[46] Altogether, the interplay of these mechanisms affects all three layers of the skin, with its biggest influence on the dermis.[47,48]

### 4.2 | The role of HIF-1 in skin aging

Hypoxia-inducible factor-1 (HIF-1) is a dimeric protein composed of two main subunits, HIF-1α and HIF-1β, which binds to the hypoxia response element (HRE) in the promoter region of target downstream genes. The functional HIF-1α subunit has two different transactivation domains (TAD): $NH_2$ terminal [N-TAD] and COOH terminal [C-TAD]. In the presence of oxygen, the HIF-1α subunit undergoes constant ubiquitination-dependent degradation via the Von Hippel-Landau (VHL) E3 ligase protein[49] after hydroxylation on both transactivation domains[50-52] by oxygen-sensitive prolyl hydroxylases (PHDs). In addition to hypoxia, lack of local free iron is also able to inhibit HIF-1α degradation.[52]

HIF-1α is essential for skin homeostasis and regeneration.[53-55] The activation of more than 100 downstream genes, which have extensive effects on angiogenesis, cell proliferation, migration, and glucose metabolism,[56-58] critically regulating skin regeneration[59] and wound healing,[60,61] are profoundly dysregulated in aging.[9] The concept of intrinsic and extrinsic damage can also be linked to age-related loss of epidermal HIF-1 expression.[8] Recent findings show that cutaneous HIF-1 expression is modulated after UVB exposure and that HIF-1α has an important role in the regulation of cellular responses to this type of genotoxic stress. Lastly, UVB induces ROS, which in turn influences HIF-1α expression affecting DNA repair and keratinocyte survival.[62]

### 4.3 | HIF-1 modulation for skin rejuvenation

Upregulation of HIF-1 reverses age-dependent functional impairments of the skin and results in improved regeneration of aged tissues.[63] The biochemical reactions regulating HIF-1 signaling provide effective therapeutic strategies to promote HIF-1α stabilization and transactivation. Our group has recently demonstrated certain advantages in utilizing iron chelators to stimulate HIF-1 and tissue regeneration.[6,63] These chelators not only deprive HIF-1 degradation of a necessary co-factor, but also reduce reactive oxygen species (ROS) stress via the binding of iron molecules, which in excess can be toxic and accelerate the aging process.[60] Well known as a treatment option for beta-thalassemia and hemochromatosis,[64,65] iron chelating drugs have shown benefits in aesthetic medicine and plastic surgery. With their regenerative potential, they have the ability to increase the retention rate of fat grafts, the survival rate of free flaps, and the healing process of diabetic wounds.[66,67]

In this study, we used an HSF™-based skin care formulation employing an iron-chelation approach for skin rejuvenation. The HIF stimulating factor employed here has been in clinical use for decades and has favorable safety characteristics promising for therapeutic HIF-1 signaling modulation. Our findings demonstrate a clinical proof of principle for the beneficial effects of HSF™-based care on aged skin. The presented data suggest a powerful role for this novel approach in the emerging field of regenerative skin care. However, the promising study results come with some limitations including the lack of the same vehicle as the active product as a control group and the lack of comparative 3D surface measurements between sides.

## 5 | CONCLUSION AND OUTLOOK

With no negative skin reactions and highly significant effects on skin roughness, wrinkles, and moisturization, the HSF™-based skin care formulation achieved satisfactory outcomes in this clinical trial. Given the promising results, this approach represents a true innovation in aesthetic and regenerative medicine.

### ACKNOWLEDGMENTS

The authors thank the team of Institute Dr Schrader (Holzminden, Germany) for support in the execution of $FOITS_{HD}$, Corneometer, and Tewameter studies.

### CONFLICT OF INTEREST

DT and DD are co-founders of, and have equity positions in, Tomorrowlabs GmbH, a commercial-stage biotech company that produces skin and hair care based on HSF Technology. Tomorrowlabs GmbH provided research grant support for the study. The other authors have no conflicts of interest to declare. The authors listed expressly wrote the content of this article. No ghostwriters were used to write this article.

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