

CLINICAL REPORT

Treatment of Acne With a 1726 nm Laser, Air Cooling, and Real-Time Temperature Monitoring, Software-Assisted Power Adjustment to Achieve a Temperature Endpoint With Selective Sebaceous Gland Photothermolysis

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Received: 6 December 2024 | **Revised:** 6 December 2024 | **Accepted:** 10 December 2024

Keywords: 1726-nm laser | acne vulgaris | air cooling | laser acne treatment | multi-pulse | sebaceous glands | temperature control | thermal imaging

ABSTRACT

Objectives: This work highlights the methods used to develop a multi-pulse 1726 nm laser system combined with bulk air-cooling for selective sebaceous gland (SG) photothermolysis using thermal imaging and software algorithms. This approach enables treating to a desired tissue temperature and depth to provide a safe, effective, reproducible, and durable treatment of acne.

Methods: We designed and built a 1726 nm laser system with a 40 W maximum power output, a highly controlled air-cooling device, and a thermal camera in the handpiece, which permits real-time temperature monitoring of the epidermis. IRB-approved safety and efficacy trials demonstrated SG damage at depth, resulting in safe, efficacious, and durable clinical outcomes. Bioheat transfer and light transport modeling confirmed that the pulsing protocols could produce therapeutic temperatures at various SG depths, while protecting the epidermis and dermis with bulk air-cooling. Similarly, we employed clinical observations and photothermal modeling to identify pain mitigation opportunities while maintaining therapeutic efficacy. Biopsies were subsequently taken for histological evaluation.

Results: Clinical and histological data, confirmed with modeling, demonstrated that multi-pulse laser delivery with bulk air-cooling selectively increased SG temperature compared to surrounding dermis and at depths unachievable by a single pulse. Subjects showed an average 71% ILC reduction at 3 months posttreatment. We identified two different pulsing protocols with similar selective photothermolysis (SP) of the SG with very different pain responses. Thus, changing the pulsing protocols allowed for pain mitigation and eliminated the need for injectable anesthetic. Histology confirmed the selective damaging of the SG at depth and the preservation of the surrounding dermis and the epidermis.

Conclusions: The multi-pulse 1726 nm laser with bulk air-cooling, thermal monitoring, treat-to-temperature (and depth) control, and a unique pulsing protocol, is capable of selectively damaging SGs at depth without damage to the surrounding

dermis or the epidermis. The system offers two different protocols that were developed with different levels of discomfort allowing for two different methods for pain mitigation (injectable vs. topical anesthesia).

1 | Introduction

Acne vulgaris (acne) is among the most common skin disorders. Acne can manifest at any time in a patient's life and accounts for nearly 30% of visits to dermatologists in the United States. Approximately 85% of the population between the ages of 12–24 years are impacted by this condition [1, 2]. The pathophysiology of this disease involves increased sebum production, blockage of the pilosebaceous duct, proliferation of *Cutibacterium acnes*, and inflammation [3].

The treatment of acne can involve combinations of topical and sometimes systemic therapies which generally require continual daily use. Long-term oral antibiotics are not recommended due to the development of bacterial resistance. More severe and treatment-resistant cases of acne are often treated with isotretinoin. This drug targets the sebaceous glands (SGs) and is associated with a number of mild and some severe side effects including teratogenicity. The use of this agent requires close supervision by a provider [4, 5] with close pregnancy monitoring in females, blood studies, and monthly monitoring before, during, and after treatment. The inconvenience and side effects of these drug therapies have provided a window of opportunity for the use of devices to treat this condition.

Numerous lasers and light sources with wavelengths of 1450, 1320, 1064, and 595 nm, as well as broadband light sources have been studied for the treatment of acne [6–13]. They have had varying degrees of success but none of these devices have demonstrated the ability of selectively damaging SGs without significant damage to surrounding skin structures, and they have not provided a durable response.

Investigators have also used exogenous topical agents applied to the surface of the skin followed by light with the goal of having the agents penetrate into the SG and activating them with different light sources. Hongcharu and others were able to successfully damage SGs and improve acne with high-dose red light and aminolaevulinic acid. Unfortunately, this was accompanied by absorption in the epidermis resulting in erythema, crusting, and superficial erosions lasting days [14–18]. Others have used indocyanine green (ICG) dye or gold nano shells applied to the skin with the goal of them being deposited in SGs, followed by exposure to infrared light [19–22]; however, the preparations used were inadequate to deliver sufficient product to the SG to be useful or practical.

In 2006, Anderson et al. studied the potential for selective photothermolysis (SP) of lipid-rich tissues such as fat, SGs, or atherosclerotic plaques. Photothermal excitation spectra were taken around the 1210 and 1720 nm bands with a free electron laser (FEL) as the light source [23]. In an effort to develop a laser treatment targeting the SG for acne, Sakamoto et al. undertook an extensive evaluation of the laser source requirements that might result in an effective long-duration treatment

for acne [24]. Sakamoto et al. hypothesized that by using sebum produced by the SG as the chromophore, irreversible damage to sebocytes should be the goal of the treatment and investigated the absorption spectra of SGs. They estimated thermal propagation and selected values for laser pulse duration, energy dosages and treatment areas. She and her team of investigators discovered sebum absorption peaks at 1210, 1726, 2306, and 2346 nm, relative to water (Figure 1).

When considering depths of penetration, differential absorption between sebum and water, and absorption peaks, they suggested that a laser at 1726 or 1210 nm with a pulse duration of approximately 100 ms would be ideal to target the SGs in human skin using sebum as the chromophore. While SGs do preferentially absorb 1726 nm light more efficiently than the dermis does, that difference is not great.

In 2011, Alexander et al. reported their experience with a 1708 nm Raman fiber laser and contact cooling to treat ex vivo human skin. They demonstrated preservation of the epidermis (with cooling) and damage to SGs, but unfortunately also to the surrounding dermis. This was likely a result of the bulk heating caused by a very long effective treatment pulse time of 1 s [25].

The 1726 nm absorption band of sebum lipids has about 30% higher absorption than water. This minimal contrast of absorption and heat capacity poses a challenge to achieve SP of SGs without injury to the surrounding dermis. Sakamoto and colleagues proposed laser preconditioning of the skin for 20 s at 0.5 W, followed by a single treatment pulse of 30–35 W with contact cooling. This approach produced consistent thermal damage at a depth of 0.5–1 mm, while consistently sparing the epidermis. Histological studies showed epidermal viability and selective thermal damage to SGs [26].

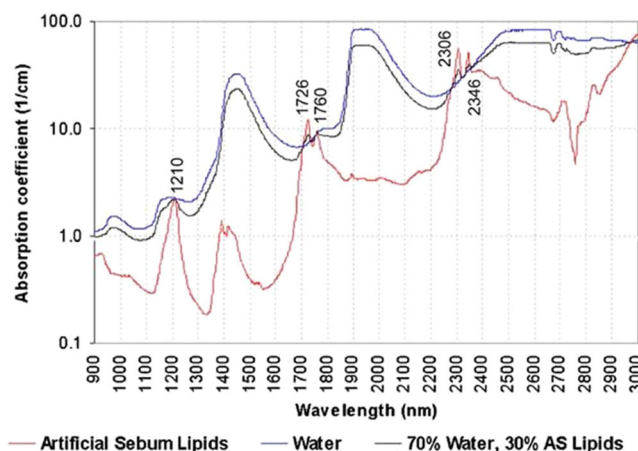


FIGURE 1 | Measured absorption coefficients (μ_a) in cm^{-1} of artificial sebum (AS) and water. For AS the 28% (w/w) solution and 1 mm pathlength cuvette used, $\mu_a = 23 \text{ OD}/0.25$, where OD is the measured optical density. Permission by Wiley from Sakamoto et al. [24].

In this paper, we report the methods used to develop a multi-pulse 1726 nm laser system combined with bulk air-cooling for SP of the SG. We used thermal imaging as a way to control the pulse delivery at the ideal temperature and depth providing for a safe, effective, reproducible, and durable treatment of acne. We employed a multi-pulse strategy to gradually heat and cool the skin to further localize the heating of the SG. Clinical, histology, and modeling data demonstrated that multi-pulse laser delivery with bulk air-cooling increased SG temperature selectively compared to surrounding dermis and at depths unachievable by a single pulse. Software control was incorporated into the device hardware to monitor surface temperatures and adjust power to arrive at a selected temperature endpoint. It also provided this device with the capability to stop the treatment if excessive cooling or excessive heating is occurring or is anticipated before a damaging temperature is reached. These safety features provide the confidence to treat patients to the point of significant SG damage that is confined only to this structure. We identified two different pulsing protocols: (1) a “standard mode,” which requires injectable anesthesia; and (2) a “boost mode,” with better patient comfort requiring only topical anesthesia. Histology confirmed the selective damaging of the SG at depth and the preservation of the surrounding dermis and the epidermis. IRB study data for these protocols for the treatment of acne is provided.

2 | Materials and Methods

2.1 | Development Approach

Our path to develop this laser treatment was iterative and involved several small clinical studies over a period of several years. Along the way, we learned that treating acne with laser energy is more than just the judicious selection of a wavelength. It required an understanding of the heating and cooling processes involved with precise control of laser power to ensure that we treat both safely and efficaciously. The system needed to be able to respond to changes in skin thermal properties between different patients, skin locations, and bulk skin cooling conditions. The process involved the close collaboration of the principal investigators and engineering team over the course of the project. It was the key to the success of our endeavor.

The multi-pulse Raman fiber laser in this report emits light at 1726 nm, with a maximum power of 40 W and laser pulses from 100 to 150 ms. It was developed by Accure Acne Inc. in collaboration with Quanta System S.p.A. (Samarate, Italy), a subsidiary of El. En. S.p.A. (Firenze, Italy). The laser is coupled with a custom skin air-cooling system, handpiece including a thermal camera, and a dedicated beam scanner. The laser spot is a square of size $4.7 \times 4.7 \text{ mm}^2$ with a uniform (flat-top) intensity profile. The beam spot is raster scanned in a Z-pattern forming a 2×2 grid with a 0.7 mm gap between spots resulting in a treated area of 1 cm^2 .

2.2 | Air Cooling

We started with contact cooling and realized quickly the limitations and chose air cooling. Air cooling, unlike contact

cooling, effectively has infinite thermal mass. That is, the cooling air blowing on the skin is never warmed up by the heat removed from the skin as it's constantly replenished with “new” cold air. By contrast, the cold window on a contact cooling system has a finite thermal mass and warms up as soon as it contacts the skin. Finally, air cooling is very consistent; it does not require perfect contact with skin like a contact cooling system does to maintain its heat extraction rate and avoid adverse events [27].

At first, we utilized a commercially available cooling system (Zimmer MedizinSysteme GmbH). An understood limitation of air cooling is the variability of the delivery of the cooling. To address this issue, we implemented a pre-cooling period to achieve a sustainable internal air temperature and monitored the output at the end of the handpiece (delivery hose) to assure that the air temperature and airflow are within a narrow set of parameters. These controls ensure that the device can be operated with consistent and reproducible cooling during use. We believe we are the first group to address these previously neglected but very important variables.

2.3 | Real-Time Temperature Monitoring

Our initial development of the laser did not include a thermal camera. We quickly discovered that the use of a thermal camera was critical to ensure a safe epidermal temperature. Once integrated, the thermal camera allowed the system to continuously monitor the skin surface temperature immediately before, during and after a pulse train is delivered. Real-time temperature monitoring during the delivery of the pulses is not feasible or practical with other cooling methods as the $8\text{--}12 \mu\text{m}$ thermal radiation emitted by the skin does not transmit through typical contact cooling materials, such as sapphire.

2.4 | Multi-Pulse Laser Exposure

We initially tried pulsing the laser as recommended by Sakamoto and colleagues with low power, long preconditioning of the skin followed by a single treatment pulse. The commercial viability of this approach was limited. We thought and validated that a multi-pulse approach combined with bulk air-cooling created selective SG damage in a commercially acceptable treatment time.

Combining bulk air cooling before, during and after the laser pulsing with multi-pulse heating over several seconds deposits heat in bursts into the upper 0.2–0.5 mm layer of the skin and then allows it to slowly diffuse to the deeper tissue of 0.4–1.5 mm, where SGs reside. This process establishes the appropriate thermal gradient deep into the skin, allowing us to selectively heat SGs while maintaining the epidermal and dermal tissue at safe temperatures.

Several skin target temperatures before laser emission were evaluated. When the skin reaches a preset temperature (e.g., -1°C) during its initial cooldown, the multi-pulse emission sequence begins. At the end of the pulse sequence, the system

displays peak epidermal temperature (PET), which is the maximum surface temperature reached at the end of the last laser pulse. The targeted PET, the basis of treating-to-temperature, is set by the user.

2.5 | Treat to Temperature

For laser systems without thermal imaging to control the pulsing, the practitioner selects the laser dosage from a range of laser power or fluence settings which produce a desired clinical end-point or have been proven to be safe settings to produce the desired outcome. Due to the narrow therapeutic window of safety due to significant water absorption at 1726 nm, variability in skin thermal response to heating and cooling, and the lack of an immediate clinical endpoint to the treatment, we found that a treat-to-temperature approach was needed. In this approach, the practitioner sets a temperature as the endpoint rather than fixing laser power or fluence. Using real-time thermal imaging as a method of controlling the laser power and monitoring the skin during a multi-pulse protocol enables the system to stop the treatment if an unwanted high temperature was measured.

To enable treat-to-temperature, we developed specialized software to control laser power delivered during the treatment. The software administers the treatment protocol set by the user by measuring a skin surface temperature at the location to be treated. Following the delivery of the first laser pulse and air cooling provided, the software estimates the relationship between the power, cooling, and the skin surface temperature to adjust the thermal energy delivered by the next laser pulse and cooling. This process continues until the target PET is reached. During this time, the software maintains the skin surface temperature within a safe operating range. The treatment is stopped if the skin temperature is outside the range.

2.6 | Clinical Studies

We conducted eight IRB-approved studies over a period spanning from March 2018 to September 2024 (Table 1). We are referencing six of the eight studies as they were significant in the development of our methodology. In all studies, subjects' safety was our primary concern. Early studies focused on determining the appropriate dosimetry and target PET for the face and back, comparing efficacy via split-face and back pilot studies, identifying pulsing protocols, and evaluating safety and efficacy via histology.

2.6.1 | IRB-Approved Study 20170790

This open-label single group single-center study assessed the safety of this laser's application to live human skin and to determine a safe range of power outputs to damage SGs for the treatment of acne vulgaris. Ten (10) subjects were enrolled in this safety trial beginning on March 22, 2018, and completed on February 7, 2020.

2.6.2 | IRB-Approved Study 20172819

This two-site pivotal study used a split-face randomized design such that each subject received the active study treatment on one side of the face only. Fifteen (15) subjects were enrolled in this study beginning October 14, 2019, and completed on July 14, 2020.

2.6.3 | IRB-Approved Study 20182416

This was a single-center non-randomized, open-label study. Each subject acted as his or her own control in the back treatment area. Subjects received up to four treatment sessions,

TABLE 1 | Eight IRB-approved studies were conducted over a period spanning from March 2018 to September 2024.

IRB identifier	Keywords	Mode	Principal investigators	N
20179790	Safety and dosimetry, face and back	Seven-pulse	Emil A. Tanghetti, MD	10
20172819	Split-face pivotal	Seven-pulse	Emil A. Tanghetti, MD Roy G. Geronemus, MD	15
20182416	Dosimetry back, pilot	Seven-pulse	Emil A. Tanghetti, MD	13
20190111	Split-face, pilot	Seven-pulse	Emil A. Tanghetti, MD Roy G. Geronemus, MD	22
20202009	Seven- and six-pulse protocols	Seven- and six-pulse	Emil A. Tanghetti, MD	6
20203414	Pivotal study	Six-pulse standard	Emil A. Tanghetti, MD Roy G. Geronemus, MD Joel L. Cohen, MD Daniel P. Friedmann, MD Mitchel Goldman, MD	53
20213875	Long-term F/U 20172819, 20182416, 20190111	Seven-pulse	Emil A. Tanghetti, MD Roy G. Geronemus, MD	—
20225675	Needle-free study	Six-pulse boost	Roy G. Geronemus, MD Daniel P. Friedmann, MD Mitchel P. Goldman, MD	25

each occurring 4 ± 2 weeks apart. Thirteen (13) subjects were enrolled in this study beginning September 28, 2018, and completed on February 28, 2020. Lesion counts were performed by the investigator.

2.6.4 | IRB-Approved Study 20190111

This two-site pilot study used a split-face design such that each subject received the treatment on selected areas on one side of the face. The purpose of this pilot evaluation was to assess the efficacy of the laser for the treatment of moderate facial acne vulgaris in preparation for a full-scale controlled pivotal trial. The Principal Investigator determined the specific area(s) of the cheek and jawline of the subject's hemiface to be treated. It was intended that each subject receive four treatment sessions. Each session occurred 3 ± 2 weeks apart. Twenty-four (24) subjects were enrolled in the study beginning March 15, 2019, and completed on July 28, 2020. Lesion counts were performed by the investigators.

2.6.5 | IRB-Approved Study 20202009

This study was a single-site, open-label, single-group, non-randomized study. This study clinically compared the seven-pulse and six-pulse protocols. Six (6) subjects were enrolled in the study beginning August 6, 2020, and completed on August 8, 2020. A grid of up to $10 \text{ cm} \times 10 \text{ cm}$ was applied to each of three selected treatment areas on the back of the neck and/or the back. Each treatment area was split in half with two different pulsing protocols applied: six-pulse and seven-pulse as described in Table 2. The laser power and corresponding target PET was increased from treatment areas 1 to 3. For each half of a treated area, up to three laser emissions were applied for each pulsing protocol. No laser emissions overlapped. Local anesthesia was administered before treatment administration.

2.6.6 | IRB-Approved Study 20213875

This study used an open-label, single-arm, long-term, follow-up design such that each subject was previously enrolled in and received treatment in, one of three studies 20172819, 20182416, and 20190111. Subject enrollment enabled ongoing long-term follow-up of the efficacy and safety of the Accure Laser treatment received in the initial study.

TABLE 2 | Two pulsing protocols.

	6-pulse	7-pulse
Number of laser pulses	6	7
Pulse duration (ms)	100	150
Time between pulses (s)	1.3	1.95
Time to deliver all pulses (s)	7.1	12.75

2.7 | Numerical Modeling

To understand how all the elements combine to make “treat-to-temperature at depth” possible, we investigated the laser heating, air cooling, and propagation of heat in biological tissue. We did this by modeling the photothermal dynamics of a treatment using numerical analysis tools and comparing it with measurable skin temperatures over a range of laser powers. We were interested in establishing the applicability of a numerical model to validate the use of skin surface temperature as a surrogate for SG temperature measurements. Most of the modeling was done to understand and define the findings observed in our clinical studies.

The first step was to model heat deposition in skin tissue. We employed Monte Carlo simulation to model the propagation of laser radiation through the target tissue. We used the Monte Carlo Multi-Layer (MCML) code, an open-source software application, for this process [28, 29]. The parameters of the configuration are shown in Table 3. The target temperature expected to initiate SG damage is given in the table as 60°C , consistent with damage onset temperature in other tissues. MCML follows the propagation of a packet of photons as it traverses a tissue composed of a series of layers. The tissue consists of five layers including one that is composed of sebum as a means of simulating a SG. The diameter of this layer is 4.0 mm, far greater than a typical gland. As already noted, this simulation assumes cylindrical symmetry, so the loss of azimuthal details is not a significant limitation. Each layer is described by the optical parameters of the tissue in that layer. The optical parameters of the tissue and the laser pulse description are given in Table 4 [30–34]. The optical coefficients for both normal skin and lipid-containing tissues, the input data to the simulations, were obtained from compendiums and numerical formulas published by Jacques and colleagues [30–34]. The output of MCML is a map of energy deposition in the tissue versus depth and lateral extent.

The next step was to determine where that deposited heat flowed. We did that by solving the heat equation using Green's Functions. The output of this step was a map of temperature

TABLE 3 | Laser exposure and sebaceous gland parameters.

Laser	
Wavelength (nm)	1726
Number of pulses	6
Pulse duration (ms)	100
Time between pulses (s)	1.3
Laser spot size (mm)	4.7×4.7 square
Exposure configuration	2×2 array
Treatment area (cm^2)	1
Air cooling ($^\circ\text{C}$)	−20
Skin precooling with air ($^\circ\text{C}$)	−1
Sebaceous gland	
Diameter (mm)	0.5
Depth (mm)	0.8–1.3

TABLE 4 | Monte Carlo inputs.

Parameter	Epidermis	Papillary dermis	Sebaceous gland	Reticular dermis	Adipose
Absorption μ_a (cm^{-1})	4.1	3.9	8.1	3.9	11.4
Scattering μ_s (cm^{-1})	247	164	97.8	164	114
Scattering anisotropy g	0.9	0.9	0.9	0.9	0.9
Refractive index	1.37	1.37	1.37	1.37	1.37
Layer thickness (μm)	60	740	500	1700	2000

versus depth and time. The details of this method are described in the Supporting Information. This numerical modeling capability allowed us to evaluate the effects of different pulsing protocols on the SP of SGs in terms of expected treatment depth, pain, and target PET. We present those results in the following section.

3 | Results

Below we summarize the results of our clinical studies and numerical modeling. Together, these results support our approach of treating to a desired tissue temperature and depth to provide a safe, effective, reproducible, and durable treatment of acne.

3.1 | Clinical Data From IRB-Approved Studies

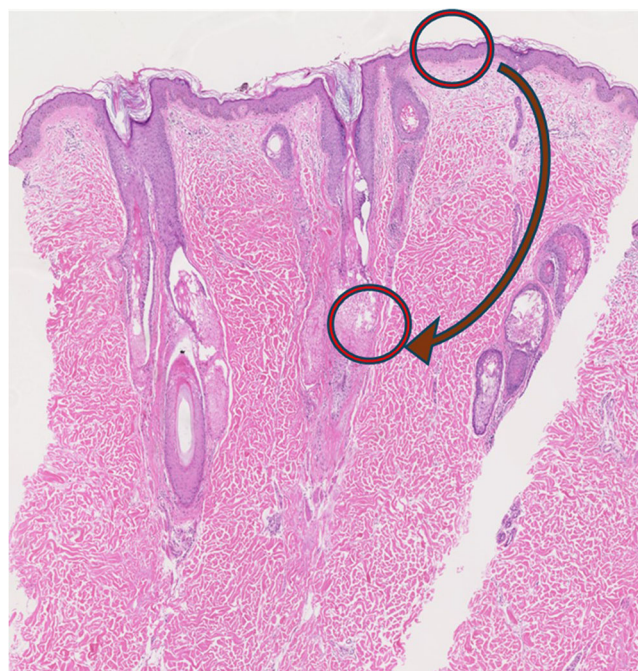
3.1.1 | IRB-Approved Study 20170790

We learned that anesthesia injected locally was needed for pain mitigation and changed the grid pulsing methodology to avoid any potential overlap of the cooling. The goals of the safety study were met across a 14-month period. Histology showed clear SG damage with no damage to surrounding tissue.

The hematoxylin and eosin (H&E)-stained histology revealed damage of the sebocytes in the SGs with eosinophilic color (pink) changes and loss of fine cellular details (Figures 2 and 3). These changes extended to but did not include the follicular canal. Some of the surrounding small vessels adjacent and directly next to the follicle appear to have small clots. The surrounding dermis, hair follicles, and other dermal structures show no microscopic changes. The following H&E-stained section of the back reveals histological evidence of thermal damage to the SGs again without any evidence of damage to the *surrounding structures* at depths from 0.4 to 1.3 mm with eosinophilic changes and loss of fine cellular details (Figure 4).

3.1.2 | IRB-Approved Study 20172819

This study was cut short due to COVID-19 restrictions. The preliminary results were encouraging. Two subjects (one at 3 months and one at 6 months posttreatment) reported being “Extremely Satisfied” compared with “Very Satisfied” for the untreated side. One subject who only had two treatments had significant improvement at a 13-month follow-up. One adverse

**FIGURE 2** | Histological evidence of thermal damage restricted to sebaceous glands.

event prompted us to reduce the target PET for treating the forehead from 43°C to 41°C.

Images from three subjects (Figures 5–7) are presented with baseline and long-term follow-up results demonstrating durable responses at 3, 6, 13, 21, and 35 months following treatment completion.

3.1.3 | IRB-Approved Study 20182416

The percentage change in inflammatory lesion count (ILC), noninflammatory lesion count (NILC), and total lesion count (TLC) across all available evaluations for sides of the back and back of the neck treated with the laser are shown in Table 5. Even with the small sample size, these progressive decreases were overall statistically significant ($p < 0.0001$) for both ILC and TLC for the treated side. NILC decreases were not statistically significant ($p > 0.05$). Histology showed clear SG damage with no damage to surrounding tissue.

As anticipated, erythema and inflammatory papules were the most commonly encountered events following treatment administration, generally occurring in about one-half to three-

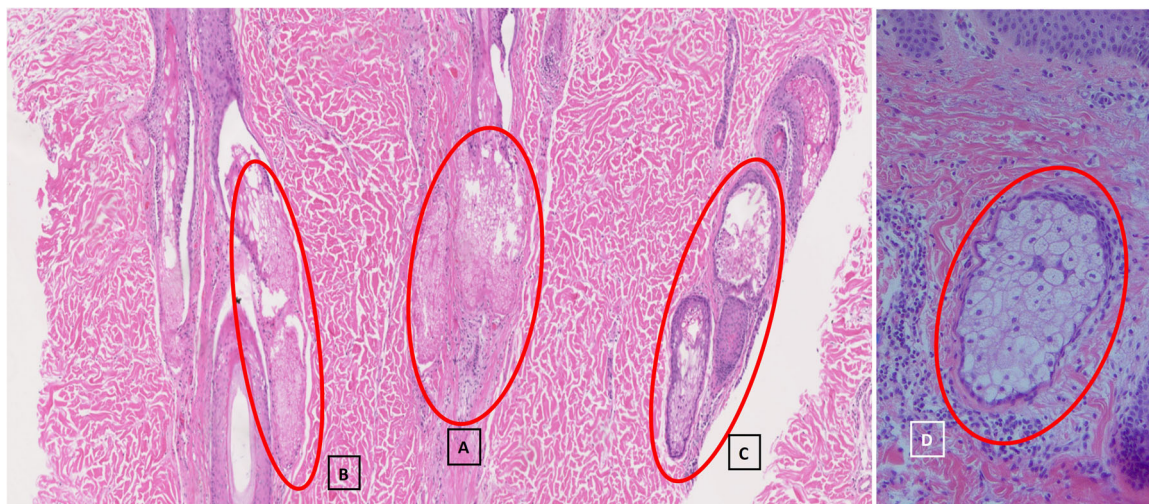


FIGURE 3 | Left side image (A–C): Histological evidence of complete (A and B) and partial (C) thermal damage to sebaceous glands without visible changes to dermis and follicle. Right side image (D): undamaged sebaceous gland for reference.

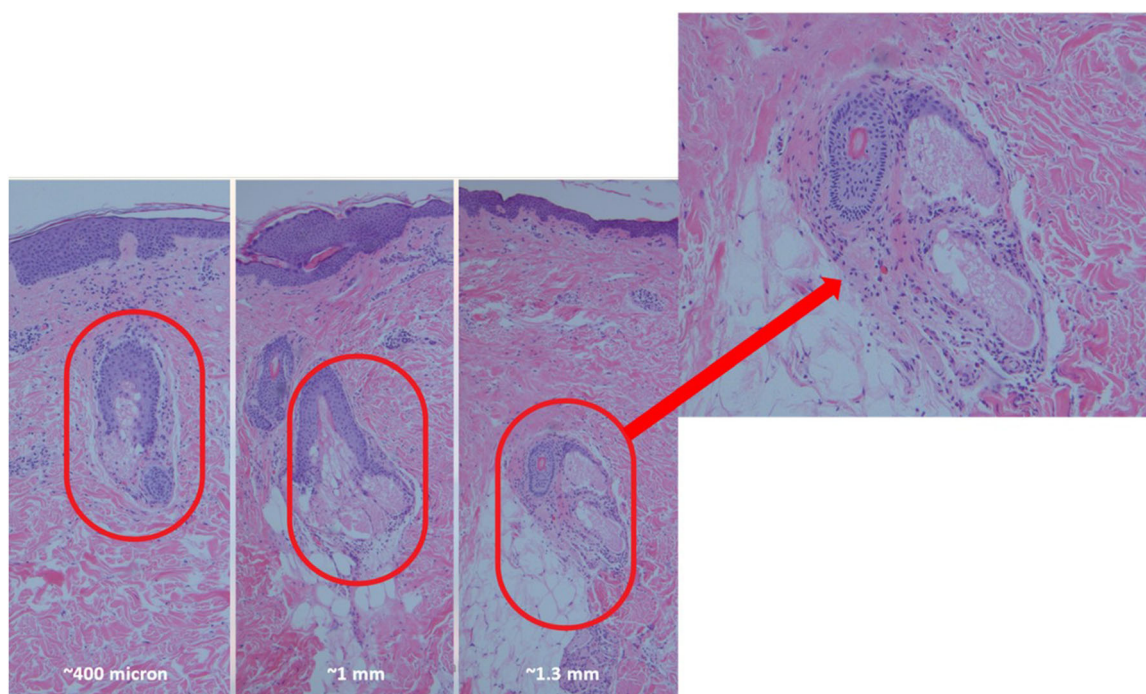


FIGURE 4 | Histological evidence of thermal damage to sebaceous glands at depths 0.4–1.3 mm.

quarters of cases. All instances were mild and restricted to the treatment area with resolution typically occurring in 72 h to 1 week, following treatment.

3.1.4 | IRB-Approved Study 20190111

This was the first study where the mean percent change for all three; baseline ILC, NILC, and TLC, showed a statistically significant positive treatment effect of the laser over control.

Three-quarters of treated subjects (12 of 16) received the full treatment protocol of four treatment administrations, two subjects received three treatments, and two subjects

received two treatments. One study site started later and encountered scheduling and recruitment conflicts due to COVID-19.

Both power (W) and PET (°C) were consistent across subjects and across all treatment administrations, with power spanning the range from 21.5 to 24.5 W, and PET spanning the range from 39.2°C to 46.5°C. The gender, age, and Fitzpatrick skin type (FST) of those treated in the study ($n = 16$), 14 subjects were female and two were male with a mean age of 24.7 years (range, 19–38 years) with FST II ($n = 5$), III ($n = 6$), IV ($n = 4$), and VI ($n = 1$). Table 6 shows the percent (%) change from Baseline for ILC, NILC, and TLC across the progressive study evaluations for treated areas. Figure 8



FIGURE 5 | Clinical photos of a 24-year-old female subject (skin type VI) taken at baseline pretreatment (left) and at 6, 21, and 35 months follow-up after the fourth treatment (right).



FIGURE 6 | Clinical photos of a 33-year-old female subject (skin type IV) taken at baseline pretreatment (right) and at 3 months follow-up after the fourth treatment (right).

illustrates the percent change in mean baseline ILC, NILC, and TLC across study time points.

The safety profile was comparable across all evaluated subjects, indicating laser application is safe for use across skin types. The progressive decrease in ILC across study progression was found to be overall statistically significant for the treated side ($p < 0.0001$). Each individual evaluation visit relative to baseline achieved a $p < 0.01$. The progressive decrease in ILC across study progression for the untreated side was also found to be statistically significant overall although to a lesser degree of significance ($p < 0.05$) and driven entirely by the single change at the treatment end evaluation visit relative to baseline

($p < 0.01$). The mean percent change for baseline ILC, NILC, and TLC at each of the progressive evaluation visits was consistently greater for treated sides, indicating a positive laser treatment effect. The decreases in lesion counts observed for untreated sides are likely explained by factors such as the general waxing and waning of acne, the systemic effect of the therapy of the laser, and subjects likely taking better care of their skin while being in a clinical study. The primary safety findings were mild erythema and mild red papules in the treatment zone following treatment administration with the laser that was quick to resolve. Overall, the pain was well controlled with injected anesthesia. Most subjects reported no to minimal pain (mild, VAS < 30) during treatment administration. Additional safety



FIGURE 7 | Clinical photos of a 16-year-old male subject (skin type IV) taken at baseline pretreatment (left) and at 13 months follow-up after second treatment (right).

TABLE 5 | Percent change in baseline acne lesion counts for sides treated with laser at progressive evaluations.

Treatment side	Lesion counts (% change)		Total
	Inflammatory	Noninflammatory	
Baseline to treatment 2	−52.4	−3.9	−39.3
Baseline to treatment 3	−53.5	−33.9	−48.2
Baseline to treatment 4	−81.8	−40.2	−70.6
Baseline to 3-month follow-up	−70.8	−80.8	−73.5
Baseline to 6-month follow-up	−74.3	−73.5	−74.0

TABLE 6 | Percent change in baseline acne lesion counts for treated sides.

Treatment sides	Lesion counts (% change)		Total
	Inflammatory	Noninflammatory	
Baseline to end of treatment	−58.4	−70.3	−62.4
Baseline to 4 weeks posttreatment	−68.8	−55.1	−64.1
Baseline to 8 weeks posttreatment	−72.4	−42.9	−62.3
Baseline to 12 weeks posttreatment	−71.0	−58.7	−66.8
Baseline to 6 months posttreatment	−77.6	−90.5	−82.0
Baseline to 9 months posttreatment	−70.2	−90.5	−75.5

factors were observed for five subjects and included mild swelling, bruising, erythematous macules, itching, slight stinging, warmth, dryness/tightness, and acne flare-ups. Long-term safety at 6- and 9-months posttreatment was demonstrated. Images from three subjects (Figures 9–11) are presented for baseline and long-term follow-up demonstrating durable responses at 3 and 28 months following treatment.

3.1.5 | IRB-Approved Study 20202009

Utilizing the six-pulse protocol equated to a 44.3% reduction in time compared to the seven-pulse protocol. This has both an impact on the practical application and the potential commercial viability of the laser. Based upon the histological damage and safety results future clinical trials will utilize the six-pulse

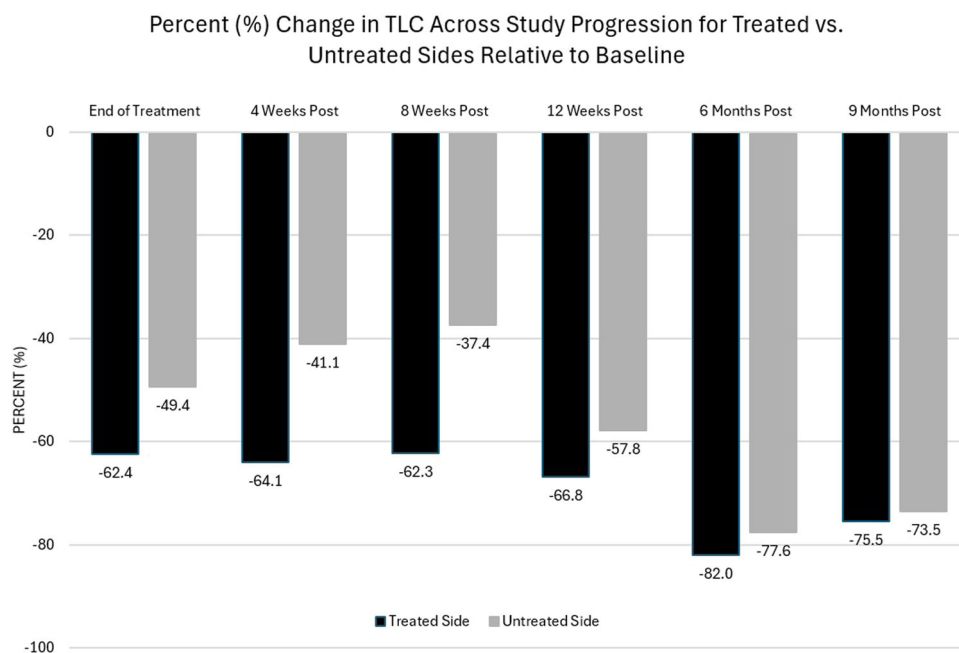


FIGURE 8 | Progressive percent change in baseline total (ILC + NILC) acne lesion counts for treated versus untreated sides.



FIGURE 9 | Clinical photos of a 27-year-old male subject (skin type II) taken at baseline pretreatment (left) and at 3 months follow-up after the fourth treatment (right).

protocol. The numerical modeling for this six-pulse “standard mode” is presented later in this section.

The range of evaluated PETs for the six-pulse and seven-pulse protocols was adjusted from 40.1°C to 48.3°C. At the 24-h posttreatment administration visit, visual assessment, photographic documentation, and evaluation of the treatment area for adverse events were performed and punch biopsies were taken. One or two punch biopsies per treatment area were obtained by the Principal Investigator. No adverse events occurred immediately posttreatment nor at the 24-h assessment.

The two pulsing protocols had a direct impact on the overall procedure treatment time. The total time to deliver each sequence of pulses comprising a single laser treatment area was confirmed to be 7.1 and 12.75 s for the six-pulse and seven-pulse protocols, respectively.

3.1.6 | IRB-Approved Study 20213875

A limited number of subjects consented to follow-up for up to 35 months posttreatment, see Figures 5 and 10.



FIGURE 10 | Clinical photos of a 19-year-old female subject (skin type II) taken at baseline pretreatment (left) and at 28 months follow-up after the fourth treatment (right).



FIGURE 11 | Clinical photos of a 23-year-old female patient (skin type II) taken at baseline pretreatment (left) and at 3 months follow-up after the fourth treatment (right).

3.2 | Numerical Modeling

3.2.1 | Intent of Modeling

As described in Section 2 above, numerical modeling allowed us to understand how all the elements of our treatment approach combine to make “treat-to-temperature at depth” possible.

Specifically, we demonstrate that: (1) predicted SG and surrounding tissue temperatures are consistent with what we observe clinically and histologically; (2) surface temperature is a good proxy for treatment temperatures at depth; (3) multi-pulse treatment enables destructively heating SGs at depth; and (4) treatment comfort may be controlled by a unique application of treat-to-temperature pulsing protocol.

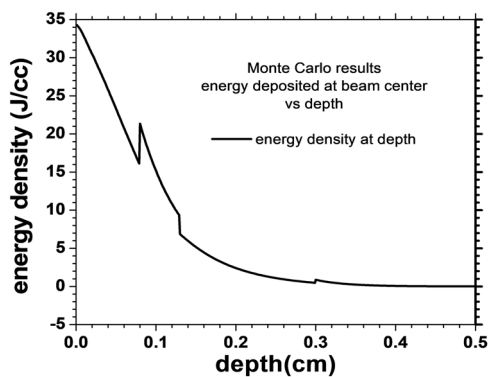


FIGURE 12 | Typical Monte Carlo Multi-Layer output graph.

3.2.2 | Numerical Modeling Outputs

The energy density deposited by a single laser pulse exposure has been simulated using the Monte Carlo Multi-Layer (MCML) code. The output of the simulation is plotted in Figure 12. The plot shows the energy density deposited in the tissue plotted versus depth inside the tissue. The heat equation scales linearly with laser power. The MCML was carried out in the case shown here with a laser power yielding 1 J total energy in a single 100 ms pulse. The energy density decreases with depth as the laser pulse is absorbed. The data shows an embedded region from 0.8 to 1.3 mm depth that exhibits a 37% greater stored energy density than surrounding tissue. This is the location of the lipid layer that simulates the effect of an SG. The data from these calculations is converted into a temperature profile and used to calculate the temperature rise.

The time resolved temperature response at the tissue surface corresponding to the MCML pulse is shown in Figure 13. Here, a 100 ms laser pulse is applied to the tissue. The output power of the laser was set to 25 W. The figure shows a rapid rise in temperature during the first 100 ms consistent with the laser application. The surface temperature is initially about -1.5°C and rises rapidly to $\sim 17^{\circ}\text{C}$. From there, the temperature decays by about 50% of the initial rise in response to the air cooling applied.

3.2.3 | Multiple Pulses to Treat at Depth

We initially tried a *single*, 150 ms laser pulse with both air cooling and contact cooling; however, we were unable to show histological damage of SGs without significant damage to the epidermis and superficial dermis. The issue, as it turned out, was that SGs at 0.4–1.5 mm below the surface are deeper than the 0.2–0.5 mm absorption depth of a single pulse of 1726 nm laser light. Additionally, the efficacious temperature window for achieving SG damage while protecting the surrounding dermis is small.

While SGs do preferentially absorb 1726 nm light more efficiently than the dermis does, that difference is not great: for a 100 ms pulse, a 0.5 mm diameter SG might heat $\sim 5^{\circ}\text{C}$ hotter than dermal tissue at the same depth. Even a shorter, 50 ms pulse, which slightly enhances the difference between SG and dermis for a short period (the thermal relaxation time of the gland), results in a temperature difference of only $\sim 6^{\circ}\text{C}$ (see Supporting Information).

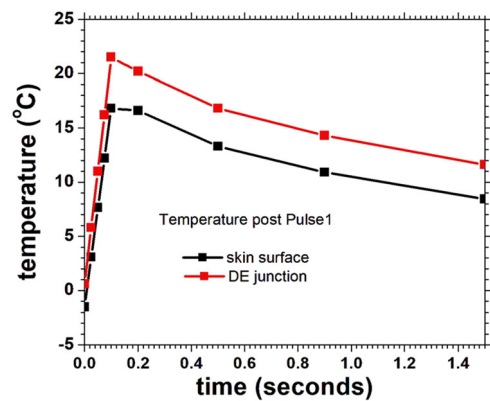


FIGURE 13 | Time resolved temperature response to a single laser pulse.

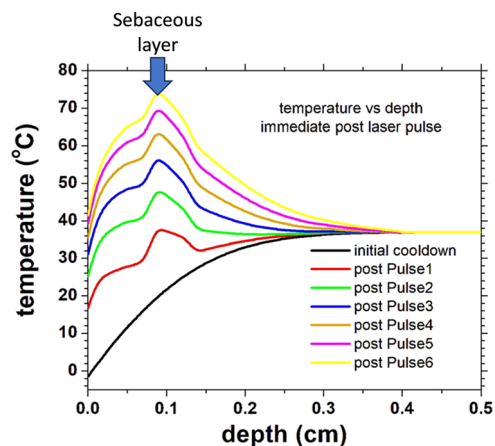


FIGURE 14 | Temperature versus depth for a six-pulse “Standard” format treatment.

Simulations have been run for a number of multiple pulse laser configurations, the details of which are presented in Table 2. Actual treatment pulses are composed of six such pulses applied sequentially. Air cooling precedes the application of the pulses and continues during the entire treatment pulse. The cooling air is delivered at approximately -20°C and at a high flow rate. That combination yields a very dry coolant with an apparent infinite heat capacity. Air cooling maintains the skin surface environment very consistently, an important factor in the “treat to temperature and depth” strategy.

Figure 14 shows the tissue temperature immediately following exposure to each of six laser pulses plotted versus depth into the skin. There are seven curves shown here corresponding to the response post each of the six applied pulses and a baseline (black curve) showing the temperature-depth profile at the start of laser pulse applications. The curves demonstrate higher temperatures at the sebaceous layer. There the temperature rises with each applied pulse and reaches a maximum around 70°C at the depth of the SG.

3.2.4 | Surface Temperature as a Proxy for Temperatures at Depth

During our clinical investigations, we discovered that skin surface temperature was a reliable surrogate measurement for

temperature at depth. Histological analysis after treatment found the laser treatment produced SG damage without alterations to the surrounding dermis. Furthermore, we were able to correlate surface temperature measurements to histological evidence of SG damage. Numerical modeling and clinical results confirm this conclusion.

The six pulses are applied sequentially to make up one treatment at a given skin treatment location. Figure 15 shows the time evolution of the treatment. There are three curves shown corresponding to three different depths in the tissue. These depths correspond to the skin surface, the dermis/epidermis junction, and the peak temperature of the sebaceous layer. There is also a set of open square data labeled “Data Square 1.” These are the actual temperature measurements recorded at the skin surface before and immediately after the application of each laser pulse [35].

It is evident from Figure 15 that the calculated surface temperature and the measured data are in very good agreement. This agreement was obtained by adjusting the heat transfer coefficient (H_t) for best fit. Measured data include skin surface temperatures during the heating and cooling phases of the treatment; the calculated temperature fits both sets of points equally well with the same value of H_t applied to both. This provides confidence that the surface temperature in conjunction with the calculated temperatures can be the needed surrogate temperature measurement.

3.2.5 | Control of Pain via Treat-to-Temperature

It is possible to take advantage of temperature measurements during the treatment pulse and make significant changes in the laser power that may allow for real-time modification to the

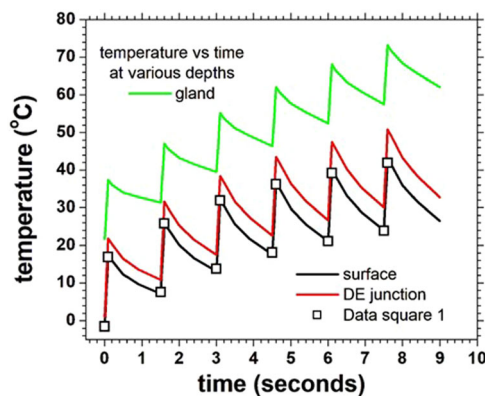


FIGURE 15 | Tissue temperature plotted versus time for six consecutive pulses in “Standard” format.

treatment. The differences between Boost six pulse and Standard six pulse are described in Table 7.

Figure 16 shows the temperature immediately after the application of each of the six pulses plotted versus depth. As before, there are seven curves shown. Unlike the previous case, laser power was widely varied here. The individual pulse powers (Watts) were 36.0, 17.7, 15.6, 14.2, 12.9, and 31.7. These pulse powers were determined in real time by software and in response to the skin temperatures as read by the thermal camera to achieve a pre-determined temperature sequence.

In this configuration, tissue temperature never exceeded 55°C, even at the gland, until the sixth pulse is applied. The tissue above the gland does not exceed 52°C [36], which is the temperature at which pain is generally assumed to be tolerable. The power of the last pulse is adjusted to increase gland temperature to be greater than 65°C, ensuring SG damage will result.

Figure 17 is the time evolution data for this pulse sequence. The calculated surface temperature shows good agreement with the measured values for all six pulses. Once again, this agreement provides confidence that the surface temperature may be used as the needed surrogate temperature measurement.

4 | Discussion and Conclusions

Based on the work of Anderson et al. and Sakamoto et al., a 1726 nm laser system was built with the goal of selectively damaging SGs and treating patients with acne vulgaris. One obstacle with this wavelength is the small difference in absorption between the lipids in SG and water in the surrounding dermis. To address this challenge, we developed a multi-pulse protocol combined with bulk air cooling enabling us to selectively and gradually heat SGs within a thermal gradient

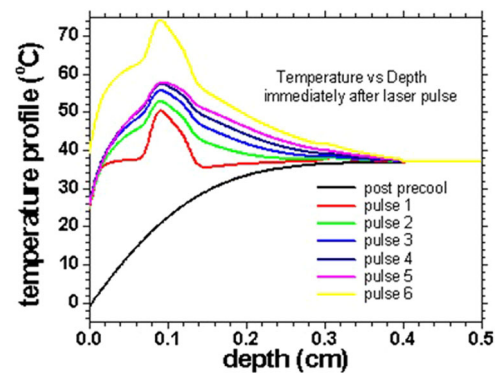


FIGURE 16 | Temperature versus depth for a six pulse “Boost” format treatment.

TABLE 7 | Differences in boost six pulse and standard six pulse.

	Standard mode	Boost mode
Pulses	Six pulses, variable energy	Six pulses, variable energy
Temperature	Rises progressively with each pulse	Maintained below pain perception threshold until the final pulse
Pain	Requires injectable local anesthesia	Topical anesthesia

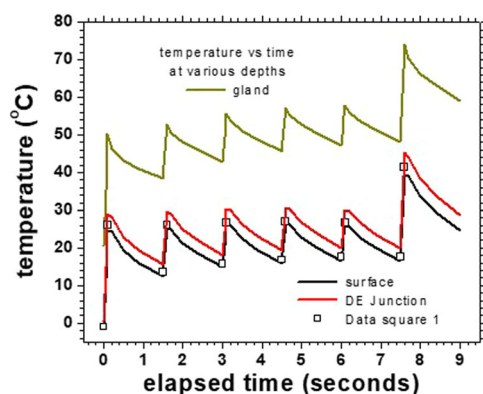


FIGURE 17 | Tissue temperature plotted versus time for six consecutive pulses in “Boost” format.

from 0.4 to 1.5 mm. The use of air cooling also permitted us to use a thermal camera to monitor surface temperature for safety. The lower heat transfer coefficient of convective air cooling, contrary to conventional wisdom, is a key enabler for bulk cooling. The reason for this is that a lower heat transfer rate through the skin results in a lower temperature drop per unit thickness and that we can only cool the skin to 0°C without freezing it. This effect is counter-intuitive; a cooling method with a lower heat transfer rate (e.g., air cooling) can cool more deeply than one with a higher cooling rate (e.g., contact cooling). Thus, bulk air cooling coupled with the multi-pulse approach enabled our device to target deep SGs.

During this journey, we discovered that surface temperature measurements are a good proxy for the temperature at depth, providing us with the opportunity to adjust the power of the laser in real time to achieve a selected temperature endpoint with consistent SG damage.

Our pulsing protocols are significantly different from those used by others, who have attempted to heat the SG in one or two pulses. In our early use of this laser, we were unable to damage the SG with a single pulse using contact or air cooling without damaging the epidermis. We have also reported that having two different pulsing protocols allowed for two distinctly different methods of anesthesia, injectable or topical.

We used clinical studies, histology, Monte Carlo analysis, and calculations based on the heat diffusion equation to validate that skin surface temperature does provide a predictable surrogate for SG temperature. In particular, the temporal profiles predicted at the tissue surface using the analysis above show good agreement with surface temperature measurements. When examining the histology for damage, we were able to correlate a surface temperature at the end of our pulse train with the Selective Photothermolysis of the SG. Two very different six-pulse formats have been investigated in some detail and the results in both cases support the use of surface temperature as a surrogate temperature to guide a “treat to temperature and depth” strategy.

The power produced by the laser and the multi-pulse strategy gave us the ability to use a larger 4.7 mm square spot which affords a more uniform depth of penetration and a wider zone of energy in each individual treatment spot.

Another unique feature of our system and methodology is our cooling system. Our unit is highly controlled and actively monitored delivering stable air cooling before, during and after the laser pulsing. This method establishes the appropriate thermal gradient deep into the skin. Another benefit of air cooling is the ability to utilize thermal imaging to measure a surface temperature reading immediately before, during and after a pulse train is delivered. Real-time temperature monitoring during the delivery of the pulses is not feasible or practical with contact cooling as 8–12 μm thermal infrared does not transmit through typical contact cooling materials, such as sapphire.

Real-time surface temperature measurement is a critical part of these efforts and the device. Initially, this type of monitoring was implemented to guide us to a safe and efficacious endpoint temperature for our treatments as no clinical endpoint is visible to the user. These measurements yielded the additional benefit of predictive modulation of laser power, clearing the path for pain reduction. Importantly, this reading does not vary between individuals, skin locations (e.g., forehead, cheek and back), and specific devices, while the energy necessary to reach these temperatures does. In all cases, the endpoint temperature (PET) was independent of Fitzpatrick Skin Type, as melanin is not a chromophore for 1726 nm. The treatment is well-suited for all patient skin types, including the skin of color. Real-time temperature measurement provides more than just safety but permits us to target a surface temperature which helps address tissue thermal variability based upon anatomy.

The laser above is currently in commercial use worldwide. Global commercial use by numerous board-certified dermatologists with the delivery of hundreds of thousands of laser emissions provides valuable patient outcomes with significant improvement to their quality of life. This yielded patient and provider self-reported satisfaction numbers of 4.38 and 4.4 out of 5, respectively [37].

We believe that the hardware, software, and techniques that we have developed with this cooling and thermal monitoring system, could have broad applications to many devices that are thermally based. It has resulted in better patient safety and enhanced efficacy due to the precise control of treatment temperatures.

Author Contributions

E.A.T., M.E., A.E., H.H., R.R.A., and F.H.S. were involved in the initial product development. E.A.T., J.L.C., D.P.F., M.P.G., H.P., J.V.W., and R.G.G. were investigators for the studies mentioned. R.S. and M.E. executed the numerical modeling. R.S. executed the Monte Carlo simulations. E.A.T., R.S., A.I., M.E., and A.E. were responsible for writing, reviewing, and editing the manuscript.

Acknowledgments

The authors acknowledge the editorial assistance of Dr. Carl S. Hornfeldt, Apothekon Inc., during the preparation of this manuscript.

Ethics Statement

Clinical data presented in this article was collected under Institutional Review Board (IRB)-approved studies (20170790, 20172819, 20182416,

20190111, 20202009, and 20213875). The IRB approving these studies is WCG North America, Princeton, NJ USA (known before acquisition as Western Institutional Review Board [WIRB] of Olympia, WA, USA). All contents of IRB studies adhered to the tenets of the Declaration of Helsinki. Subjects have consented to the publication of images.

Conflicts of Interest

Emil A. Tanghetti—principal investigator, consultant for the company, stock options. Rafael Sierra—consultant for the company, stock options. Michael Estes—employee of company, investor, stock options. Aubrey Eck—employee of the company, stock options. Alfred Intintoli—an employee of a company, stock options. Henrik Hofvander—former employee of the company, consultant of the company, investor, and stock options. Joel L. Cohen—investigator, consultant for the company, stock options. Daniel P. Friedmann—investigator, and consultant for the company. Mitchel P. Goldman—investigator, investor. Hyemin Pomerantz—investigator, and consultant for the company. Jordan V. Wang—investigator. Roy G. Geronemus—investigator, investor, stock options. R. Rox Anderson—clinical advisory team, investor. Fernanda H. Sakamoto—clinical advisory team.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.