A PROSPECTIVE, MULTICENTER, SINGLE-ARM CLINICAL STUDY EVALUATING THE SAFETY AND EFFECTIVENESS OF THE TIXEL FRACTIONAL SYSTEM IN THE TREATMENT OF PERIORBITAL WRINKLES

Study Protocol No: **CLN 0749**

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Investigational Product: **Tixel Fractional System**

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Contents

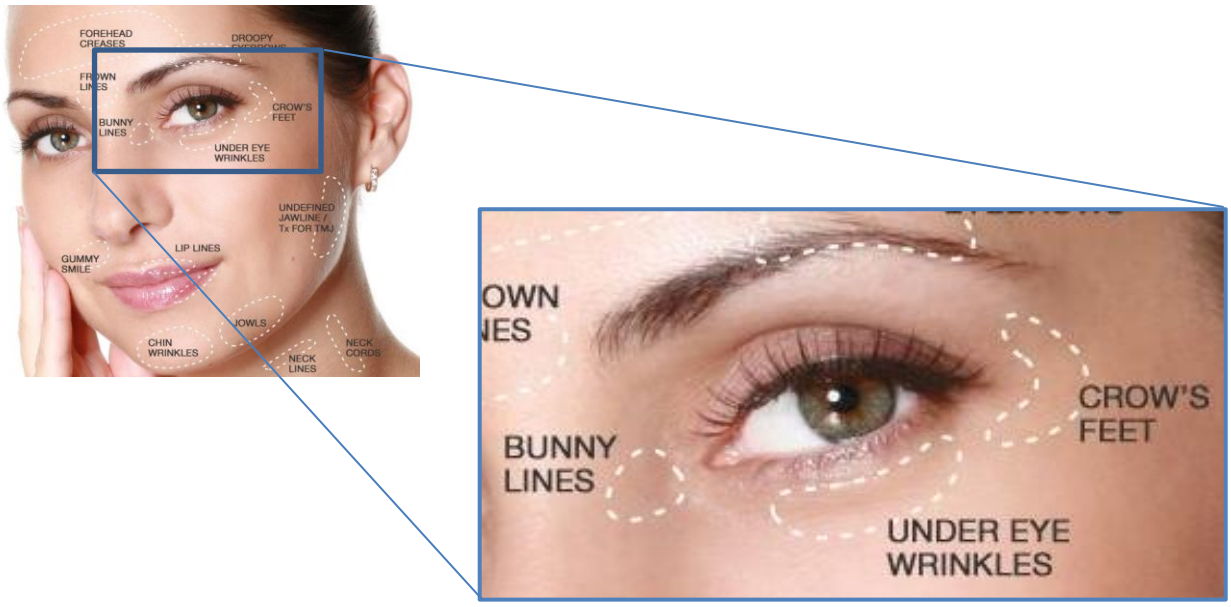
1 INTRODUCTION

1.1. Study Background

Periorbital Wrinkles are an early manifestation of facial wrinkles[1]. They are lines or creases that form in the skin in the periorbital regions of the face. This is a significantly common multifactorial phenomenon, influenced by natural aging, photo aging (including UV exposure), facial expressions, skin type, hormonal status, genetic inclination, ethnicity, nutrition and various pathological disorders. These intrinsic factors contribute to epidermal thinning, loss of elasticity, skin fragility, etc. These are part of the human aging process, which affects the skin in its entirety and the facial skin in particular. Additional environmental factors, such as smoking, pollution and skin care, also affect periorbital wrinkles[2].

Wrinkles, in general, are reported to appear in people even younger than thirty years of age[3]. In the same manner as any other facial wrinkle, periorbital wrinkles increase gradually and affect one's appearance and facial expression. Such effect also reflects on quality of life, due to impact on social interactions, occupational functioning and self-esteem in general[4]. Therefore, periorbital wrinkle reduction treatments are sought by many worldwide.

Figure 1 - Conventional Segmentation of Periorbital Wrinkles



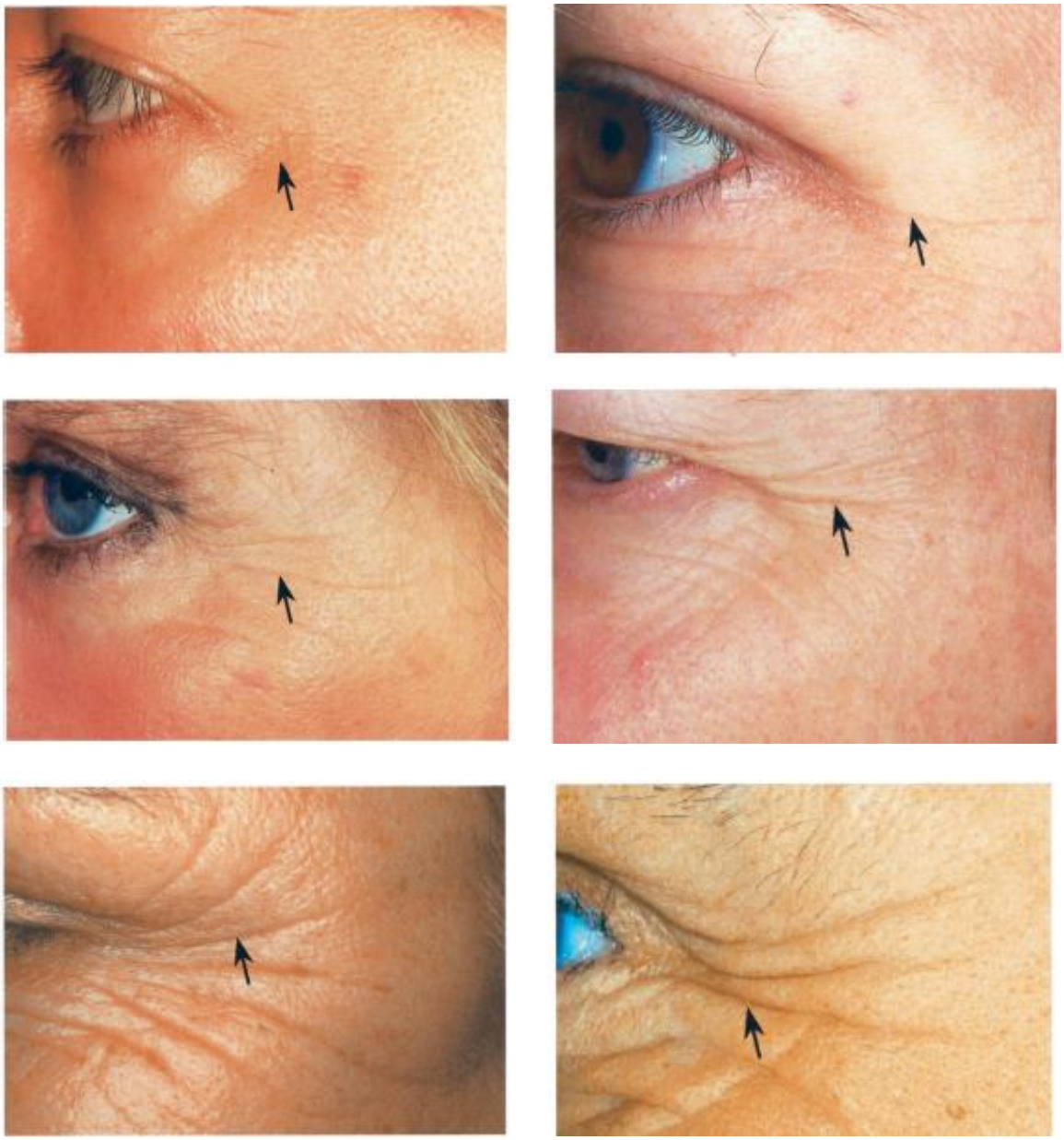
[1] "A Prospective Split-Face Comparative Study of Periorbital Wrinkle Treatments: Fractional Erbium Doped Yttrium Aluminum Garnet Laser Intense Pulsed Light, and Topical 0.1% Tretinoin Cream",
So Eun Park, Sang Seok Kim, Chul Woo Kim, Young Her, Department of Dermatology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul,
1Department of Dermatology, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Korea

[2] https://www.mayoclinic.org/diseases-conditions/wrinkles/symptoms-causes/syc-20354927

[3] "Wrinkles", Juan Manríquez, Daniela Majerson Grinberg, and Claudia Nicklas Diaz, Clinical Evidence 2008;12:1711

[4] Gupta MA, Gupta AK. Photodamaged skin and quality of life: reasons for therapy.
J Dermatol Treat 1996;7:261–264

Figure 2 - Various Severity Levels of Periorbital "Crow's Feet" Wrinkles[1], by left-to-right, downward order of severity



1.1.1 Treatment modalities

Skin resurfacing or peel procedures have become an established non-surgical method for reducing certain skin imperfections such as wrinkles, dark spots, scars, or blemishes. Traditional fully ablative and fractional lasers are the most commonly used devices for skin resurfacing.

The skin is composed of three layers: the epidermis, the dermis, and the hypodermis. The dermis contains well-organized and oriented collagen fibers that contribute to the firmness and smoothness of the skin. As people age, these collagen fibers reduce in number and become less organized, resulting in sagging and/or wrinkled skin. When esthetic procedures are scheduled for older adults, the rate of the epidermal turnover associated with a slower wound healing and less

effective desquamation (shading of outer layers of the skin), needs to be taken into consideration[5]. In most skin resurfacing procedures, an energy source (heat, radiofrequency energy, etc.) is used to selectively damage the skin and prompt a healing response that stimulates the growth of new collagen fibers in the dermis that are well-organized. The healing response and new collagen formation results in skin that is smoother and firmer. There are numerous traditional fully ablative and fractional lasers on the market today used for skin resurfacing. Traditional and fractional lasers differ in their method of treatment. Traditional lasers have a single beam that burns or damages all of the epidermis within the treatment area of the beam. Fractional lasers divide the beam into multiple smaller beams and treat only a "fraction" of the epidermis to affect changes in the deeper epidermis or dermis. This results in multiple small cores of laser damage surrounded by areas of healthy tissue. When compared to traditional lasers, fractional lasers deliver a more superficial treatment resulting in less risk for complications and reduced time for healing. However, this also means more treatments may be required to achieve the desired results especially in areas of deep lines or wrinkles. Healing times vary by amount of treatment, but fractional laser recovery time is typically one week compared to three to four weeks for traditional lasers. In the wake of the demonstrated safety and efficacy of laser skin resurfacing, multiple additional treatment modalities have been developed for this application including the use of radiofrequency (RF) energy. The fractionated radiofrequency results in epidermal and subepidermal ablation under the conductive pins that reproduces similar effects as a fractional CO2 laser with dermal heating, seen in the non-ablative lasers and devices[6]. The combination of epidermal ablation and dermal heating with radiofrequency, called sublative resurfacing in some studies, is suitable for skin types I–IV, for the treatment of skin laxity, wrinkles, enlarged pores, pigmented lesions, acne, telangiectasias, and scarring from trauma or acne. Subject recovery and downtime periods are significantly lower when compared with ablative laser healing times, with minimal adverse effects[7].

1.1.2 Wrinkle Classification and Severity Assessment

Wrinkles are traditionally classified by most dermatologists into dynamic and static wrinkles.

Static wrinkles are wrinkles that are visible when the facial musculature is rested (without facial expressions), and dynamic wrinkles are those that transiently appear when facial expressions are pronounced[8].

[5] Ganceviciene R, Liakou A, Theodoridis A, Makrantonaki E, and Zouboulis C. Skin anti-aging strategies, Dermatoendocrinol. 2012 Jul 1; 4(3): 308–319.

6 Hruza G, Taub AF, Collier SL, Mulholland SR. Skin rejuvenation and wrinkle reduction using a fractional radiofrequency system. J Drugs Dermatol. 2009;8(3):259–265.

7 Mulholland RS, Ahn DH, Kreindel M, Paul M. Fractional Ablative Radio-Frequency Resurfacing in Asian and Caucasian Skin: A Novel Method for Deep Radiofrequency Fractional Skin Rejuvenation. Journal of Cosmetics, Dermatological Sciences and Applications. 2012;2(3):144–150.

[8] "Facial dynamics and emotional expressions in facial aging treatments", Thierry Michaud, MD,[1] Veronique Gassia, MD, [2] & Lakhdar Belhaouari, MD[2 1] Private Practice, Mulhouse, France [2] Private Practice, Toulouse, France, Journal of Cosmetic Dermatology, 0, 1--13

1.1.3 Fitzpatrick Wrinkle Classification Scale (FWCS)

Facial wrinkles are conventionally classified according to Fitzpatrick's classification scale for facial wrinkles, described in the following Table 1[9,10,11]:

Table 1 - The Fitzpatrick Periorbital and Perioral Wrinkle Classification

Class	Description	Score	Description
I	Fine wrinkles	1-3	**Mild**: Fine texture changes with subtly accentuated skin lines.
II	Fine to moderate depth wrinkles, Moderate number of lines	4-6	**Moderate**: Distinct papular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	7-9	**Severe**: Multipapular and confluent elastosis (thickened, yellow, and pallid) approaching or consistent with cutis rhomboidalis.

[9] "Pulsed carbon dioxide laser resurfacing of photo-aged facial skin", Fitzpatrick, R. E., Goldman M. P., Satur, N. M., and Tope, W. D. Arch. Dermatol. 132: 395, 1996.
[10] A Fractional Bipolar Radiofrequency Device Combined with a Bipolar Radiofrequency and Infrared Light Treatment for Improvement in Facial Wrinkles and Overall Skin Tone and Texture.
Gold AH, et al. Aesthet Surg J. 2016.
[11] https Fractionated microneedle radiofrequency for the treatment of periorbital wrinkles.
Kim JK, et al. J Dermatol. 2013

1.2. Study Rationale

All current technologies available in worldwide markets nowadays do not offer full permanent clearance of periorbital wrinkles and cause certain levels of discomfort to the patients, accompanied with varying durations of downtime. Appearance is often improved to some degree of satisfaction of the subject, but not to the extent of complete solution for the condition. Due to the psychological impact of the conditions and its negative effect on life quality, better modalities are always sought. The Tixel technology aims to offer a more user friendly, radiation free, safety googles free, anesthesia/analgesia free al low device settings, toxic fumes free, safe and efficacious modality for fractional skin resurfacing of periorbital wrinkles, with results similar or better to currently market-available devices in the US[12].

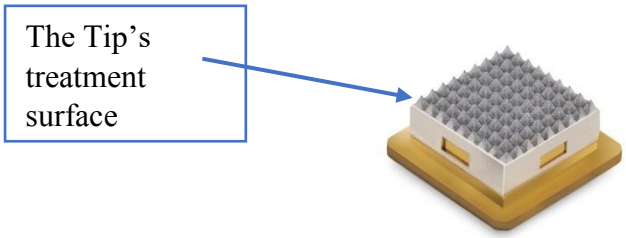
1.3. Study Device Description-The Tixel system

The Tixel family of products (for example Tixel 2 as in Figure 3) employs a thermo-mechanical technology that has been designed to provide a comparable clinical effect as a pulsed non-ablative laser and surface RF devices, which can be used as a treatment modality for a variety of dermal applications. The Tixel technology is based on the supply of contact-transferred heat from a high temperature (385°- 405°C) metal element (called a "tip") consisting of an array of miniature pyramids. The tip (see Figure 4 and Figure 5) generates thermal coagulation in the tissue (usually 200-300 microns deep) within 5 – 18 milliseconds pulse duration (contact duration between the tip and the skin), thus mimicking pulsed laser or surface RF action.

The device has been cleared for marketing in multiple countries including European Union (EU), Australia, South Korea, Taiwan, Israel and other.

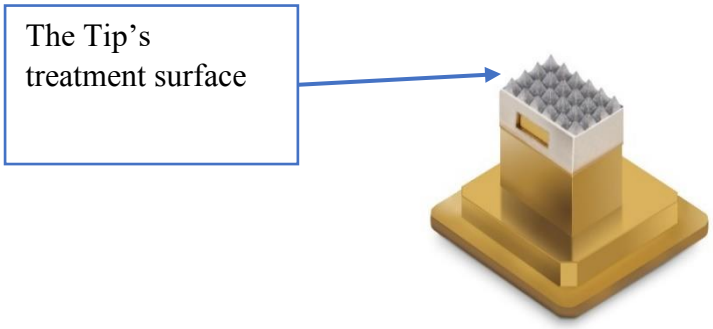
Figure 3 - The Tixel 2 Device

Figure 4 - The Tixel Standard Tip



[12] https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150409.pdf

Figure 5 - The Tixel Small Tip



1.3.1. Safety Features of the Tixel

The device is fully IEC-60601 compliant (safety and EMC).

Over 750 Tixel devices have been sold to dermatologists and aesthetic doctors in the past 5 years, in over 25 countries.

The Tixel device is designed with core safety, which is ensured via several aspects of its components:

1. The device has an over-temperature automatic thermal shutdown in case of undesired temperature rise. This component is strictly hardware based.
2. In case of a power fail, the Tip will always be retracted backwards to its home position detached from the skin.
3. The system is always in a rested (home) position and activated only when the trigger is pressed.
4. An air-cooled system for handpiece cooling which does not contain any type of liquid.
5. Mechanical BIT (Built-In Test) – Before commencing operation mode, the system verifies free motion of the mechanical system.

1.3.2. Expected Possible Side Effects

In the same manner as all fractional skin treatment devices, there is risk of: Temporary swelling; Skin redness; Pain and/or burning sensation; Forming of large scabs or scabs lasting more than 15 days; Significant/thick skin peeling; Post Inflammatory Hyperpigmentation (PIH); Hypo-pigmentation; Sensitivity to sun exposure; Local burns; Scars, edema, erythema and watery eye for few hours after the treatment.

1.3.3. Benefits

A possible benefit of using Tixel is the potential for improvement in wrinkle severity. Additional potential benefits of improving the appearance of wrinkles could include enhanced well-being, with improved satisfaction with the appearance of less peri-orbital wrinkles or the perception of a having a more youthful appearance.

1.3.4. Intended Use and Indications for Use

Skin rejuvenation by fractional non-ablative treatment of the skin.

The Tixel System is intended for cutaneous procedures requiring coagulation of soft tissue and skin resurfacing procedures. Treatments are performed by physicians and trained clinicians.

1.4. Study Objective

To demonstrate the safety and performance of the Tixel fractional system for treatment of periorbital wrinkles.

1.5. Study Design

A Prospective, Multicenter, Single-Arm Clinical Study of 51 subjects who are seeking a procedure to reduce the appearance of the periorbital wrinkles, and meet study eligibility criteria, and have provided informed consent will be enrolled in the study. Up to 5 investigational centers in Israel and the United States will participate in the recruitment. Each study subject will receive **four treatments** with Tixel 2 in a monthly interval. Follow-up will occur at 1 month and 3 months following the last treatment.

1.6. Treatment parameters in the study and treatment area:

1. Protrusion- between 400-600 microns,
2. Pulse duration- between 10-12 milliseconds (lower for skin-type V e.g. 6-8).
3. Single or double pass, except crow's feet which can be treated in crisscross when severe wrinkles exist.
4. The treated area outside of the orbital rim should encompass below and above the brow, lower eyelid and at beyond (1-2 cm at 45 degrees above and below) the most lateral aspect of the most lateral wrinkle.
5. Treatment directly on the eyelid is forbidden.

1.7. Study Endpoints

1.7.1. Primary Efficacy Endpoint

Comparison of the proportion of subjects with a ≥ 1-score improvement on the FWCS at the 3-month visit compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers.

The study design assumes a 65% success rate of subjects with a ≥ 1-score change on the FWCS, therefore, greater or equal to 65% of subjects must be rated with a ≥ 1-score improvement 3 months after treatment and must be statistically significantly.

1.7.2. Secondary Efficacy Endpoint

Assessment of improvement at each visit compared to baseline by the handling physician.

The following assessment methods will be applied (frontal clinical assessment or by images):

- FWCS - Fitzpatrick Wrinkle Classification Scale
- GAIS - Global Aesthetic Improvement Scale Assessment

Patients' Reported Outcomes (PROs):

- Subject Satisfaction Questionnaire

1.7.3. Primary Safety Variable

Evaluation of related adverse events up to the 3-months FU visit.

1.7.4. Secondary Safety Variable

- Evaluation of the pain and discomfort of the treatment as reported by the subject on a visual analog scale (VAS).
- Subject Subjective Downtime Assessment.

2 STUDY POPULATION

2.1. Inclusion Criteria

1. Male or female 35-70 years old diagnosed with clinically evident static periorbital wrinkles.
2. Willingness and ability to comply with all required study activities including returning for follow-up visits and protocol requirements.
3. The subject is able to provide written informed consent and perform the study's activities according to HIPAA guidelines and/or Israeli law, depending on each specific study site.
4. Fitzpatrick wrinkle score of 3-7 in the peri-orbital areas per the treating investigator and clinically noticeable wrinkles in the treating area.
5. Stable body weight during the study period.
6. Skin Type I – V as per Fitzpatrick Skin Scale.

2.2. Exclusion Criteria

1. Past treatment with Tixel device.
2. The subject may not undergo treatment by the Tixel device according to the device's contra-indications for use, as defined in the User Manual and in the Instructions for Use and by any other labeling of the device.
3. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
4. Female subjects who are pregnant, or planning to become pregnant, or have given birth less than 3 months ago or are lactating.
5. Subjects with significant exposure to critical amounts of ultraviolet light (Sun-tan).
6. Subjects who have had the following treatments:
   a. a cosmetic procedure to improve peri-orbital rhytides (i.e. periorbital or eyelid/eyebrow

surgery, brow lift, CO2/Erbium/similar laser/fractional resurfacing, radiofrequency treatment) within 12 months

b. prior facial treatments with laser, surgical, chemical or light-based facial treatments within the previous 12 months, over the periorbital area including botulinum toxin injections, microdermabrasion or prescription level glycolic acid treatments.

c. Injectable filler in cheeks (mid face) temples and in the upper face area to be treated within 12 months of investigation.

7. Any subject who have visible scars or other visible changes over the treated areas that may affect evaluation of response and/or quality of photography.

8. Subjects with any type of active cut, wound, inflammation, lesion (benign, premalignant or malignant) or active bacterial, viral, fungal, or herpetic infection on the skin on the designated treatment sites or in close proximity to it.

9. Existing or history of the following (when discussing skin conditions, refers only to the periorbital sites):

   a. skin malignancy, or any diagnosis of suspected malignancy

   b. Collagen or vascular or bleeding disease

   c. Immunosuppression or autoimmune disease

   d. Erythema with or without blistering

   e. History of post inflammatory hyperpigmentation.

   f. Active Acne Vulgaris, HSV-1, or any existing skin condition/disease that in the investigator's opinion would interfere with the evaluation of the safety of the study treatment and evaluation.

   g. Any skin pathology which can induce bullous lesions, urticaria, or demonstrate a Koebner phenomenon (psoriasis, lichen planus, etc.).

   h. Any disease that inhibits pain sensation

   i. History of keloid formation, or hypertrophic scarring

   j. Conditions affecting healing rate (i.e. diabetes mellitus I or II, vascular condition, etc.)

   k. neuromuscular disorders

10. Subjects who have used, within 30 days, any medication that can cause dermal hypersensitivity or affect skin characteristics over the treated area (i.e. topically applied Retinoids, Hydroquinone, Chemical peel of any strength: glycolic acid, lactic acid, salicylic

acid)

11. Subjects who have used, systemic treatment which may induce dyspigmentation, such as amiodarone, clofazinmine, minocycline or chloroquine.
12. Subjects currently taking or have taken an oral retinoid in the past six months; Subjects currently taking long-term oral steroid treatment.
13. Concurrent therapy that, in the principal investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study treatment.
14. Subjects who anticipate the need for major surgery or overnight hospitalization during the study that can affect the study schedule or treatment evaluation.
15. Enrollment in any active study involving the use of investigational devices or drugs.
16. Any other cause per the principal investigator’s discretion.

Study visits procedures (see Table 2)

3 STUDY FLOWCHART AND FOLLOW-UP ASSESSMENTS

Table 2: Study Flowchart and Follow-Up Assessments

Procedure	**Visit 1 (V1) Tx 1[b]**	**Phone call visit**	**Visit 2 (V2) Tx 2**	**Visit 3 (V3) Tx 3**	**Visit 4 (V4) Tx 4**	**Visit 5** 1 month **Follow-up 1**	**Visit 6** 3 months **Follow-up 2**
	V1	V1 + 3d (± 1d)	V1 + 4wk (± 7d)	V2 + 4wk (± 7d)	V3 + 4wk (± 7d)	V4 + 4wk (± 7d)	V4 + 12wk (± 7d)
Subject Screening, Enrolment Procedure & Informed Consent[d], Post treatment care instructions sheet	X						
Weight and Height	X						
Weight			X	X	X	X	X
Facial dermatological skin examination	X		X	X	X	X	X
Inclusion/ Exclusion criteria	X						
Medical/Surgical history from the last five years	X						
Demographics	X						
Fitzpatrick Skin Scale (FSS)	X						
Concomitant Therapy/Medication	X[a]		X	X	X	X	X
Verbal Inquiry regarding pregnancy	X		X	X	X	X	X
Photography of Treatment Area(s) – prior to treatment	X (baseline)					X	X
Investigational Device Treatment	X		X	X	X		
GAIS Assessment by the Investigator						X	X
FWCS Assessment	X[c]					X	X[c]
Subject VAS Pain assessment	X		X	X	X		
Subject Subjective Downtime	X		X	X	X		

Procedure	**Visit 1 (V1) Tx 1[b]**	**Phone call visit**	**Visit 2 (V2) Tx 2**	**Visit 3 (V3) Tx 3**	**Visit 4 (V4) Tx 4**	**Visit 5** 1 month **Follow-up 1**	**Visit 6** 3 months **Follow-up 2**
	V1	V1 + 3d (± 1d)	V1 + 4wk (± 7d)	V2 + 4wk (± 7d)	V3 + 4wk (± 7d)	V4 + 4wk (± 7d)	V4 + 12wk (± 7d)
Assessment Questionnaire – given to subject							
Collect Subject Subjective Downtime Assessment Questionnaire (regarding skin erythema, redness and scabs)			X	X	X	X	
Adverse Events	X		X	X	X	X	X
Subject Compliance	X		X	X	X	X	X
Post Treatment Care Instructions	X		X	X	X		
Subject Experience Questionnaire						X	X
Post treatment reaction assess via phone		X					

a. At Screening, the review of concomitant medications should include those taken within the past year.
b. All assessments on treatment days are to be performed prior to treatment; the assessments performed prior to Treatment 1 will be designated as Baseline.
c. Blinded assessment performed in addition to physician assessment. Shall be performed at the end of the subject's activities.
d. First visit may be split into two separate visits, with no more than 7 days between the two separate visits: part I: screening, enrollment, post treatment care instructions sheet and informed consent, and part II: rest of visit content.

4 EVALUATION TOOLS

The following evaluation tools will be used in this study:

4.1. Fitzpatrick Skin Scale (FSS)

Assessment of subject's skin color will be determined prior to study procedure by the Investigator using the FSS. The scale delineates skin color into the categories as shown in Table 3- Fitzpatrick Skin Scale Evaluation. See **שגיאה! מקור ההפניה לא נמצא.**.

Table 3- Fitzpatrick Skin Scale Evaluation

Skin Type	Description
Type I	White skin that never tans and always burns easily
Type II	White skin that tans slightly and always burns easily
Type III	Light brown skin that tans gradually and can burn moderately
Type IV	Moderately brown skin that tans well and burns slightly
Type V	Dark brown skin that tans profusely and burns rarely
Type VI	Black skin with deep pigmentation that never burns

4.2. Fitzpatrick Wrinkle Classification Scale (FWCS)

Assessment of subject wrinkles will be performed by the Investigator and in addition, will be performed by three board-certified independent dermatologists or plastic surgeons ("Raters"), using the Fitzpatrick Wrinkle Classification Scale (FWCS) categories as shown in Table 4. The FWCS is a clinically validated assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9, where the lower score is considered better.

The investigator will assess FWCS at baseline, 1-months and 3 months follow up visit, while the raters will assess only at baseline and 3 months follow up visit.

4.3. Blinded Identification of 3-Month Images

Assessment of each subject's baseline and 3-month follow-up images viewed simultaneously will be performed by the Independent Photographic Reviewers ("Raters") who will be blinded to the study subject's visit (baseline and 3-month follow-up visit). Each rater will view each subject's randomized baseline and 3-month follow-up images and assess which set of images represent the subject's post-treatment images. Each photograph will have a unique identification number, but the sets of images will not be arranged in any specific order. The Raters will assign a single FWCS score per subject at each time point. A subject will be considered a success if at least 2 out of the 3 Raters correctly identify the 3-month images and the FWCS score is ≥1.

Table 4- Fitzpatrick Wrinkle and Elastosis Scale

Class	Description	Score	Description
I	Fine wrinkles	1-3	**Mild**: Fine texture changes with subtly accentuated skin lines.
II	Fine to moderate depth wrinkles, Moderate number of lines	4-6	**Moderate**: Distinct papular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	7-9	**Severe**: Multipapular and confluent elastosis (thickened, yellow, and pallid) approaching or consistent with cutis rhomboidalis.

4.4. Global Aesthetic Improvement Scale (GAIS)

Treatment results compared to pre-treatment. The Investigator will grade the overall improvement of treatment area as indicated in Table 5 by comparing the subject's appearance in each of the follow up visits, against a photograph taken prior to procedure.

Table 5- Global Aesthetic Improvement Scale Evaluation (GAIS)

Score	1	2	3	4
Assessment	0-25% - Poor response	25-50% - Fair response	50-75% - Good response	75-100% - Excellent response

4.5. Visual Analog Scale (VAS)

The study subjects will be asked to complete a 10-point Visual Analog Scale (VAS) for the following assessments:

Level of pain and discomfort associated with study procedure – to be completed by the subjects on the day of the procedure, immediately following the procedure. Scoring will consist of making a mark on a 10-points scale. Each line will be awarded a score of 0 - 10 according to the level of pain when 0 is no pain and 10 is the maximum pain possible. See **שגיאה! מקור ההפניה לא נמצא.**.

Additional patients' Reported Outcomes (PROs)

- Subject Subjective Downtime Assessment - Downtime defined as the period of time following the procedure during which the subject felt unable/unwilling to go out in public due to edema and/or erythema. The determination of "downtime" is measured in hours or days following the procedure. This will be recorded following every treatment visit (see **שגיאה! מקור ההפניה לא נמצא.**).
- Subject experience questionnaire will be filled by the subject at each follow-up visits (see **שגיאה! מקור ההפניה לא נמצא.**).

5 ADVERSE EVENTS ASSESSMENT AND REPORTING

5.1. Adverse Events Evaluation

Safety evaluation for this study includes an interview with the study subject at each visit by the Investigator or Research Coordinator to elicit information about any medical occurrence that meets the definition of Adverse Event. This information will be documented in CRF without regard for cause or relation to device and/or procedure. In addition, study subjects will be instructed to report all of complications experienced post study procedure to the site personnel as soon as they occur/are observed. It is the Investigator's responsibility to determine seriousness, severity, and relatedness of the Adverse Event to the device and procedure using the definitions below.

All adverse events, anticipated or unanticipated, will be monitored until they are adequately resolved or explained.

5.2. Reporting Requirements

All adverse events (AEs) observed by study subjects, investigators, or other study staff from first exposure to the study product through last study follow-up visit will be recorded. If a device related AE, SAE, or unanticipated serious device related effect is ongoing at the final study visit, the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator should make every effort to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate, as completely as practical, the nature and/or causality of the AE or SAE. This may include unscheduled follow up visits for AE assessment.

Study subjects will be instructed to report all AEs to the clinical study staff. AE information will be collected throughout the study and recorded on CRFs.

5.3. Contact email for SAE immediate reporting:

Study personnel must report to the sponsor any SAE or UADE by telephone as well as by email, as soon as possible and no later than 24 hours of the awareness of the event. The initial telephone notification (or email) should be followed by a written report (Serious Adverse Event report form) describing the SAE or UADE and signed by the investigator.

Study personnel must forward follow-up information and complete event report to the sponsor as the event continues and/or subsides/resolves, or in the case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained. The SAE report (initial and/or follow up) should be sent via e-mail to the sponsor at Safety@novoxel.com.

5.4. Severity of Adverse Events

The severity of adverse events will be categorized using the following criteria:

- **Mild**: easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. These events generally do not require treatment.
- **Moderate**: sufficiently discomforting to interfere with normal everyday activities. These vents are usually relieved by simple therapeutic measures.
- **Severe**: prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

5.5. Relationship to the Study Device and/or Procedure

Each AE should be assessed for its relationship to the device or procedure as identified as follows:

Device: This category should be restricted to adverse events directly attributable to the effect of the device.

Procedure: A procedure is any activity that supports the usage of the device.

Use the following categories for assigning the certainty of the relatedness:

Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.

Probably Related: An AE is probably related if cannot be explained by a concomitant illness or by other medicinal products.

Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.

Not Related: An AE is not related if it is determined that there is no plausible association.

Unknown: Use this term if there is insufficient information to determine if the AE is related to the device or procedure.

5.6. End of Study

The end of study will be defined as completion of all study visits by all enrolled subjects. If a device-related AE, SAE, or unanticipated serious device-related effect is ongoing at the final study visit, the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up.

Study closure visits may be conducted at all clinical sites in order to review record retention requirements, device disposition requirements, etc., with site personnel. The Sponsor may choose to conduct the closure visit via telephone contact if appropriate.

5.6.1. Premature Termination or Suspension of the Study or a Study Site

Novoxel Clinical/RA department may terminate the participation of a center before the completion of the investigation due to one or more of the following reasons:

- The investigator is unable or unwilling to continue the investigation,
- The investigator is unable or unwilling to comply with the protocol requirements,
- The Monitoring audit results indicate study staff non-compliance.

The Sponsor may also terminate a study prematurely in case of:

- Safety concerns,
- Inability to obtain the number of subjects required by the protocol,
- Any other reason, pre-defined within the protocol.

5.7. Audits / Inspections

The Sponsor, their designee, and the reviewing IRB may monitor or audit the study centers. Likewise, regulatory authorities may inspect Sponsor or study vendors/CRO files or any study center to evaluate the conduct of the study. The Investigator must allow access to the subject files and inspection of their clinical research protocol procedures when requested.

6 STATISTICAL METHODOLOGY

This section describes the statistical analyses foreseen at the time of study planning. Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close will be summarized in the Clinical Study Report.

6.1. Determination of Sample Size

- The objective of this study is to demonstrate that study participants positively respond to the Tixel, thus the primary endpoint will be assessed via the percentage of study participants that demonstrated an improvement in the FWCS from baseline to the 3-month visit.
- An improvement is clinically important when FWCS $\geq$ 1 score.

The sample size calculation is based on the rate of subjects for which a score improvement on the FWCS at 3-month compared to baseline (success rate). The success rate is expected to be 65%.

When the sample size is 44, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.14 from the observed proportion for an expected proportion of 0.65.

To account for possible missing data (up to 15% attrition), 51 subjects will be enrolled.

- Total N: up to 51 study participants

A study investigating the effects of RF device on the improvement of appearance of peri-orbital wrinkles (VIVACE K150409 Class II FDA approved device) utilized a FWCS cutoff as 60%, supporting this value in the present sample size computation.

6.2. Analysis Sets

The full analysis set (FAS) will be used for analysis of safety parameters and secondary endpoints in this study.

6.2.1. Full Analysis Set (FAS)

All subjects enrolled in the study who received at least one treatment, will be included in the FAS.

6.2.2. Per Protocol Set (PPS)

The PPS is the subset of subjects in the FAS without major protocol deviations and only if received the full treatments and have quality photos in the baseline and in the 3 months follow-up visit. Major protocol deviations will be decided and finalized by an independent reviewer prior to database lock. The primary efficacy analyses and also the secondary efficacy endpoints (in addition to the FAS) will be analyzed on the PP population.

6.3. Endpoints for Analysis

6.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWCS at the 3- month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 65% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWCS; therefore, even or greater than 65% of subjects must be rated with a ≥ 1-score improvement 3 months after treatment. and must be statistically significantly.

6.3.2. Secondary Efficacy Endpoint

shall be assessed and quantified by the handling physician.

The following assessment methods will be applied (frontal clinical assessment or by images):

- FWCS - Fitzpatrick Wrinkle Classification Scale (at each FU visit)
- GAIS - Global Aesthetic Improvement Scale Assessment (at each FU visit)

Patients' Reported Outcomes (PROs):

- Subject Experience and Satisfaction Questionnaire (in the 2 FU visits)
- Subject Subjective Downtime Assessment (following each treatment visit)

6.4. Statistical Analysis for Safety Variables

6.4.1. Primary Safety Variable

The primary safety variable is the evaluation of adverse events up to the 3-month visit after treatment. Adverse events reported at each scheduled study visit will be summarized. A descriptive analysis including type, onset after treatment, duration, severity, and relationship to study device and/or procedure will be provided.

6.4.2. Secondary Safety Variables

6.4.2.1. Visual Analog Scale (VAS)

Evaluation of the pain and discomfort of the treatment as reported by the subject on a 10-point visual analog scale (VAS). Results of the VAS on a scale of 0 (no pain) to 10 (most severe pain) will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean.

6.4.2.1.1. Subject Downtime Assessment

Downtime defined as the period of time following the procedure during which the subject felt unable/unwilling to go out in public due to edema and/or erythema. The determination of "downtime" is measured in hours or days following the procedure. This will be recorded following each treatment visit. See appendix D.

6.4.3. Handling of Missing Data

- Every effort will be made to obtain all FWCS data at month-3 evaluation from all subjects who have been enrolled to minimize missing data. However, in the event when there is missing data the following imputation methods will be used.

- Imputation using mean values: the missing FWCS value will be replaced by the average of non-missing FWCS values at month-3 in the same treatment group by the same evaluator.
- Imputation using baseline values: the missing FWCS value will be replaced by the subject's baseline FWCS value by the same evaluator.
- The MMRM model (Mixed-effect Model for Repeated Measures), which is based on MAR (missing at random) assumption will be applied to all enrolled subjects.

  Sensitivity analyses will be applied for testing the effect of the imputation on the treatment effect. This will show the influence of the imputation on the study results.

6.4.4. Data Collection

Subject demographic information, procedural data, adverse events, device observations, and study required assessments will be documented on the CRFs. Study subjects will complete Visual Analog Scale (VAS) and Downtime assessment following each treatment visit and Experience questionnaire at each follow-up visit.

6.5. Confidentiality of Data

The Principal Investigator will oversee the conduct of the study and all data will be kept confidential. Confidentiality will be maintained by using subject identification numbers instead of names. Informed consent forms, data collection sheets and records, linking a subject's name with their ID number will be maintained in a locked cabinet or locked office. Information to be stored on the computer will be identified by subject ID and will be password protected. Data disclosed outside the study team will be de-identified or will only include general group demographic information. Protected Health Information and/or identifiable study data will not be shared with anyone outside the study team or Health System, with the exception of the study sponsor, and federal regulators/ institutional officials for the purposes of auditing.