A PROSPECTIVE, RANDOMIZED, DOUBLE-ARM, CONTROLLED STUDY WITH BLINDED ASSESSMENT TO EVALUATE THE SAFETY AND EFFECTIVENESS OF THE TIXEL FRACTIONAL SYSTEM IN THE TREATMENT OF PERIORBITAL WRINKLES IN COMPARISON WITH FRACTIONAL LASER

Version Date: **November 24, 2019**

Investigational Product: **Tixel Fractional System (Model No. TXLD0002)**

Sponsor: **Novoxel Ltd.**
43 Hamelaha St.
Poleg Ind. Zone, Netanya,
Israel 4250573

Contact:

Ran Iakobovski,

Director of Clinica

Ran@novoxel.com

Raphi Shavit,

Chairman, Novoxel Ltd.

Raphi@novoxel.com

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1. INTRODUCTION:

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.

Study Title:

A Prospective, Randomized, Double Arm, Controlled Study with Blinded Assessment To Evaluate The Safety And Effectiveness Of The Tixel Fractional System In The Treatment Of Periorbital Wrinkles In Comparison With Fractional Laser

Investigational Product:

Tixel by Novoxel, model No. TXLD0002

The Tixel system was designed to fulfill a clinical need for fractional treatment for aging skin with reduced side effects and safety related complications, associated with current available treatment modalities, together with increasing patient comfort. The Tixel employs a thermo-mechanical

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[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.

technology that has been designed to provide a comparable clinical effect as a pulsed laser, which can be used as a treatment modality for a variety of applications, including fractional treatment of human skin. The Tixel technology is based on the supply of contact-transferred heat from a high temperature (385°- 400°C) metal element (called a "tip") consisting of an array of miniature pyramids. The tip creates a thermal effect in the tissue (usually 200-300 microns deep) in the tissue within 5 – 16 milliseconds, thus mimicking the pulsed laser action. The tip thermally generates a matrix of coagulation sites (or "micropores") on the skin. Dermal heating and coagulative effect that occur during the treatment session provide for dermal remodeling and collagen restructuring that promote wrinkle reduction and general wrinkle appearance improvement.

Protocol Number:

CLN 0460

Study Design:

Prospective, single-blinded, randomized, controlled study

Number of Study Sites:

2

Study Population:

Male and female subjects between 40-70 years of age (inclusive) diagnosed with clinically evident periorbital wrinkles

Study Treatment:

Subjects will be treated with the Tixel for periorbital wrinkles every 4-6 weeks for a series of 3 to 5 treatment sessions followed by 3 follow up sessions (see flowchart for full schedule details and options). The number of treatments may vary from subject to subject and shall be determined by the investigators' assessment of the subjects' improvement.

The minimal estimation for study duration per subject is 27 weeks, and the maximal estimation is 47 weeks (please see study flowchart for further details).

Comparator Treatment:

The ResurFX Non-Ablative Laser with the M22 device by Lumenis (1565 nm) for treatment of periorbital wrinkles

2. STUDY OBJECTIVES:

To demonstrate the safety and performance of the Tixel fractional system for treatment of periorbital wrinkles in comparison to the selected market-cleared comparator.

2.1. Primary Outcome Endpoints:

Each subject shall be assessed based on FWCS. Each subject shall contribute two separate data time points to the study.

2.2. Safety

Physical and dermatological examinations, erythema, and adverse events (such as PIH, burns, etc.) monitoring will be performed and assessed at every visit (including follow up visits).

2.3. Effectiveness/Performance

Effectiveness/Performance shall be assessed and quantified by 3 blinded assessors.

The following assessment method will be applied by the blinded assessors (by images only):

- FWCS - Fitzpatrick Wrinkle Classification System

2.4. Secondary Outcome Endpoints

The following criteria will be assessed as secondary outcome endpoints:

- Secondary Effectiveness/Performance shall be assessed and quantified by a handling physician (one of the team's investigators of the study).

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

- FWCS - Fitzpatrick Wrinkle Classification System
- GAIS - Global Aesthetic Improvement Scale Assessment
- WAS - 5-point Wrinkle Assessment Scale
- Subject Experience
- Pain Level VAS Scale
- Subject Subjective Downtime Assessment

- Subject redness, edema and crust assessment (time for resolution)
- End-User Experience Assessment

Clinic Visits Baseline, 4wk, 8wk, (optional 12wk and 16wk), 20wk, 28wk, 42wk

3. INCLUSION CRITERIA

1. Male or female 40-70 years old diagnosed with clinically evident fine (mild) to moderate depth periorbital wrinkling
2. Willingness and ability to comply with all required study activities 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. EXCLUSION CRITERIA

1. The subject may not undergo treatment by the Tixel or comparator 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.
2. Female subjects who are pregnant, or planning to become pregnant, or have given birth less than 3 months ago or are lactating.
3. Subjects with significant exposure to critical amounts of ultraviolet light (Sun tan).
4. Subjects who have had the following treatments:
   a. a prior cosmetic procedure to improve facial rhytides (i.e., rhytidectomy, 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 6 months, such as for botulinum toxin injections, retinoid, microdermabrasion or prescription level glycolic acid treatments
   c. Injectable filler in area to be treated within 9 months of investigation.
   d. permanent facial implant
5. Any subject who have visible scars that may affect evaluation of response and/or quality of photography.

6. 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.
7. 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.
    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
8. Subjects who have used, within 30 days, any medication that can cause dermal hypersensitivity or affect skin characteristics (i.e. topically applied Retinoids, Hydroquinone, Chemical peel of any strength: glycolic acid, lactic acid, salicylic acid)
9. Subjects who have used, systemic treatment which may induce dyspigmentation, such as amiodarone, clofazinmine, minocycline or chloroquine.
10. Subjects currently taking or have taken an oral retinoid in the past six months (risk of scarring with therapy); Subjects currently taking long-term oral steroid treatment (causing fragility of the skin, risk of hematoma and bullae formation); Subjects taking Isotretinoin (Accutane or Roaccutan) within past 12 months.
11. Concurrent therapy that, in the principal investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study treatment.
12. Subjects who anticipate the need for surgery or overnight hospitalization during the study.

13. Enrollment in any active study involving the use of investigational devices or drugs.
14. Any other cause per the principal investigator's discretion.

5. SUBJECT SELECTION: NUMBER OF SITES/INVESTIGATORS

There will be two investigational sites participating in this study, including one site in the U.S. and one in Israel.

5.1. Number of Subjects

A total of 82 subjects will be recruited to the study. They will be randomly split to two separate arms (41/arm) in each site, and undergo periorbital fractional treatments.

5.2. Study Arms

Subjects will be randomly assigned to one of the following groups:

- **Group I:** Tixel
- **Group II:** The ResurFX Non-Ablative Laser with the M22 device by Lumenis (1565 nm)

5.3. Intended Population

Male or female 40-70-year-old diagnosed with clinically evident periorbital wrinkling**.**

At least one of each Fitzpatrick skin type I to IV must be included in the study. In addition to this definition, all Fitzpatrick skin types (I-VI) may participate in the study. For clarity's sake, it is emphasized that not every site must have all skin types I-IV, but the entirety of the study's population.

6. STUDY DESIGN

The study is designed to explore the safety and effectiveness of the Tixel, a novel fractional device, in treatment of periorbital wrinkles in comparison to a currently market-available product, which applies fractional treatment. The study is designated to compare between the effect of a currently available fractional pulsed laser modality (the "comparator"), market-cleared in the US for the said purpose, and the Tixel.

This is an interventional, double-arm, controlled, randomized, prospective, multi-center (US, Israel), clinical study with single-blinded evaluation. The Tixel treatment results will be compared to a laser modality indicated for the same purpose.

7. PROCEDURE

Prior to beginning treatment, the subject will be given post-care instructions regarding skin care after treatment. Once the post-care instructions are reviewed with the subject, treatment may commence.

The subject's face should be gently cleansed with water and soap (hypoallergenic allowed) or any other cleansing materials customary for use prior to fractional treatment sessions, in order to remove any excess material from the skin such as natural oil, mascara clumps, etc. No materials with active ingredients shall be used in order to avoid interference with the study's objectives. All materials applied shall be documented in the CRF including method of application.

The study team member performing the cleansing shall be responsible for closely examining the subject's facial skin to ensure it is clean and dry. In case other cleaning procedures are customary in the study sites, they are acceptable as long as supervised and approved by one of the study's investigators, and as long as they are performed uniformly on the entire periorbital site and its immediate peripherals.

8. STUDY BLINDING

This study is single blinded with limited access to the randomization code. Every effort will be made to retain the integrity of the blinding. Subjects will be randomized post-screening.

The treatment each subject shall receive will not be disclosed to any of the investigators until subject screening and enrollment is complete. The same shall apply regarding study site personnel, subjects, monitors, or the Sponsor staff except as required for the purposes of conducting this study.

The blinded evaluators shall not be exposed to the information, as well, in order to keep their assessment objective.

9. STUDY FLOWCHART AND FOLLOW-UP ASSESSMENTS

Procedure	**Visit 1** **Treatment 1**[c]	**Visit 2** **Treatment 2**	**Visit 3** **Treatment 3**	**Visit 4** **Treatment 4** Optional	**Visit 5** **Treatment 5** Optional	**Visit 6** 1 month **Follow-up 1**	**Visit 7** 3 months **Follow-up 2**	**Visit 8** 6 months **Follow-up 3**
	T_0 [f]	T_0 + 4w (± 5d) ± Δ[ef]	T_0 + 8w (± 5d)± Δ	T_0 + 12w (± 5d) ± Δ[e]	T_0 + 16w (± 5d) ± Δ[e]	T_0 + 20w (± 8d) ± Δ [e]	T_0 + 28w (± 8d) ± Δ [e]	T_0 + 42w (± 8d) ± Δ [e]
Max duration	-	4w+5d	8w+10d	12w+15d	16w+20d	20w+25d	28w+33d	**40w+41d ~ 47w**
Min duration	-	4w-5d	8w-10d	-	-	12w-15d	20w-23d	**32w-29d ~28w**
Subject Screening, Enrolment Procedure & Informed Consent[g], Post treatment care instructions	X							
Facial dermatological skin examination	X	X	X	X	X	X	X	X
Inclusion/ Exclusion criteria	X							
Medical/Surgical history	X							
Demographics	X							
Limited Physical examination[a]	X							
Concomitant Therapy/Medication	X_b	X	X	X	X	X	X	X
Verbal Inquiry regarding pregnancy	X	X	X	X	X	X	X	X
Photography of Treatment Area(s) – prior to treatment	X (baseline)	X	X	X	X	X	X	X
Photography of Treatment Area(s) – After treatment			X					
Investigational/Comparator Device Treatment	X	X	X	X	X			
Subject experience and satisfaction questionnaire	X		X*	X*	X*	X*		X

Procedure	Visit 1 Treatment 1[c]	Visit 2 Treatment 2	Visit 3 Treatment 3	Visit 4 Treatment 4 Optional	Visit 5 Treatment 5 Optional	Visit 6 1 month Follow-up 1	Visit 7 3 months Follow-up 2	Visit 8 6 months Follow-up 3
GAIS Assessment		X	X	X	X	X	X	X
FWCS Assessment	X_f	X	X	X	X	X	X	X_f
WAS Assessment	X_f	X	X	X	X	X	X	X_f
Subject VAS Pain assessment	X	X	X	X	X			
Subject Assessment Questionnaire (regarding downtime, skin erythema, redness and scabs)		X	X	X	X	X		
Adverse Events	X	X	X	X	X	X	X	X
Subject Compliance	X	X	X	X	X	X	X	X
Post Treatment Care Instructions	X	X	X	X	X			

a. A limited physical examination will be performed at Screening to support the eligibility determination. System review will include general appearance, and a routine physical examination, according to the standard of care and as customary for fractional treatments.

b. At Screening, the review of concomitant medications should include those taken within the past year.

c. All assessments on treatment days are to be performed prior to treatment; the assessments performed prior to Treatment 1 will be designated as Baseline.

d. Treatment sessions 4 & 5 are optional for both treatment options, based on the investigator's assessment of the subject's response.

e. The sign Δ signifies the possibility of the change of the study's duration. Any delay of this sort will be documented and explained in writing.

f. Blinded assessment performed in addition to physician assessment. Shall be performed at the end of the subject's activities.

g. First visit may be split into two separate visits: part I: screening, enrollment and informed consent, and part II: rest of visit content (see in **שגיאה! מקור ההפניה לא נמצא.**)

* The * symbol is designated to show that filling out the Subject experience and satisfaction questionnaire is optional and should only be performed in one of the visits marked by the symbol. This is because it may be determined in a specific treatment visit (no. 4 or no. 5) that no more treatments are required. Therefore, the questionnaire

should be filled out in the last treatment visit or in a following visit. For convenience purposes, it is also allowed to have the questionnaire filled out by the subject in the first follow-up visit.

10. SAMPLE SIZE CONSIDERATIONS

The rationale for sample size calculation was based on difference between treatments arms in the improvement post treatment in FWCS scores.

Improvement=$FWCS_{6\ months} - FWCS_{Baseline}$

NIM=$Improvement_{Tixel} - Imrovement_{Laser} \geq -0.5$

The assumption that Tixel is non inferior as compared to Laser in the effectiveness as evaluated by FWCS 6 months after first treatment.

FWCS ranges from fine to deep wrinkles in a 1 to 9 scale.

Previous studies demonstrated that the standard deviation of the change in FWCS post 6 months is 0.75.

Assuming that the non-inferiority margin is NIM≥–0.5, and the SD=0.8 a sample size of 32 completers per group will enable to conclude that Tixel in non inferior to ResuFx with 95% confidence and with 80% power.

Taking into account a dropout rate of 20% a total of 40 cases per group should be recruited.To allow for the possibility of a higher dropout rate a total of 41 cases per group will be recruited.

11. STATISTICAL METHODS

11.1 General

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables summary tables will be provided giving counts and percentages.

For continuous variables summary tables will be provided giving count, arithmetic mean, standard deviation, median, 25th and 75th percentile, minimum and maximum of variables by device.

All tests will be two-tailed, and a p-value of 5% or less will be considered statistically significant.

The data will be analyzed using the SPSS version 925.0.

11.2 Primary Performance Endpoint

FWCS scores will be summarized per subject and time point. Changes from baseline to the last follow-up visit will be summarized as well. For analyzing the changes over time within each arm, the Repeated

measures or Friedman paired test followed by Dunn's post hoc test (as appropriate based on Shapiro and Wilk test for normality) will be applied. For comparison between devices two-sample T-test or Non-parametric, Mann-Whitney Rank sum test (as is appropriate) will be applied.

In addition, in order to keep the study's power, data of the two sites will be pooled together and an Analysis of Covariance (ANCOVA) model will be applied for analyzing the primary endpoint, with adjustment to suspected confounders (baseline measure and site).

11.2.1 Safety Assessment

Frequency and incidence of physical and dermatological examinations will be summarized.

Adverse events will be reported in tabulated format based on all ITT (intent to treat data set).

11.3 Secondary endpoints

All parameters below will be summarized at baseline condition and all post-baseline conditions. The change from baseline to the last follow-up will be analyzed using Wilcoxon paired test.

The following secondary endpoints will be summarized in appropriate tables by device and visit:

11.3.1.1 FWCS - Fitzpatrick Wrinkle Classification System

11.3.1.2 GAIS - Global Aesthetic Improvement Scale Assessment

11.3.1.3 WAS - 5-point Wrinkle Assessment Scale

11.3.1.4 Subject Experience

11.3.1.5 Pain Level VAS Scale

11.3.1.6 Subject Subjective Downtime Assessment

11.3.1.7 Subject Response Questionnaire (redness, edema and crust - time to resolve)

11.3.1.8 End-User Experience Assessment

11.3.1.9 Repeated measures or Friedman's test (as is appropriate) will be applied for analyzing the changes within side (device) and .The two-sample T-test or Non-parametric Mann-Whitney Rank test (as is appropriate) will be applied for comparative analysis of the changes between the devices.

12 RISK ANALYSIS

By enrollment to the study and following its procedures, the subjects shall face the risk of all side effects of both the Tixel and the comparator device, listed in the devices' labeling. The risks are, in general, the known risks of non-ablative fractional lasers (for comparator treatments), and similar risks (for Tixel treatments), excluding radiation and fume hazards.

Due to randomization, the subject will be notified of worst case, meaning the known risks of the non-ablative fractional laser.

Potential side effects exist. See following section.

13 EXPECTED POSSIBLE SIDE EFFECTS (FOR BOTH DEVICES)

In the same manner as all fractional skin treatment devices, there is some 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 and/or peeling; Post Inflammatory Hyperpigmentation (PIH); Hypo-pigmentation; Sensitivity to sun exposure; Local burns; Scars; Local bacterial infection.

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There is also the risk of loss of confidentiality. However, safeguards will be implemented to reduce this risk, including coding of data and images.

14 BENEFIT TO SUBJECTS

By enrollment to the study and following its procedures, the subjects shall have the following benefits from the study:

- Dermatological examination by an experienced physician.
- Periorbital Wrinkles assessment and treatment by fractional skin resurfacing by an expert physician.
- The chance to contribute to the scientific exploration and to the market clearance of a fume-free, radiation free, eye-safe non-ablative fractional device.