Post Market Follow-up Study Report

Tience® - product suitability for treatment of periorbital skin defects and age- related changes

Investigational product:	Tience
Design:	An open explorative, single centre post-market follow-up study
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Study plan ID:	CT-010 version 1.0, 7.3.2025
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Regulatory compliance:	This post-market follow-up study was conducted in, and essential study documentation archived following, as applicable, the requirements set forth in: • Declaration of Helsinki • Tissue Act (101/2001) • Fimea Regulation 3/2014 • Good Clinical Practice principles • General Data Protection Regulation
Date and version of report:	3.11.2025, version 2

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Author	Date	Version	Changes
Camilla Heiniö Aurevia Oy, Minna Höst Linio Biotech Oy.	03.11.2025	2	Correction of a few spelling mistakes, clarifying: changing clinical investigation to post- market follow-up study.
Camilla Heiniö Aurevia Oy, Minna Höst, Linio Biotech Oy.	25.09.2025	1	Initial version

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse events
CA	Competent Authority
CIP	Clinical Investigation Plan
eCRF	Electronic Case Report Form
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions For Use
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SEC	Single European Code
SoHo	Substance of Human origin
PRP	Platelet-Rich Plasma
ATE	Adipose Tissue Extract
VMM	Vancouver– Manchester Modified Scar Scale
PI	Principal Investigator
SGE	Subject Global Evaluation
HIVAbAg	HIV Antibody/Antigen test
HIV- Nh	HIV non-reactive (Nh) result
TrpaAb	Thyrotropin Receptor Antibody
HBVsAg	Hepatitis B surface antigen
HBCAb	Hepatitis B core antibody
HBV-NhO	Non-reactive or negative for hepatitis B virus
HCV-Nh	Non-reactive for hepatitis C virus
HVCAb	Hepatitis C virus antibody
HTLV1/2 Ab	Human T-cell Lymphotropic Virus type 1 and 2 antibodies

TERMS

SAE (serious adverse event):
a) any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity;
b) any undesired occurrence associated with procurement, testing, processing, preservation, storage or distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity (Tissue Act 101/2001).

SAR (serious adverse reaction):
a) any unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation, which is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity;
b) any unintended response, including a communicable disease, associated with the procurement of tissues and cells or their use in the donor or the recipient, which might be fatal, life-threatening, disabling or incapacitating, or which might result in, or prolong, hospitalization or morbidity (Tissue Act 101/2001).

AE (adverse event), adverse occurrence
An adverse event refers to a harmful medical occurrence, unintended illness or injury, or adverse clinical symptoms (including abnormal laboratory results) experienced by study participants, users, or other individuals in connection with a clinical investigation, regardless of whether it is related to the investigational device (MDR 745/2017, Article 2(57)).

Fitzpatrick Scale
A scale developed in 1975 by dermatologist Thomas B. Fitzpatrick, used to assess the risk of scarring and the skin's reaction to sunlight and medical procedures.
The scale classifies skin types into six categories based on pigmentation:

1. **Type I:** Very fair skin, does not tan, burns easily.
2. **Type II:** Fair skin, tans slightly, burns easily.
3. **Type III:** Medium fair skin, tans, may burn.
4. **Type IV:** Medium brown skin, tans easily, rarely burns.
5. **Type V:** Dark brown skin, tans quickly, very rarely burns.
6. **Type VI:** Very dark skin, does not burn, tans very darkly.

Single European Code (SEC)
A traceability system used within the EU, designed to ensure the safety, traceability, and quality of human tissue and cell products. The SEC is part of the requirements set out in EU directives on the handling of tissues and cells, with the aim of preventing misuse and facilitating quality control and product safety.

SoHo (substance of human origin)
Tissues, cells, or organs of human origin, or their derivatives, used in medical treatment or research, such as in allogeneic (from another person) tissue transplantation or cell therapies. In this study, the term refers to cell free adipose tissue technology i.e. Tience® product, which supports the skin's natural regeneration process.

3 SUMMARY

Post Market Follow-up Study title

Tience® - product suitability for treatment of periorbital defects and aged-related skin changes

Introduction

The periorbital area goes through age related changes and defects occur throughout the persons lifetime due to, but not limited to, the collagen matrix and adipose tissue deterioration. This study aimed to investigate the use of Tience on the under-eye region to investigate the suitability, safety and efficacy of undereye wrinkle treatments.

Purpose of Post- Market Follow-up Study

The purpose of the study was to monitor the effects of the Tience product in the treatment of periorbital skin defects and age-related changes.

Date of Study initiation	**Study completion date**
21.3.2025	2.9.2025

Study population

Ten healthy adults, aged 40-65 with visible age-related signs in the under-eye region.

Study method

An open explorative, single centre post-market follow-up study.

Study results

The study showed that a 100% of the participants experienced satisfaction with the treatment, and the vast majority, 80-90% of the participants felt that the treatment was beneficial for the periorbital area. When analyzed with Visia® Gen7 skin analysis system, the results supported the subjective evaluation results. The Visia® Gen7 system normalized wrinkle score improved drastically. It showed statistically highly significant improvement ($p<0.001$***) by Tience treatment, the score decreasing to 79,1 compared to the baseline value in four (4) months.

Conclusion

Tience product is safe to use and improves significantly the appearance of the periorbital skin defects and age-related changes as analyzed by Visia® Gen7 skin analysis system and patient self-assessment questionnaire.

4 REGULATORY COMPLIANCE AND IMPLEMENTED LAWS

The product is regulated as a tissue product under the EU Tissues and Cells Directive (2004/23/EC)[1], its subdirectives[2-5], the corresponding national Tissue Act (101/2001)[6], and Fimea Regulation 3/2014[7]. The product is authorized by the competent authority Fimea for clinical use for treatment of wounds, scars and soft tissue defects. Linio Biotech holds a tissue establishment lisence (# TE4008) for the procurement, transportation, processing, preservation, storage, distribution, export and import of adipose tissue. This post-market follow-up study was conducted using a tissue product already in clinical use and in accordance with its approved intended use.

5 ETHICAL CONDUCT

This post market follow-up study was supported by an ethical evaluation provided by the Principal investigator (Appendix 1. Principal Investigator's Ethical Assessment)

5.1 Participant information and informed consent

All participants received written and verbal information regarding the investigation prior to any investigation-related procedures. The informed consent brochure (see Appendix 2. Informed Consent Form) emphasized that participation in the investigation is voluntary and that the participant may withdraw from the investigation at any time and for any reason. Before any investigation-related procedures, the informed consent was signed and dated by the participant and by the study coordinator who gave the participant the verbal and written information.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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7 INTRODUCTION

Tience is an allogenic tissue product (SoHO) of human adipose tissue origin, designed for treatment of soft tissue defetcs such as under eye skin defects and age -related changes the product is processed and handled according to the EU Tissues and Cells Directive (2004/23/EC)[1], the corresponding national Tissue Act (101/2001)[6], and Fimea Regulation 3/2014[7].

7.1 The Skin

The skin is the largest organ of the human body, and its function is to protect the body against chemicals, ultraviolet radiation from the sun, abrasion, and impacts.[8] In addition, it prevents water evaporation, regulates temperature, produces vitamin D, and transmits sensory stimuli. Damage to the skin occurs naturally through aging as well as due to various accidents or, for example, as a consequence of medical treatments.[9] On the cellular and tissue level, these damages often manifest as excessive formation of abnormal connective tissue (scars) and as reduced or insufficient blood circulation.[10]

The investigational product of this study, the Tience® tissue product (hereafter referred to as the product), has been shown in laboratory, animal, and experimental studies to be capable of promoting the formation of healthy skin, adipose tissue and connective tissue, as well as blood vessel formation in the damaged area.[11-13] This has been observed to repair pre-existing damage[13] and the effects of aging on the skin.[14]

7.2 Current Treatments of Periorbital Skin

Periorbital skin state-of-the-art treatments include CO2 laser therapy and radiofrequency treatment.[15] Device-based treatments, such as lasers, radiofrequency, and ultrasound, can stimulate collagen production and tighten the skin through controlled trauma, but their effects are somewhat limited, particularly on the thin and sensitive periorbital skin. More importantly, device-based treatments have side effects such as swelling and redness of the skin, excessive tissue damage and long recovery times.[16] Hyaluronic acid–based fillers have also been used in periorbital area to restore lost volume, however, fillers bear safety concerns and cause adverse events and even complications.[17]

The third group - biostimulatory treatments—such as combinations of skin boosters and amino acids, as well as PRP (platelet-rich plasma) treatments—support skin regeneration, but there are no standardized methods for their use, and comprehensive clinical evidence of their effectiveness on periorbital skin is lacking.[18] Most current treatments focus either on adding volume or improving superficial skin quality, but there is no widely available safe and effective treatment method that supports the natural regenerative process. This highlights the need for new therapies that promote the skin's own regenerative capacity and whose effects and safety must be studied.

7.3. The Tience® Product

The Finnish manufacturer, Linio Biotech Oy, has developed the Tience® product, a cell-free preparation derived from the extracellular matrix of adipose tissue. It contains various proteins that support the regeneration of connective and soft tissues. The product is allogeneic, meaning it is manufactured using adipose tissue from a volunteer human donor. The product has been tested for infectious diseases as required by law[6] and is processed in a lisenced tissue establishment (#TE4008), fulfilling the requirements of the directive and respective laws and regulations of Finland.[1,6,7]

7.2.1 Study results up to date

Tience® has been found to be safe when injected subcutaneously, based on preclinical and clinical studies.[19,20] The manufacturer has previously together with Terveystalo performed a monitored clinical safety study. In the study, performed during the winter of 2022-2023, a group of 39 persons were injected subdermally a large volume of 4,5 ml (3 vials) of the Tience product, and the effects were followed for three months. No adverse effects related to the tissue product were observed in the study.[20] The manufacturer has also other clinical studies ongoing, the results of which have been encouraging.

A study on Tience use for superficial wound healing is currently ongoing in Jyväskylä, Hospital Nova, with 24/30 patients treated so far. The conduct of study is expected to be finished during 2025. No adverse effects related to the use of the product have been reported to the manufacturer in this study so far.[21]

7.3.2. Current knowledge

The safety and efficacy of the autologous version of the product (ATE, adipose tissue extract) on superficial wounds were studied in a clinical study at Tampere University Hospital.[13] In the study, the split-thickness skin graft donor sites were treated with ATE or PRP. The ATE treatment group was compared with platelet rich plasma (PRP) blood product treatment group. The results showed that compared to PRP, ATE treatment significantly induced the skin epithelial layer renewal, i.e. epithelialization, and also the scar maturation during a 60 day follow up period. The quality of the scar was also estimated to be better. The scar was more mature, softer and lighter in color, when was evaluated with the Vancouver– Manchester Modified scar scale.[13]
To our knowledge, no comparable products have been developed and reported that could induce optimal skin healing or the healing of soft tissue. Current available treatments are either autologous treatments, such as the classical fat transfer, nanofat transfer or platelet rich plasma or animal or plant derived products with one or few growth factors or extracellular matrix proteins. The efficacy and safety of the above-mentioned products are not demonstrated and autologous methods, on the other hand, cannot be offered to patients as allogenic off the shelf products.

This study planned to follow Tience effects on the periorbital defects and age-related changes.

8 INVESTIGATIONAL PRODUCT AND METHODS

8.1 Intended use of the Tience product

Tience is intended to be used in the human body for its original purpose to supplement and replace local extracellular matrix deficiencies in soft tissue, including skin. Tience provides a temporary conductive environment into the injured area. This facilitates the ability of local cells to re-populate the damaged soft tissue and skin area, thereby enabling the deposition of extracellular matrix and repair of the tissue. Tience is authorized for treatment of wounds, scars and soft tissue defects.[22]

8.2 Tience product description

Tience is a cell-free preparate of human adipose tissue, a substance of human origin. Tience supports skin repair and skin regeneration. Tience is a sterile ready-to-use product, a pink, red or red-brown liquid, in a 1,5 ml vial. Each vial has an SEC code for identification and traceability. Tience is stored in the freezer in -15°C to -25°C.

Tience is a blend of proteins, peptides and lipids. The material for the product is received from a healthy living donor. The donor has been tested, and the product has been prepared in accordance with the Finnish law and respective regulations.[1-7] Donors are screened for their medical, family and travel history and serologically tested (HIVAbAg, HIV-Nh, TrpaAb, HBVsAg, HBCAb, HBV-NhO, HCV-Nh, HVCAb, HTLV1/2 Ab). Each batch is quality control tested for sterility, endotoxins and protein concentration. The product is intended only for one intended recipient, on a single occasion only. Tience offers a transitional growth scaffold in the damaged skin and soft tissue, which supports local cell's outer matrix development and tissue renewal.

Tience can only be used by a healthcare professional (Appendix 8. Principal investigator's CV), who is responsible for informing the patient about the origin and use of a substance of human origin. In addition, the patient shall be informed of the storage of their data in the tissue establishment registry (patient identification data and possible follow-up information in case of suspected adverse reactions).An informative and more detailed description of the use of the product can be found in Appendix 3. Package leaflet.

9 POST-MARKET FOLLOW UP STUDY PLAN

The post-market follow up study plan was followed throughout the study. No amendments were made to the study plan during the study. The Post-Market Follow-Up Study Plan can be found as attachment, Appendix 4.

9.1 Study objectives and endpoints

9.2 Purpose of the study

The purpose of the study was to monitor the effects of the Tience product in the treatment of periorbital skin defects and age-related changes.

9.3 Primary objectives

The primary objective of the study was to determine whether the use of Tience product results in a visually perceptible and aesthetically acceptable treatment outcome.

9.4 Secondary objectives and endpoints

The secondary objective was to show that the Tience product is safe to use in the treatment of the periorbital skin.

9.5 Hypothesis

Based on the clinical use of Tience, the Sponsor predicted that Tience is suitable for treatment of periorbital skin defects and age related changes. Additionally, based on the same data, the second assumption was, that the product is safe to use, and no serious adverse events were going to occur during the study.

9.6 Study design and treatment allocation

The study consisted of 4 visits. During the first visit, the study coordinator assessed the suitability of the participant for the study according to the inclusion and exclusion criterias. Included participants that had given informed consent, were photographed using Visia® Gen7 skin analysis system. During the second visit, the Study Physician confirmed the participant's eligibility for the study according to the inclusion and exclusion criterias prior to the Tience treatment. The treatment was performed according to the study plan. A questionnaire was collected seven days after the initial treatment, to confirm the participant's well-being and to document their reactions to the treatment. The follow-up consisted of two visits where the participant's responses to the treatment were evaluated with Visia® Gen7 skin analysis system. In addition, treatment satisfaction was assessed through a self-evaluation questionnaire. The questionnaires used in this study are included in this document as follows: Appendix 5a. Participant self-assessment form, and Appendix 5b. Satisfaction Questionnaire: Subject's Global Evaluation.

All treatments and follow-ups were performed within four months.

Table I. Study flowchart

Procedure	***Visit 1***	***Visit 2***	***AEs, local reactions***	***Visit 3***	***Visit 4***
Day	*Pre- treatment*	*Day 0*	*Day 7*	*6 weeks*	*4 months*
Informed consent	*X**				
Inclusion and exclusion criteria	*X**	*X**			
Visia® Gen7 skin analysis system measurements	*X*			*X*	*X*
Tience treamtents		*X*			

Questionnaire			*X*	*X*	*X*
Adverse events		*X*	*X*	*(x)*	*(x)*

**During Visit 1, a coordinator discussed the study flow and explained the consent process. Written informed consent was required from all study participants prior any study related procedures were conducted. However, the investigator confirmed the consent and checked the suitability of the participant. Imaging was performed pre-treatment.*
(x)= the well-being of the participant was followed by visual observation.

9.7 Control group

The study was internally controlled and comparted to participant's "before treatment"- information. No blinding was used in this study.

9.8 Collected variables and measurements

The treatment results were evaluated both through the participant's self-assessment questionnaire and by means of periorbital skin image analysis by Visia® Gen7.

The image material was collected using the Visia® Gen7 skin analysis system (Figure 1–3), which captures and automatically analyzes the images. The images enable monitoring of changes in the skin.

Figure 1–3. Visia® Gen7 skin analysis system® -skin analysis device

9.9 Safety variables and measurements

All AEs that occurred during study, and therefore up until a maximum of 4 months after the first measurement was performed, were documented according to procedures outlined in the study plan. Frequency, severity, device-relationship and outcome of all AEs was recorded. The principal investigator assessed the adverse events reported by study participants upon completion of the study. A detailed summary is provided in Appendix 6. Principal Investigator's Report of Adverse Events and Adverse Reactions.

List of foreseeable AEs listed in the Study Plan:

- Cutaneous irritation due to injections (erythema)
- Skin irritation (from stretching) following injection therapy
- Infection of the treatment site
- Nausea or faintness during injection therapy
- Minor ecchymoses may occur at the site of intradermal injection
- Mild pain or burning sensation
- Erythema and tenderness at the treated site

Foreseeable AEs according to the IFU:

- Pinpoint bleeding
- Acute bruising
- Acute swelling
- Injection site pain

- Itching
- Tingling
- Needle marks

9.10 Ethical considerations

9.10.1 Potential risks, disadvantages and stress for the participant posed by the investigational product.

Adverse reactions related to the product itself have not been previously observed in clinical trial in humans,[20] However, adverse reactions related particularly to the application method, such as injection, are possible such as pinpoint bleeding, acute bruising, acute swelling, injection site pain, itching, tingling and needle marks.[20,22]

9.11 Overall benefit-risk assessment and conclusion

No additional risks were posed to the participant by either the product or by participation in this study. Given that the study results could lead to aesthetically improved under eye skin, the Sponsor judged this study to have a favourable overall risk/benefit profile. As no other than fore-seeable adverse events and no severe adverse events occurred, the risk benefit profile of the product was considered to be favourable.

9.12 Data quality assurance

9.12.1 Data and quality management

The study data was collected via an electric case report form (eCRF) and completed by the site's responsible persons and finally approved by the Principal Investigator. The data reported in this Study Report was derived from source documents and in consistent with these. The sponsor was responsible for database creation, data entry, quality control of the eCRF vs. database, database cleaning and data extraction for analysis. Data storage was conducted according to the Sponsor's internal data management policies.

9.12.2 Monitoring, audits and inspections

The data accuracy was controlled by sponsor quality checks, the sponsor proof-read the data to ensure its quality. No audits/inspections by representatives of the Sponsor were conducted during the study.

9.13 Study population

9.13.1 Inclusion criteria

Participants were to meet all of the following criteria to be eligible to enter the study:

The study will include voluntary, generally healthy individuals aged 40– 65 years who have visible signs of aging on the periorbital skin (skin around the eyes).

9.13.2 Exclusion criteria

The following individuals were not be included in this study:
Persons referred to in Sections 7–10 of the Finnish Medical Research Act (so-called special groups), and individuals who have:

- Fitzpatrick skin type 4–6
- Active skin disease
- Systemic medication affecting the immune system
- Cancer
- A known disorder affecting blood clotting (bleeding or thrombosis tendency), such as Von Willebrand disease
- Undergone surgical procedures, filler treatments, or device-based treatments on the periorbital skin within the past year

- Or who:
- were pregnant
- were breastfeeding
- were allergic to the investigational product or its components (Ringer's acetate solution, adrenaline, lidocaine, clindamycin, or cephalexin)
- were smoking

9.13.3 Stopping or suspending the study

The study was not stopped or suspended early, a decision to stop the study was not made and the study was completed according to the Study Plan.

9.14 Treatment

9.14.1 Treatment administered

Treatment was administered once, and treatment was performed according to IFU. Tience was administered to the under-eye area via approximately 35-40 needle injections. A single vial, with a total volume of 1.8 ml, was administered per participant.

9.15 Statistical analysis

9.15.1 Sample size

A total of 10 participants was planned to be enrolled in the study according to the study plan. At investigation closure, a total of 10 healthy participants had been enrolled and completed the study, while one participant was a screening failure.

9.16 Procedures

After informed consent was given, the study physician ensured the participant's eligibility for the study. If no obstacles were found, the treatment according to the study protocol was initiated. The study physician administered the planned injection treatment to the participant's periorbital area. The skin was disinfected prior to injection. Treatment areas were marked, no anesthetics were used, only cold anesthesia was used 3 min/eye. Approximately 15-20 pricks/ eye (a total of 35-40 pricks per participant) by a 32-34 gauge needle (TSK) were administered and a 1 ml syringe (luer-lock) was used. After the treatment, the participant's condition was monitored for 15 minutes for possible side effects.

9.16.1 Disposition of the product

In this study, the Sponsor and the Principal Investigator maintained records documenting the location of all products including components/supplies allotted in this study.

The Sponsor is obliged to maintain traceability records of Tience products, as required by the Finnish Law.[6] This consists of full traceabililty chain from donated raw material to the use of the final Tience product for the recipient in the clinic. The tracebility form, filled by the PI at the clinic, contains the following information: site no, number of products delivered, date of delivery, number of products returned, SEC code (batch number) and comments. The form is presented in Appendix 7a. Traceability form and 7b. privacy policy).

One single vial of tissue product was used for each individual participant, and all participants received same tissue batch and there was no blinding of product usage.

9.16.2 Professional users

Tience can only be used and was only used by a healthcare professional (Appendix. 8 Investigator's CV, Appendix 9. Investigator's brochure), who is responsible for informing the patient about the origin and use of a substance of human origin.

9.16.3 Reference system

The study did not have a comparison method, but the treatment results were evaluated both through the participant's self-assessment and by Visia® Gen7 image analysis of the skin around the eyes.

The image material was collected using the Visia® Gen7, which captures and automatically analyzes the photographs. The images enable monitoring of changes in the skin. Three Visia® Gen7 measurements were used to analyse the results of Tience treatments: Score and percentage and feature count.

Score: For reporting from the Visia® Gen7 skin analysis system, the 'Score' is the more accurate numbers for reporting treatment efficacy. It is reporting the intensity of the feature within the masked area, so reporting the fractional area of involvement and intensity of the involvement in that area.

Percentage: tells how your skin compares to others in the same age and skin type database. Example: "Wrinkles – 78%" → your skin is better than 78% of people in the same category (age, gender, skin type) and 22% score higher.
Feature count: individual wrinkle features that have been detected within the masked area of the face.

9.17 Concomitant medications/treatment

No concomitant treatments or medications were used in this study.

9.18 Questionnaire

A self-assessment questionnaire regarding adverse events was collected from participants 7 days after treatment. At the 6-week and 4-month follow-up visits, participant satisfaction was assessed using Subject Global Evaluation questionnaire, administered following the Visia® Gen7 skin analysis. All participant's filled the questionnaires.

9.19 Adverse events and product deficiencies

This study, as a whole, followed the tissue act 2004/23 and Act 101/2001 where serious AE (SAE), serious AR (SAR), were defined as stated below, however, the Study Plan definitions were honoured, and if ambiguous situations were to arise, the more strict definitions were applied [1,6]

9.19.1 Adverse events recording and assessment

Any undesirable event affecting health, illness, injury, or clinical symptom (including abnormal laboratory findings) occurring in study participants, users, or other individuals, regardless of whether it was related to the investigational product or whether the event is foreseeable.

An adverse medical occurrence, unintended illness or injury, or adverse clinical sign (including abnormal laboratory findings) in participants, users, or other persons in the context of a clinical investigation, regardless of whether it is related to the investigational product.

Note: This definition includes both anticipated and unanticipated events.

The definition includes events related to the investigational product, comparator, or study-related procedures. For safety reporting purposes, all activities related to the use of the investigational product may be considered procedures.

9.19.2 Serious Adverse Event (SAE)

a) any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity;

b) any undesired occurrence associated with procurement, testing, processing, preservation, storage or distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity (Tissue Act 101/2001)

SAR (serious adverse reaction):
a) any unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation, which is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs,hospitalisation or morbidity;
b) any unintended response, including a communicable disease, associated with the procurement of tissues and cells or their use in the donor or the recipient, which might be fatal, life-threatening, disabling or incapacitating, or which might result in, or prolong, hospitalization or morbidity (Tissue Act 101/2001)

Note: Planned hospitalization for pre-existing conditions or for procedures required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.

Recording and reporting of adverse events

Adverse events were reported and recorded according to the Study Plan and international guidelines.

During the study, information on adverse events and adverse reactions was recorded and reported to the authorities in accordance with applicable requirements. In the event of an adverse event, the study physician notified Linio biotech of the event/deficiency in the agreed manner. The study physician were to report such events and product deficiencies without delay.

9.4.1. Reporting to authorities

Linio biotech must report the following events to the authorities: suspected Serious adverse event of serious adverse reaction as defined in 9.18.2 following Linio Biotech Tissue Establishment Standard Operating Porcedures. No such events were recorded in this study.

9.19.3 Product deficiencies recording and assessment

PI was to report any product deficiency according to IFU to the Sponsor without undue delay.

9.20 Duration of follow-up

The participants were followed for four months.

9.21 Statistical design

The statistical analyses were calculated with Microsoft Excel by using two-tailed paired Student's T-test. The values were normalized to mean value of "before" results, so that the "before" value received mean value of 100. Variance between the test values was calculated using standard error of means.

9.22 Changes in the study and analyses

There have been no amendments to the study plan since the Study Plan version 1 was written and approved.

9.23 Termination, Suspension, or Premature Discontinuation of the Study

The study ended once the participation of the last study participant had been completed. The study was not temporarily suspended or terminated prematurely, and no observed risks to the health of the study participants affected the advancement study.

10 RESULTS

10.1 Disposition baseline characterization and demographics of participants

Initially 11 participants were recruited to the study, all healthy adults of 40-65 years of a mean age of 50,7 years. The study was not randomized, and all fully enrolled participants received the treatment. One participant was a screening failure, subsequently the study was performed with 6 female and 4 male participants, meaning that 10 participants completed the study. No participants were withdrawn or excluded from the analysis or study.

The first participant was enrolled 21-Mar-2025 according to The Study Plan v. 1.0. The actual date of completion of the investigation was 2-Sep-2025. To this study, only healthy participants that fulfilled the inclusion criteria, were enrolled.

10.2 Disposition of the product

All of the product was accounted for and full traceability of each vial was recorded. During the study the participants were administered 1,5 ml of the product according to the Study plan.

10.3 Deviations to the study plan

No minor or major plan deviations were made.

10.4 Primary performance results and analysis - Visia® Gen7 skin improvement measurements

Visia® Gen7 skin analysis system was used for analyzing skin changes after treatment at six weeks and four months and pre-treatment to set the baseline. According to the analysis, the treatment was effective for both periorbital areas of the individual participants, left and right. There were some differences in the analysis results between sides, but overall, no difference was found between different sides treated. On average, the relative wrinkle score for the left eye improved by 6,1679 score units, from an average score of 28,5608 to 22,3929 in four months. When compared with the start of the study 9/10 participants had improved wrinkle scores at 4 months. On average, the relative wrinkle score for the right eye improved with 4.446,7 from an average of 27,9691 to 23,5224, from the start of study.

When both eye wrinkle score measurements were combined and normalized, the normalized relative wrinkle score showed a significant improvement of the score ($p<0.001$*** actual p value=0.000008) and dropped to 79,1 compared to baseline in four months (Figure 4). This result shows that the Tience treatment, when analyzed with Visia® Gen7, decreases significantly the degree of deep measurable wrinkles with only one treatment.

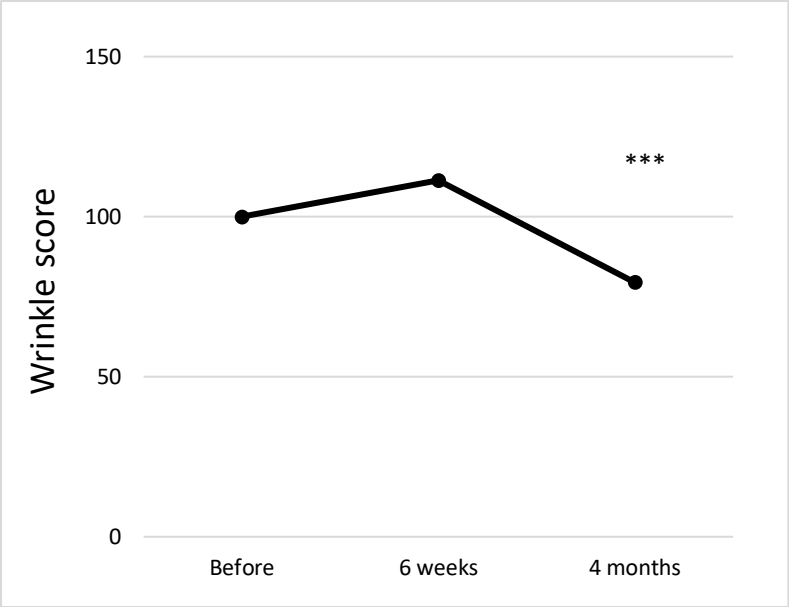
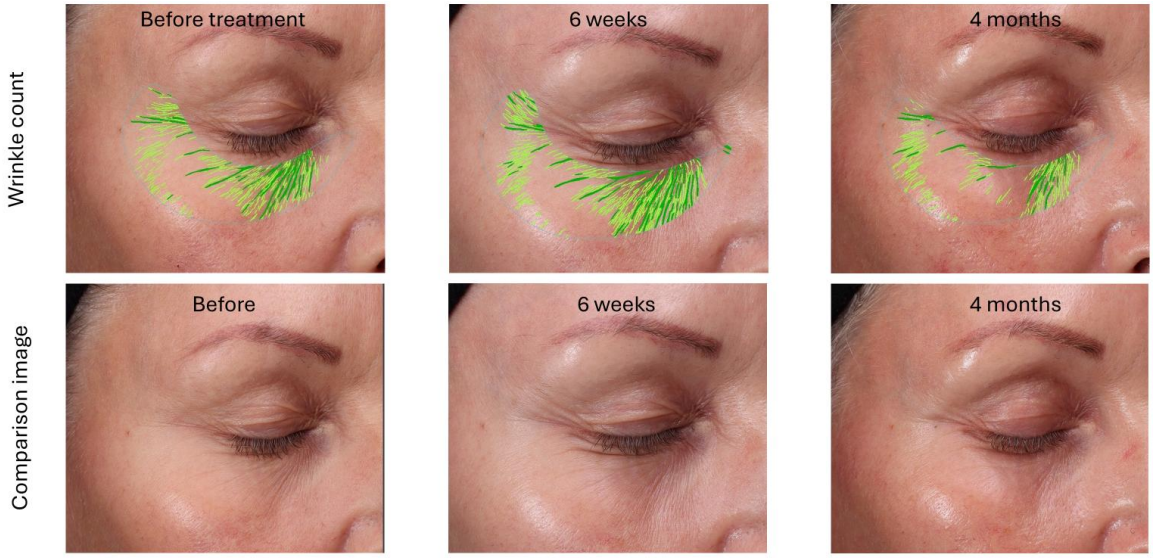


Figure 4. Wrinkle score values before the treatment, at 6 weeks and at 4 months after the treatment showing significant difference and decrease in score at 4 months when analyzed with two-tailed paired Student's T-test ($p<0.001$***).

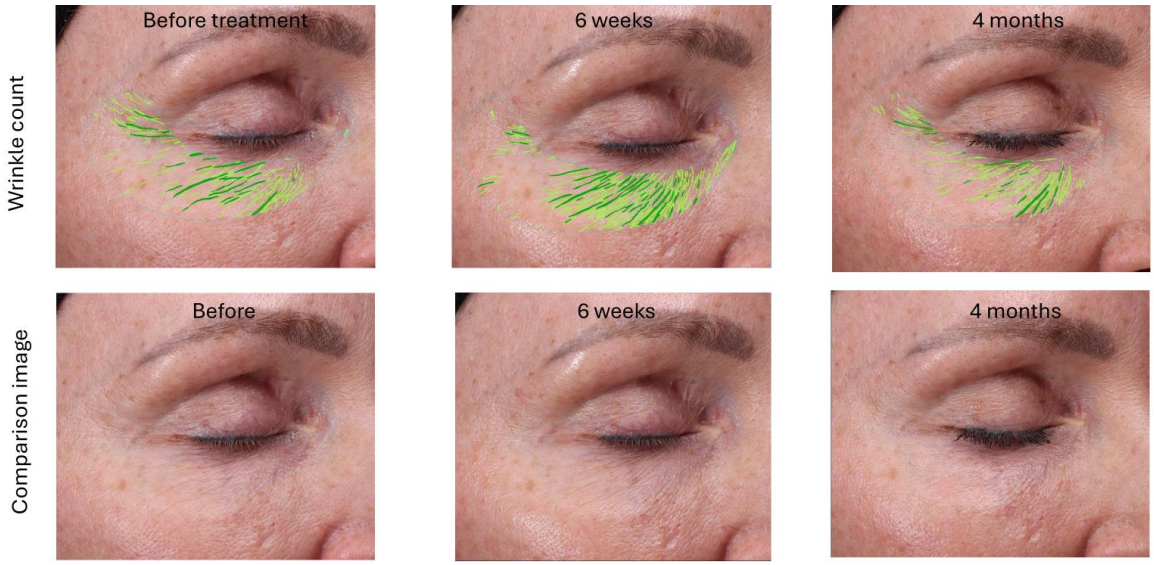
Visia® Gen7 calculates a percentage which indicates how prominent your skin's features are compared to people of similar age. When Visia® Gen7 image percentage was calculated for the left eye, the mean improvement was 17%. This positive change was recorded in 9/10 participants. One participant's percentage score declined from 80% to 73% during the study. Right eye percentage measurements are in line with the other Visia® Gen7 data. The Right eye percentages mean improved with 14,20% on average, from 50,10% to 64,3% in four months. The Visia® Gen7 percentages are, however, only representative and not definitive as the comparator database and Visia® Gen7 algorithms are not disclosed.

Additionally, the Visia® Gen7 calculated the feature count of the participants. For example, in picture 5 the participant's Visia® Gen7 feature count decreased from 145 to 123. On average, when calculating the average for both eyes, the feature count stayed the same throughout the study.
Figures 5 and 6 illustrate how Visia® Gen7 recognizes wrinkles and features and analyses the effect of the treatment. The diminishment of the green line or decrease in the number of green lines indicate that the wrinkles are smoother and less prominent than before the Tience treatment.



Score	39,557	Score	49,288	Score	27,176
Percentage	15	Percentage	9	Percentage	55
Feature count	145	Feature count	165	Feature count	123

Figure 5. Participant A treatment effects as measured by Visia® Gen7 skin analysis system.



Score	25,967	Score	38,372	Score	19
Percentage	57	Percentage	16	Percentage	79
Feature count	87	Feature count	127	Feature count	93

Figure 6. Participant B treatment effects as measured by Visia® Gen7 skin analysis system.

10.5 Secondary performance result and analysis - Self assessment questionnaire

Satisfaction questionnaire was used to assess the participant contentment with the Treatment results.

The results showed that 100 % of the participants were satisfied with the treatment. 10/10 participants were at least somewhat satisfied and out of them 3/10 were “very” or “extremely satisfied” with the results.

A vast majority of the participants, 90 %, noticed improvement “in the overall look of the periorbital area”, the “smoothness and evenness of the periorbital area” and “the brightness and the evenness of the tone of the undereye region”.
80% noticed a improvement in “firmness and tautness” and "reduction of dark tones” in the undereye region. Furthermore, 90 % of the participants noticed improvement in the evenness of the wrinkles in the preorbital area.

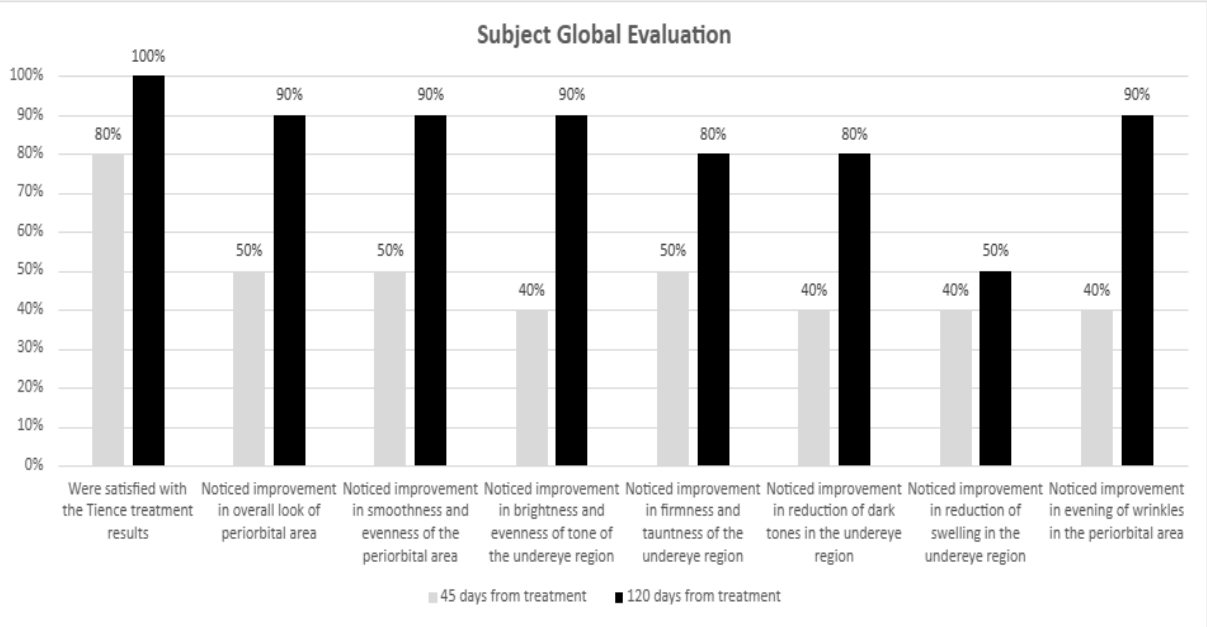


Figure 7. Satisfaction Questionnaire: The Subject global evaluation, results shown as % of participants.

When asked about the perceived improvement, 9/10 participants saw at least some improvement after treatment and out of these 3/10 were saw at least substantial or major improvements.

When asked how much smoother and less wrinkly participants undereye area looked, 9/10 thought that their under-eye skin looked at least a little – to very much smoother than pre-treatment, only one participant did not see a difference. Similarly, when asked how much clearer the under-eye area was perceived after the treatment 9/10 saw a difference, and out of these 3/10 gave the two highest scores for perceived positive change.

The third evaluation question asked “how much firmer and elastic do you think your skin is?”. Tience was perceived to have an positive effect on 8/10 participants under- eye skin’s firmness.

10.6 Summary of adverse events and adverse product effects

Throughout the study, the study personnel followed the participant’s well-being. Zero unexpected adverse events were recorded. The main category of the expected adverse events was bruising/marking of the injection site that lasted for most participants for less than 7 days.

A single participant reported a headache following the injection treatment. The headache was mild to moderate in intensity, transient in nature, and did not result in any long-term consequences. It resolved either spontaneously or with the use of standard analgesics (e.g., paracetamol or ibuprofen) and did not require any specific medical intervention. Headache is a common symptom in the general population and may be associated with various other factors such as stress, sleep deprivation, or environmental influences. This case was considered an isolated, non-serious adverse event related to the procedure, with no impact on the study’s outcomes.

9.5. Summary of product deficiencies

No product deficiencies were observed during this study.

11 DISCUSSION AND OVERALL CONCLUSIONS

In this study, the use of Tience, a novel substance of human origin, in the treatment of periorbital skin defects and age-related changes was evaluated. The periorbital area is a prominent area of the face, as eye contact is of essence in human communication. Currently, chemical peels, microneedling, lasers and fillers/boosters such as HA, and most recently, different biostimulatory treatments are used for enhancing the skin texture, reducing wrinkles and improving the appearance of the undereye area.[15] Unfortunately, only few studies have been performed and thus there is only limited clinical data available on the efficacy and safety of these treatments.

In this study, 10 healthy adult participants, with a mean age of approx. 51 years, were enrolled and their periorbital area was treated with Tience. A self-assessment questionnaire for adverse events was collected at 7 days post treatment. Visia® Gen7 imaging was performed before treatment, at 6 weeks and at 4 months after the treatment. Participant satisfaction was evaluated using the Subject Global Evaluation (SGE) questionnaire, which was completed by participants following the Visia Gen7 assessments at both 6-week and 4-month follow-up visits. Only one participant was a screening failure, and all other 10 participants completed the study. This is a strong indication of that the treatment was well received and that the study setup was not overburdening. Furthermore, this also shows that participants found the study setup and treatment manageable as there were no dropouts.

Patient safety is always the key issue when any new treatment is developed. Subsequently, the safety of the participants was followed throughout the study. Encouragingly, not a single unforeseen AE and no SAE/SAR were collected or reported during the study. This is in line with previous safety data observed with Tience[20] and underlines the safety of the Tience- injection treatment. Only foreseeable AE's that were evaluated to be present due to treatment administration; the needle pricks, were documented throughout this study. Moreover, the principal investigator followed the participants' well-being and concerns during the study, leading to no reportable issues. This indicates that Tience is safe to use in the clinical treatment of the periorbital area.

In order to gain more safety data on the use and treatment procedure of Tience, a self-reporting questionnaire was used for the participant self-evaluations. None of the participants reported infections or inflammatory reactions. Tience was administered as an injection, and therefore, like with any injection, it accompanies some risks of pinpoint bleeding, acute bruising, acute swelling, injection site pain, itching, tingling, needle marks and/or nausea. Many participants considered bruising to be minimal (4/10) and for most of the participants, it was gone in less than a week based on their self-evaluation. Some considered the needle prick bruises to be uncomfortable, but that did not affect their satisfaction with the product, satisfaction being 100%.

The self-reporting questionnaire enquired and set out to determine the participants' subjective satisfaction on the treatment and the Tience experience. The results showed that 100% of the participants were satisfied with the results set forward by the Tience treatment. The uniformity of participant satisfaction (100%) suggests strong acceptance and functionality of the Tience product. Furthermore, a vast majority 80-90%, reported that they saw a positive change in the appearence of the periorbital area (under eye smoothness, color enhancement and wrinkle diminishment) in only one treatment, indicating that Tience is a strong enhancer of the undereye skin.

When wrinkle scores were combined and normalized, the calculated normalized relative wrinkle score was significantly improved ($p<0.001$***) and dropped to 79,1 from a 100 by only one Tience treatment in only four months. In similar fashion, the other Visia® Gen7 analysis data also showed improvement of the participants' periorbital skin, measured as percentages. This result is reflective of the nature of

the Tience as a tissue product, and supported by our clinical user data[14], that the efficacy of the Tience treatment appears typically not earlier than in 3-4 months.

The Visia® Gen7 percentage compares the participants' features to Visia® Gen7 skin analysis system's own feature database, with people of the same age through a non-disclaimed algorithm. Thus, it is not the most accurate measurement. It is nevertheless encouraging that the percentage results for Tience also show improvement of the skin attributes after treatment in 9 out of 10 participants. Moreover, one participant's skin was already in good condition according to Visia® Gen7analysis when the treatments started. The measured Visia® Gen7 percentage for left and right eye respectively were 79%, 96%, while score was 17.991 and 6.55. Thus, there was not much room for improvement, and this was reflected in the overall results of this study for that individual participant. This study studied the efficacy and safety of a single injection treatment with a small set of participants. In the future, even longer follow-up time, up to a year and a larger number of participants could reveal more statistically significant changes.

All in all, taken together the data, this study indicates that the Tience injection for periorbital area treatment is very well perceived and tolerated giving results of skin improvement to the periorbital area, and thus, the benefits overweigh the risks of the treatment.

12 TABLES, LISTINGS AND FIGURES

Table A. Analysis results of individual participants (feature count, percentages, score) on both treated sides and in each time point, as obtained from Visia® Gen7 skin analysis system Gen7 analysis system.

	BEFORE						AFTER 6 WEEKS						AFTER 4 MONTHS					
	Feature count		Percentages		Score		Feature count		Percentages		Score		Feature count		Percentages		Score	
Participant	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
001	52	51	35%	44%	28.937	26.788	117	111	13%	23%	37.697	32.450	73	75	74%	47%	19.639	26.004
002	N/A		-		-		-		-				-		-		-	
003	87	64	30%	29%	35.146	35.420	64	59	82%	60%	20.711	27.952	75	96	59%	41%	28.162	32.659
004	86	145	80%	15%	19.333	39.557	144	165	47%	9%	29.122	49.288	73	123	86%	55%	16.621	27.176
005	38	35	80%	84%	18.415	14.192	53	53	76%	84%	19.951	16.872	54	39	73%	84%	20.984	16.466
006	89	87	66%	57%	23.559	25.967	117	127	23%	16%	34.927	38.372	78	93	89%	79%	14.722	19.708
007	75	80	9%	13%	49.217	44.974	70	73	18%	12%	42.051	45.740	67	78	19%	47%	41.226	32.536
008	72	73	53%	71%	28.436	23.785	112	115	42%	14%	31.574	41.920	72	83	89%	80%	15.592	20.685
009	79	66	66%	76%	25.599	22.453	69	81	79%	71%	22.525	24.136	67	64	72%	90%	24.079	14.801
010	98	97	18%	16%	38.967	40.000	101	103	10%	13%	44.907	42.378	97	76	33%	26%	33.906	36.169
011	66	40	79%	96%	17.999	6.555	58	35	87%	92%	14.123	11.079	34	47	94%	94%	8.998	9.020

Table B. Characteristic of all 10 participants

Age (years)	Total number	Male	Female
40-44	2	1	1
45-49	2	1	1
50-54	4	2	2
55-59	2	-	2
Mean age (years)	50,7	49,3	51,7

Table C. Self-assessment results. The results indicates that the treatment was well tolerated and had minimal negative impact on the participants.

Subject ID	Starting time	Finishing time	Tience-treatment date	Redness	Redness: duration	Sensitivity	Sensitivity: duration	Ichyness or burn	Ichyness and burn: duration	Bruising	Brusing: duration	Inflammation of treatment area	Inflammation of treatment area: duration
1	4.7.2025 11:35	4.7.2025 11:41	3.30.2025	2	2	1	1	0	0	6	8*	0	0
3	4.7.2025 11:55	4.7.2025 12:00	3.31.2025	0		0	0	0	0	8	7+	0	0
4	4.7.2025 11:39	4.7.2025 11:43	3.30.2025	0	1	0	0	0	0	2	5	0	0
5	4.7.2025 13:46	4.7.2025 13:51	3.30.2025	2	<1	1	<1	1	<1	1	<1	1	<1
6	4.7.2025 14:02	4.7.2025 14:06	3.31.2025	6	7+	2	1	5	3	8	7+	0	0
7	4.17.2025 12:48	4.17.2025 12:52	4.10.2025	4	1	1	1	0	0	8	7+	0	0
8	4.8.2025 20:32	4.8.2025 20:36	3.31.2025	4	3	4	1	2	1	2	4	0	0
9	4.24.2025 0:15	4.24.2025 0:21	4.10.2025	0		0	0	0	0	1	7+	0	0
10	4.7.2025 11:22	4.7.2025 11:25	3.30.2025	0		0	0	0	0	5	7*	0	0
11	4.17.2025 10:41	4.17.2025 13:51	4.11.2025	2	<1	1	0	0	0	5	7	0	0

Subject ID	Irritation	Irritation: duration	Swelling	Swelling: duration	Allergic reaction	Allergic reaction: Duration	Spot bleeding at injection site	Spot bleeding at injection site: duration (days)	Dizzyness or nausia during treatment	Dizzyness or nausia during treatment: duration	Pain during procedure	Other symptoms
1	0	0	1	1	0	0	0	0	0	0	1	0
3	0	0	1	<1	0	0	0	0	0	0	8	0
4	0	0	0	0	0	0	0	0	0	0	4	0
5	2	<1	1	<1	0	0	0	0	2	<1	8	head ache <1
6	1	0	5	3	0	0	1	1	0	0	7	0
7	0	0	3	2	0	0	2	<1	0	0	7	0
8	0	0	5	1	0	0	6	<1	0	0	7	0
9	0	0	0		0	0	1	5*	0	0	3	0
10	0	0	1	<1	0	0	0	0	0	0	8	0
11	0	0	1	0	0	0	0	0	0	0	6	0

Duration in days
* only on one eye

13 REFERENCES

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14 SIGNATURE PAGE

15 APPENDIX

Appendix 1. Principal Investigator's Ethical Assessment

Appendix 2. Informed Consent Form

Appendix 3. Package leaflet

Appendix 4. Post market follow-up Study Plan

Appendix 5a. Participant Self-Asessment

Appendix 5b. Satisfaction Questionnaire: Subject's Global Evaluation.

Appendix 6. Principal Investigator's Report of Adverse Events and Adverse Reactions

Appendix 7a. Traceability form

Appendix 7b. Privacy policy

Appendix 8. Principal Investigator Curriculum Vitae

Appendix 9. Investigator's Brochure