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CLINICAL INVESTIGATIONAL PLAN

LUB0116MD

Final Version 2.0 – 13 December 2016

A 2 week, randomized, double-masked, controlled, parallel group study to evaluate tolerability, safety, permanence on the ocular surface and efficacy of two concentrations of Lubricin (20 and 50 µg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with ocular discomfort following refractive surgery.

Study Phase: Pre-market

Manufacturer/Sponsor: Dompé farmaceutici s.p.a. Via Santa Lucia, 6 20122 MILANO Italy	**Materiovigilance Contact (Serious Adverse Event (SAE) reporting):** Dompé Drug Safety Dompé farmaceutici s.p.a. - Milano Fax: PPD E-mail: PPD
Medical Monitor/Medical Expert: Flavio Mantelli, MD, PhD Dompé farmaceutici s.p.a. - Milano Phone: PPD e-mail: PPD	**CRO:** PPD PPD

CONFIDENTIAL

This document contains strictly confidential information and cannot be disclosed or used, unless authorized in writing by Dompé farmaceutici s.p.a.

This study will be conducted in compliance with the protocol, attachments VIII and X of legislation decree 24 February 1997, n.46 and s.m.i., Declaration of Helsinki, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization (ICH) guidelines on GCP (ICH E6), ISO14155-2012 and applicable local regulatory requirements.

CLINICAL INVESTIGATION PLAN HISTORY

CIP No:	Version No:	Date:
LUB0116MD	Final 1.0	CCI

Amendment No:	Version No.:	Date:
|0|1|	|Final 2.0|	|1|3| - |1|2| - |1|6|
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DOMPE' APPROVAL OF THE CLINICAL INVESTIGATION PLAN (CIP)

Approved and Signed by **Date**

Flavio Mantelli, MD, PhD PPD PPD

Dompé farmaceutici s.p.a.

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Dompé farmaceutici s.p.a.

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Dompé farmaceutici s.p.a.

PPD

CO-ORDINATING INVESTIGATOR'S APPROVAL OF THE CIP

I have read and agree to the protocol LUB0116MD, entitled "**A 2 week, randomized, double-masked, controlled, parallel group study to evaluate tolerability, safety, permanence on the ocular surface and efficacy of two concentrations of Lubricin (20 and 50 µg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with ocular discomfort following refractive surgery.**"

I am aware of my responsibilities under the attachments VIII and X of legislation decree 24 February 1997, n.46 and s.m.i., Declaration of Helsinki, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization (ICH) guidelines on GCP (ICH E6), ISO14155-2012 and applicable local regulatory requirements.

I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

I agree not to administer or supply the study ID/Control ID to subjects other than those included in the study.

I understand that, should the decision be taken by the Sponsor to terminate prematurely or suspend the study at any time for whatever reason, such decision will be communicated to me in writing. Likewise, should I decide to withdraw from execution of the study, I will communicate immediately such decision in writing to the Sponsor/CRO

Clinical Site Name: Università La Sapienza- Policlinico Umberto I
Dipartimento "Organi di Senso"
Viale del Policlinico 155
00161 Rome (RM) - Italy
PPD

Site Number: 01

Site Co-ordinating Investigator: PPD

Signature: PPD

Date: PPD

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TERMS AND ABBREVIATIONS

AE = Adverse Event
ADE = Adverse Device Event
ANOVA = Analysis of variance
BCDVA = Best Corrected Distance Visual Acuity
CPL = Clinical Project Leader
CDISC = Clinical Data Interchange Standards Consortium
CI = Clinical Investigation
CIMF = Clinical Investigation Master File
CIP = Clinical Investigation Plan
CIR = Clinical Investigation Report
CRF = Case Report Forms
CRO = Contract Research Organization
DD = Device Deficiencies
DEWS = Dry Eye WorkShop
DMC = Data Monitoring Committee
EC= Ethics Committee
ETDRS = Early Treatment Diabetic Retinopathy Study
FAS = Full Analysis Set
GCP = Good Clinical Practice
GLP = Good Laboratory Practice
HA = sodium hyaluronate
IB = Investigation Brochure
ICF = Informed Consent Form
ICH = International Conference on Harmonization
ID = Investigational Device
IF = Investigator File
IOP = Intraocular Pressure
IEC = Independent Ethics Committee
IS = Investigational Site
IV = Intravenous
MedDRA = Medical Dictionary of Regulatory Activities
MD = Medical Device
ml = milliliters
mmHg = millimeters of Mercury
µg = Micrograms
NA = Not Applicable
NGF = Nerve Growth Factor
NK = Neurotrophic Keratitis
PI = Principal Investigator(s)
PT = Preferred Term
PTAE = Pre-Treatment Adverse Event
PR = Pulse Rate
TID = Three times per day
RA = Regulatory Authorities
SAE = Serious Adverse Events
SADE = Serious Device Events

SANDE = Symptom Assessment iN Dry Eye
SAP = Statistical Analysis Plan
SLE = Slit Lamp Examination
s.m.i. = following change and /or additions
SOC = System Organ Class
SOP = Standard Operating Procedure
SDTM = Study Data Tabulation Model
ST = Schirmer's test
TEAE = Treatment-Emergent Adverse Event
TF = Technical File
TFBUT = Tear Film Break Up Time
VA = Visual Acuity
VAS = Visual Analogical Scale
WHODDE = World Health Organization Drug Dictionary Enhanced

1. STUDY SUMMARY

1.1 OVERALL STUDY SYNOPSIS

CLINICAL STUDY SYNOPSIS:
Study Number: LUB0116MD
Title of Study: A 2 week, randomized, double-masked, controlled, parallel group 1 week follow-up study to evaluate tolerability, safety, permanence on the ocular surface and efficacy of two concentrations of Lubricin (20 and 50 µg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with ocular discomfort following refractive surgery.
Study Sites: 1 site in Italy
Phase of Development: pre-market
Study Objectives: The primary objective of the study is to assess the tolerability and safety of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks in patients with ocular discomfort following refractive surgery. Secondary objectives of the study are aimed at studying efficacy, including ocular surface permanence, of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks versus sodium hyaluronate (HA) 0.18% eye drops solution in patients with ocular discomfort following refractive surgery.
Study Design and Methodology: A 2 week randomized (1:1:1), controlled, double-masked, parallel group, pre-market study. Patients with ocular discomfort following refractive surgery procedure (within 6 months from enrollment into the investigation) will be evaluated at baseline (Day 1), at Week 2 (day 15±2 days) and at Week 3 follow-up visit (day 22±2, or early exit).
Number of Patients: Thirty (30) patients (10 per arm) randomized 1:1:1 to Lubricin 20 µg/ml eye drops solution or Lubricin 50 µg/ml eye drops solution or sodium hyaluronate (HA) 0.18% eye drops solution will be enrolled. As the primary objective of this study is to evaluate the tolerability and safety of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks in patients with ocular discomfort following ocular refractive surgery, sample size was calculated based on clinical feasibility and no formal sample size calculation has been performed.

Diagnosis and Criteria for Inclusion/Exclusion:

Adult patients with ocular discomfort (defined as SANDE score ≥ 30 at baseline) following ocular refractive surgery (within 6 months from enrollment).

Inclusion Criteria:

1. Patients 18 years of age or older.
2. Patients undergone ocular refractive surgery within 6 months from Day 1 Visit.
3. Patients with ocular discomfort defined as SANDE score ≥ 30 at baseline.
4. Average VAS score (dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ≥ 25 mm;
5. Best corrected distance visual acuity (BCDVA) score ≥ 0.1 decimal units in both eyes at the time of study enrolment.
6. Only patients who satisfy all Informed Consent requirements may be included in the study. The patient and/or his/her legal representative must read, sign and date the Informed Consent document before any study-related procedures are performed. The Informed Consent form signed by patients and/or legal representative must have been approved by the IEC for the current study.

Exclusion Criteria:

1. Patients with a severe Dry Eye condition (severity level 4 according to the Report of the International Dry Eye Workshop -DEWS, 2007)
2. Best corrected distance visual acuity (BCDVA) score of < 0.1 decimal units in either eye at the time of study enrolment
3. Evidence of an active ocular infection in either eye
4. History or presence of ocular surface disorders other than ocular discomfort in either eye
5. Use of any ocular topical medication other than the study medications for the treatment of ocular diseases including artificial tears during the study period
6. Use of topical cyclosporine, topical corticosteroids or any other topical medication for the treatment of dry eye in either eye within 30 days of study enrolment
7. History of any ocular surgery (excluding laser or refractive surgical procedures) in either eye within 30 days before study enrolment. Ocular surgery will not be allowed during the study treatment period and elective ocular surgery procedures should not be planned during the duration of the follow-up period
8. Known hypersensitivity to one of the components of the study or procedural medications
9. Participation in another clinical study at the same time as the present study or within 90 days of screening/baseline visit
10. History of drug, medication or alcohol abuse or addiction.
11. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:
    - **a.** are currently pregnant or,
    - **b.** have a positive result on the urine pregnancy test at the Screening/Baseline Visit or,
    - **c.** intend to become pregnant during the study treatment period or,
    - **d.** are breast-feeding or,
    - **e.** not willing to use highly effective birth control measures, such as: Hormonal contraceptives – oral, implanted, transdermal, or injected and/or mechanical barrier methods – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD during the entire course of and 30 days after the study treatment periods.

TEST Investigational Medical Device, Dosage and Mode of Administration:

Treatment period:

Sterile isotonic aqueous solution for ocular administration containing Lubricin 20 µg/ml eye drops solution or Lubricin 50 µg/ml. In all patients, both eyes will be treated, unless only one eye meets the eligibility criteria. If just one eye is treated, that will be the "Study/Primary eye". If both eyes are

treated, the worst one (highest VAS average score) should be chosen as "Study/Primary eye"; in the event average VAS score was equal in both eyes, right eye will be chosen as "Study/Primary eye".The investigator will administer the morning study dose on Day 1 then patients will self-administer the drops at home/site, as applicable.
Eligible patients will self-administer 1 drop of Lubricin 20 µg/ml or Lubricin 50µg/ml in the eye(s) which underwent refractive surgery three times a day (TID) approximately every 6h for 2 weeks.

No other ocular topical treatments allowed, including artificial tears/lubricants.

Follow-up period:

Follow-up period of 7 days, any ocular topical treatments allowed, including other artificial tears/lubricants as prescribed by the treating physician.

Duration of Investigational Device Treatment:

Treatment duration 14 days (2 weeks) ±2 days (maximum treatment duration 16 days).

Follow-up period of 7 days, any ocular topical treatments allowed, including other artificial tears/lubricants as prescribed by the treating physician.

REFERENCE Investigational Medical Device, Dosage and Mode of Administration

Treatment period:

Sodium hyaluronate (HA) 0.18% eye drops (Vismed®) multidose. In all patients, both eyes will be treated, unless only one eye meets the eligibility criteria. If just one eye is treated, that will be the "Study/Primary eye". If both eyes are treated, the worst one (highest VAS average score at enrolment at enrollment) should be chosen as "Study/Primary eye"; in the event average VAS score was equal in both eyes, right eye will be chosen as "Study/Primary eye". The investigator will administer the morning study dose on Day 1 then patients will self-administer the drops at home/Site, as applicable.

Eligible patients will self-administer 1 drop of Sodium hyaluronate (HA) 0.18% in the eye(s) which underwent refractive surgery three times a day (TID) approximately every 6h for 2 weeks.

No other ocular topical treatments allowed, including artificial tears/lubricants.

Follow-up period:

Follow-up period of 7 days, any ocular topical treatments allowed, including other artificial tears/lubricants as prescribed by the treating physician.

Study procedures:

Visit 1 – Day 1 – Baseline – Pre-Dose

- Explanation to the patient of study aims, procedures and possible risks
- Informed consent signature
- Screening number (as S01, S02, etc.)
- Demographic data
- Medical and surgical history/current medical conditions
- Prior/concomitant medications
- External Ocular Examination
- AE monitoring
- Ocular examination in both eyes:

1. Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)
2. Assessment by SANDE questionnaire
3. Assessment of best corrected distance visual acuity
4. Slit lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid Erythema, Eyelid – Oedema, Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal transparency, Corneal neovascularization
5. Assessment of central corneal sensitivity by Cochet-Bonnet aesthesiometry
6. Tear collection for Lubricin dosing (both eyes) using tear wash technique with 40 µL of sterile

saline solution

At least 10 minutes break

7. Tear Film Break Up Time (TFBUT)
8. Corneal fluorescein staining (Oxford score)

At least 15 minutes break

9. Schirmer's test (ST) I (without anaesthesia)
10. Intraocular pressure (IOP)

- Pregnancy test for female patients.
- Inclusion/exclusion criteria evaluation
- Patient eligibility confirmation and randomization number assignment

Visit 1 – Day 1 - Dose

- At the completion of the pre-dose assessments, the investigator will administer the study product (morning dose) into the eligible eye(s)

Visit 1 – Day 1 – 15 minutes post-dose

- Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)
- Tear collection for Lubricin dosing in the right eye

Visit 1 – Day 1 – 30 minutes post-dose

- Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)
- Tear collection for Lubricin dosing in the left eye
- The Investigator will deliver to the patients the investigational medical device for the treatment period (15±2 days)

At home: From Day 1 to Week 2 Visit:

- Self-administration at home of the Investigational medical device TID approximately every 6h into the eligible eye(s)

Visit 2 – Week 2 ± 2 Days (prior the morning dose)

- Review of current medical conditions (ocular and systemic: including External Ocular Examination)
- AE and concomitant medications
- Ocular examination in both eyes, consisting of the assessments detailed for the baseline visit (points 1-10), in the same order and with the same intervals
- Urine Pregnancy test (only female)

Visit 2 – Week 2 ± 2 Days - Dose

- At the completion of the pre-dose assessments, the investigator will administer the study product (morning dose) into the eligible eye(s)

Visit 2 – Week 2 ± 2 Days – 15 minutes post-dose

- Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)
- Tear collection for Lubricin dosing in the right eye

Visit 2 – Week 2 ± 2 Days – 30 minutes post-dose

- Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia)
- Tear collection for Lubricin dosing in the left eye

Visit 3 – Final Follow-up Visit - 7±2 days after last administration (day 22 ± 2)

- Review of current medical conditions (ocular and systemic: including External Ocular Examination)

- AE and concomitant medications
- Ocular examination in both eyes, consisting of the assessments detailed for the baseline visit (points 1-10), in the same order and with the same intervals
- Patient discharge

Criteria for Evaluation:

Evaluation of the clinical tolerability, safety and efficacy of treatment with Lubricin eye drops in patients with moderate to severe dry eye, on the basis of the following assessments.

Primary outcomes:

- Tolerability using a Visual analogue scale (VAS) for dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia
- Treatment-emergent adverse events (TEAEs), assessed throughout the study

Secondary outcomes

- Ocular surface vital staining with Fluorescein (Oxford scale)
- Schirmer-I test (without anaesthesia);
- Permanence of Lubricin on the Ocular Surface Tear film break-up time (TFBUT);
- Best corrected distance visual acuity (BCVA);
- SANDE questionnaire scores – discomfort improvement entity;
- SANDE questionnaire scores – discomfort improvement speed;
- Signs evaluated by Slit lamp examination (SLE) (blepharitis, eyelid hyoeremia/oedema, lashes, conjunctiva hyperemia)
- Intraocular pressure (IOP)
- Corneal sensitivity by Cochet-Bonnet aesthesiometry

Variables will be compared between groups at each time point.

Statistical Methods:

The data documented in this study will be listed by patient, dose, eye (left and right, if applicable) and evaluation time point.

Appropriate descriptive statistics will be used according to the nature of the variable.

Not available data will be evaluated as “missing values”. The statistical analysis will be performed using SAS® version 9.3 (TS1M1) for Windows® or higher.

A statistical analysis plan (SAP) will be issued before database lock. Final statistical analysis models will be presented in detail in the SAP.

1.2. Study Flow Chart

Evaluation	Visit 1 Day 1 Baseline	Visit 2 Day 15 ± 2	Visit 3 Final Visit follow-up Day 22 ± 2/ETV
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Pregnancy test for females	X	X	
Eligibility/Enrolment	X		
Demography	X		
Medical/Surgical history (ocular &systemic)	X		
Review of current medical conditions (ocular & systemic)		X	X
Prior and concomitant medications (ocular & systemic)	X	X	X
External Ocular Examination	X	X	X
VAS ocular tolerability assessment	X**	X**	X
SANDE questionnaire	X	X	X
Best corrected distance visual acuity	X	X	X
Slit lamp examination (SLE)	X	X	X
Central corneal sensitivity by Cochet-Bonnet aesthesiometry	X	X	X
Tear collection for Lubricin dosing	X***	X***	X****
Tear Film Break Up Time (TFBUT)	X	X	X
Corneal fluorescein staining (Oxford score)	X	X	X
Schirmer's test (ST) I without anesthesia	X	X	X
Intraocular pressure (IOP)	X	X	X
Self-administration at home	X*	X*	
First Administration at study site	X	X	
Compound Dispensing	X		
Adverse events	X	X	X

*Self-administration at home during the study period
** pre-dose, 15 minutes post–dose, 30 minutes post–dose
*** pre-dose – in both eyes, 15 minutes post–dose in the right eye, 30 minutes post–dose in the left eye
**** both eyes

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1. Investigational Devices

2.1.1. Lubricin

Lubricin, also called Proteoglycan 4 (PRG4), is a mucin-like glycoprotein originally discovered in synovial fluid, as a secreted product of cells that line the joint tissues, which is present at the surface of articular cartilage **(1,2)**.

In vitro studies have shown that lubricin in saline buffer acts as a lubricant between various surfaces, as well as in synovial fluid, providing evidence that lubricin is a principal lubricating protein in joints. Besides the lubricating property, lubricin has been shown to exert anti-adhesive action, strain energy dissipation, anti-bacterial and a protective effect on underlying cells **(3-6)**.

The lubricating, anti-adhesive, protective and anti-bacterial properties of Lubricin raised interest on its roles at the ocular surface, in normal and pathologic conditions such as dry eye **(see Lubricin Investigator's Brochure, CCI) (7).**

The expression of Lubricin in animal models and in human ocular surface and meibonian gland was first described by the team of D. Sullivan **(8,9)**.

As previously mentioned, lubricin has recently been discovered at the ocular surface, where its boundary lubricating properties may play a critical protective role as they do at the articular cartilage surface. Specifically, human corneal and conjunctival epithelial cells have been shown to express PRG4 mRNA, and PRG4 protein has been observed in human meibomian gland secretions via proteomic analysis **(8,9)** .

The discovery of this molecule responsible for boundary lubrication at the ocular surface supports the hypothesis of Ehlers, who already in 1965 theorized that boundary lubrication must take place between the eyelid wiper region and the cornea **(10)**.While a normal tear film containing mucins in the acqueous layer surely contributes to the normal hydrodynamic lubrication of the ocular surface, in pathologies such as dry eye disease where there is an altered tear film, boundary lubrication involving lubricin may be a primary method of friction reduction. Boundary lubrication may also be dominant at the cornea–contact lens interface where there is a relative lack of aqueous tear **(5, 6, 8-11)**.

Therefore, the absence of lubricin may also promote ocular surface damage. Supporting this hypothesis, a higher fluorescein staining of the ocular surface has been demonstrated in animal models lacking lubricin. Since increased fluorescein staining is commonly associated with dry eye disease, a reduction in lubricin content may likely increase shear stress at the ocular surface, which, in turn may lead to inflammation and accumulation of inflammatory mediators in the tear film, triggering the typical symptoms of discomfort observed in dry eye patients. Supporting these hypothesis, the team of Sullivan and Schmidt **(8)** has recently described that the use of exogenous lubricin at the ocular surface provides a dramatic friction-lowering effect at the cornea-eyelid interface. Furthermore, given the known ability of lubricin to reduce friction on articular cartilage in a synergistic manner with hyaluronic acid, the current mainstay in dry eye symptoms' relief, and the broad commercial availability of ophthalmic formulations containing hyaluronic acid intended to provide lubrication, lubricin may also function synergistically with hyaluronic acid to reduce friction at the ocular surface.

Based on the available preclinical studies lubricin may be an important barrier to the development of corneal and conjunctival epitheliopathies in dry eyes and its use as a novel lubricating and anti-adhesive eye drop is under investigation in this clinical investigation.

2.1.2 Preclinical Toxicology Profile

The following Biocompatibility studies have been performed so far:
LUBRICIN EYE DROPS has been tested for cytotoxicity by direct contact on BalbC 3T3 monolayer cells according to ISO 10993-5:2009 and resulted not cytotoxic.
Guinea-pig maximixation test was performed according to ISO 10993-10:2010 in order to evaluate the possible sensitization effects of LUBRICIN EYE DROPS, according to these results the ID was considered not sensitizing
Ocular irritation test in rabbit was also performed according to ISO 10993-10:2010. Following ocular examination with ophthalmoscope after 1, 24, 48 and 72 hours, the test item resulted not irritant. Ocular examination included the assessment of cornea, iris and conjunctiva.
The compatibility of LUBRICIN EYE DROPS with soft contact lens was tested according to ISO 11981:2009. The results obtained proved that the ID exerts physical compatibility to soft contact lens according ISO 11981:2009

Overall the preclinical toxicity data obtained in vitro and in vivo tests indicate a low risk of adverse side effects in humans under the circumstanced of the intended clinical plan.

2.1.3 Hyaluronic acid (HA)

Hyaluronic acid is a linear polysaccharide found in all living organisms and is a universal component of the extracellular matrix of body tissues where it is distributed ubiquitously in all tissues **(12)**. It is a molecule with negative charges and can form in the presence of H_2O a highly viscous solution. HA is a glycosaminoglycan present in the human vitreous and is able to bind a large number of water molecules and, therefore, creating a twisting ribbon structure which in physiological structure may occupy a very large domain, this also allows an very high swelling factor, up to 10.000 **(13)**. The chemical structure of HA is formed by units of D -glucuronic acid and N-acetylglucosamine and remains constant throughout the phylogenetic chain. This identity is largely used clinically because if injected or administered to human it eliminates theoretically all the possible risks of allergic reactions, which instead are potentially present in the use of non-human natural products, such as non- human collagen **(14)**. From the industrial point of view HA can be obtained by extraction from animal tissue, usually cockscomb, for bacterial fermentation and recombinant biotechnology. Natural HA has a relatively short half-life (1-2 days) in all connective tissues except the vitreous body of the eye **(15)**.

2.2. Manufacturers

Lubricin Eye Drops manufactured by Dompé farmaceutici s.p.a. via Campo di Pile SNC, 67100 L'Aquila. Produced (bulk and masked packaging) by PPD **(See Annex A – Lubricin eye drops -Instruction for the subjects).**

Sodium hayluronate (HA) 0.18%: (Vismed®) multidose manufactured by PPD **will supply the HA for the Clinical Investigation in masked packing. (See Annex B – Vismed® 0.18% - Instruction for the subjects).**

2.3. Investigational Devices (ID)

2.3.1 Treatment Period (Investigational Medical Devices)

TEST: Lubricin 20 µg/ml or Lubricin 50 µg/ml : is aseptically filled multidose container, suitable for products for ocular instillation. Lubricin 20 µg/ml or Lubricin 50 µg/ml will be supplied for the Clinical Investigation in masked packing.

For additional details on *Lubricin* please refer to Annex A.

A single multidose container will supply treatment for both weeks of treatment. Instructions for use will be provided to the subject during visit 1.

CONTROL: Sodium hyaluronate (HA) 0.18% eye drops (Vismed®) multidose, commercially available in Italy will be supplied for the Clinical Investigation in masked packing.

For additional details on Vismed® please refer to Annex B.

A single multidose container will supply treatment for both weeks of treatment. Instructions for use will be provided to the subject during visit 2.

2.3.2 Follow-Up Period

During the follow-up period patients may receive any ocular topical treatments allowed, including other artificial tears/lubricants as prescribed by the treating physician.

2.4. ID Identification and Traceability

Patients will be randomized 1:11 to LUBRICIN EYE DROPS solution (20 µg/ml or 50µg/ml – Drop: 50µl – 1 µg/drop or 2.5 µg/drop respectively) or sodium hyaluronate (HA) 0.18% (Drop: 50µl - 90 µg/drop) eye drops solution. The randomization groups will be generated with a computer procedure.

The randomization system will be prepared and implemented by the CRO.

Individual treatment codes will be provided in a closed envelope to the Investigators and to Dompé Materiovigilance Department for safety procedures.

Each eligible subject will be assigned to a randomization number according to the sequence of study entry, from 01 to 30. The Investigational Site (IS) will be delivered in adequate quantity to provide treatment for 30 subjects**.**

All containers will be also identified by a codified batch to maintain the masked condition and ensure traceability.

2.5. Instructions for Use and Intended Purpose of IDs

The instruction for use are reported in Annex A (Lubricin eye drops) and B (Vismed®).
The intended purpose of Lubricin eye drop is the use as a novel lubricating and anti-adhesive agent in patients suffering from ocular discomfort following refractive surgery.

2.5.1 Packaging and Labelling

The ID labelling will report all the information requested according to the Annex 13 of the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4) as follows:

a. Name, address and telephone number of the sponsor, contract research organization or investigator (the main contact for information on the product, clinical study and emergency un-masked)
b. ID dosage form, route of administration, quantity of dosage units, and in the case of open studies, the name/identifier and strength/potency
c. The batch and/or code number to identify the contents and packaging operation
d. CIP reference code allowing identification of the study, site, investigator and sponsor if not given elsewhere
e. The KIT identification number and where relevant, the visit number
f. The name of the investigator (if not included in (a) or (d))
g. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)
h. “For clinical study use only” or similar wording
i. The storage conditions
j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
k. “Keep out of reach of children”

Labels will be in Italian.

2.6. Population and Indications

EYE DROPS are intended to be used in subjects suffering from ocular discomfort following refractive surgery in order to contribute to normal hydrodynamic lubrication of the ocular surface by boundary lubrication.

Thirty (30) subjects (1:1:1 randomization experimental vs experimental vs control) will be randomized in the study.

To participate in the study, male and female subjects must be 18 or older with ocular discomfort (defined as SANDE score ≥ 30 at baseline) following ocular refractive surgery (within 6 months from enrollment)

Subjects must fulfil all of the study inclusion and none of the exclusion criteria.

Recruitment will proceed until the planned number of subjects is randomized.

2.7. IDs Description

As other proteins for ocular use (e.g. sodium hyaluronate acid), recombinant human Lubricin (rhLubricin) is produced from fermentative synthesis.

The protein is produced in mammalian CHO (Chinese hamster ovary) cells by extracellular excretion into the media. CHO cell lines have frequently been used as substrates for production with no reported safety problems related to viral contamination of the products. For these cell lines, endogenous particles have been extensively characterized and clearance has been demonstrated. However, Lubricin Starting Material undergoes viral inactivation and viral removal.

CCI [redacted], is expressed by transfected Chinese Hamster Ovary cells PPD .
Validations and specifications of production of Lubricin Starting material and the final product are reported in IB § 2.4 Summary of Manufacturing Process and Validation.

Sodium haluronate 0.18%: (Vismed®) multidose, Manufacturer TRB CHEMEDICA AG), commercially available in Italy. The instruction for use is reported in Annex B.

2.8. Training and Experience on ID use

The Investigator/s will ensure that all staff who may participate to the study is adequately informed on procedure reported by the CIP, the treatments provided in this study, their functions and tasks in the study. The investigator will keep a list of the staff, duly qualified, who has been delegated into a significant part of duties related to the study.

Any particular training for the use of the eye drops is not required considering that it is a very common route of administration.

2.9. Methods and Medical Procedures in the Use of ID

The methods and the medical procedures for a correct use of the Test ID/Control ID are reported in detail in the "Instruction for Use" (Annexes A and B).

3. STUDY DESIGN JUSTIFICATION

Laser refractive surgery for the correction of refractive errors has become an affordable and safe procedure. However, a large number of patients complain of ocular surface symptoms after refractive surgery. In fact, both photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) can induce or exacerbate dry eye, that manifests as an increase in degree and frequency of symptoms, corneal findings, such as superficial punctate keratopathy, and abnormal results of dry eye tests, such as the Schirmer test and tear break-up time. The cause mainly involves decreased corneal sensation, resulting in decreased feedback to the lacrimal gland and reduced tear production. Other causes may include increased evaporation, inflammation, or toxicity of medications. Dry eye symptoms are usually transient, lasting only a few weeks, but in a significant percentage of patients these symptoms can last up to 1 year. **(17)**.

In addition, refractive surgery procedures have been described to exert a neurotrophic damage to the cornea, along with other changes in corneal shape, that affect tear dynamics causing ocular surface alterations. As a consequence, symptoms of dryness may occur in more than 50% of patients after LASIK, with other complications such as fluctuating vision, decreased best corrected visual acuity, and severe discomfort occurring in approximately 10% of patients **(18)**.

As a consequence of the widespread use of refractive surgery, a safe and non-toxic treatment that can improve ocular surface symptoms after the procedures is highly sought after by patients and clinicians.

Lubricin, also called Proteoglycan 4 (PRG4), is a mucin-like glycoprotein originally discovered in synovial fluid, as a secreted product of cells that line the joint tissues, which is present at the surface of articular cartilage.

In vitro studies have shown that lubricin in saline buffer acts as a lubricant between various surfaces, as well as in synovial fluid, providing evidence that lubricin is a principal lubricating protein in joints. Besides the lubricating property, lubricin has been shown to exert anti-adhesive action, strain energy dissipation, and a protective effect on underlying cells.

Lubricin has been investigated on its roles at the ocular surface, in normal and pathologic conditions such as dry eye. In fact, Lubricin is a natural human protein with most potent lubricant and anti-adhesive properties present on the ocular surface and on meibonian gland. The presence of this protein at the ocular surface was first described by the team of Sullivan D. **(14,16).**

Based on the available preclinical and clinical investigations Lubricin may be an important barrier to the development of corneal and conjunctival epitheliopathies as a consequence of refractive surgery procedures.

Its use as a novel lubricating and anti-adhesive eye drop is under investigation in this clinical investigation. During the previous clinical investigations conducted it has been demonstrated that a Lubricin 150 µg/ml eye drop formulation is non-inferior to ocular surface lubricant sodium hyaluronate 0.13% and sodium hyaluronate 0.18%.

The objective of this study is to evaluate tolerability, safety, permanence on the ocular surface and efficacy of two concentrations of Lubricin (20 and 50 µg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with ocular discomfort following refractive surgery.

3.1. Relevant Pre-Clinical Tests

The expression of Lubricin in human corneal, conjunctival epithelial cells, along with corneoscleral rims, conjuntival tissues, and conjunctival impression cytology samples in vitro was already demonstrated **(8)**. .Expression of Lubricin was also observed in human meibomian gland epithelial cells and in other human tissues (uterine, cervical, bladder prostatic samples as well as in articular cartilage and synovial membranes). The in vitro test on human cornea-eyelid interface showed an effective friction-lowering boundary lubricant activity for Lubricin which resulted in statistical significant ($P< 0.001$-0.05) lower static friction as compared to Aquify (eye drops containing 0.1% Hyaluronic acid; CIBA Vision) and saline at all velocities.
Similar trends were observed from kinetic friction experiments, where the highest values were observed in saline which were not statistically different from AQuify at all velocities. Lubricin showed lower values as compared to saline at all velocities and only at the lower velocity as compared to AQuify **(8).**
LUBRICIN EYE DROPS have been tested for cytotoxicity by direct contact on BalbC 3T3 monolayer cells according to ISO 10993-5:2009 and resulted not cytotoxic
Guinea-pig maximization test was performed according to ISO 10993-10:2010 in order to evaluate the possible sensitization effects of LUBRICIN EYE DROPS, according to these results the ID was considered not sensitizing.
The compatibility of LUBRICIN EYE DROPS with soft contact lens was tested according to ISO 11981:2009. The results obtained proved that the ID exerts physical compatibility to soft contact lens according ISO 11981:2009.

Other relevant preclinical results are reported in IB §3.1 (Preclinical Testing).

3.2. Clinical Data

3.2.1 LUB0114MD: A MULTICENTER, RANDOMIZED, DOUBLE-MASKED, CONTROLLED, NON-INFERIORITY STUDY TO EVALUATE TOLERABILITY, SAFETY AND EFFICACY OF LUBRICIN EYE DROPS VERSUS SODIUM HYALURONATE EYE DROPS (OCUYAL®) ADMINISTERED FOUR TIMES A DAY FOR 4 WEEKS AND 1 WEEK FOLLOW-UP IN SUBJECTS WITH MODERATE DRY.

The study, which enrolled 56 subjects, was a multicentre, randomized (1:1), double-masked, controlled, non-inferiority study to evaluate the tolerability, safety and efficacy of Lubricin eye drops (monodose; 150µg/mL) versus with a widely used commercial 0.13% sodium hyaluronate eye drop formulation administered 4 times a day for 4 weeks in subjects with moderate dry eye disease.
The primary objective of this study was to demonstrate that lubricin 150 µg/mL is non-inferior to a widely used commercial 0.13% sodium hyaluronate eye drop formulation in improving signs and symptoms in patients with moderate dry eye.
Since the lubricin effect was expected to be similar to that of hyaluronic acid, it was hypothesised that the largest clinically acceptable effect to declare non-inferiority between treatments was a change in SANDE questionnaire results (Symptom Assessment iN Dry Eye) overall score (primary parameter) of 12 mm, with an estimated standard deviation (SD) of 13 (about 70% of mean at 28 days post-treatment).
Results obtained from this clinical investigation allow claiming the efficacy, the safety and the tolerability of use of the test IMD. The investigation results demonstrated the non inferiority of lubricin 150 µg/mL eye drops versus the comparator sodium hyaluronate 0.13% eye drops thus confirming the use intended for lubricin as ocular surface lubricant. No limitation in the use of lubricin 150 µg/mL eye drops, when used according to the recommendations provided, either as IMD in future clinical investigations or as marketed medical device, is envisaged as compared to sodium hyaluronate 0.13% eye drops. On the basis of the results and the observations done during the clinical investigation, the benefit/risk ratio observed for the test IMD did not differ from that of the comparator.

3.2.2 LUB0115MD: A 2 WEEK, RANDOMIZED, DOUBLE-MASKED, CONTROLLED, PARALLEL GROUP AND 1 WEEK FOLLOW-UP STUDY TO EVALUATE TOLERABILITY, SAFETY AND EFFICACY OF LUBRICIN (150 µG/ML) EYE DROPS VERSUS SODIUM HYALURONATE (HA) 0.18% EYE DROPS (VISMED®) IN PATIENTS WITH MODERATE DRY EYE (DE).

The study, which enrolled 40 subjects, was a 2-week, monocentric, randomized (1:1), double-masked, controlled, study to evaluate tolerability, safety and efficacy of lubricin 150 µg/mL eye drops in comparison with a widely used commercial 0.18% sodium hyaluronate eye drop formulation in patients with moderate dry eye.

Eligible patients self-administered 1 drop of Lubricin 150 µg/ml in both eyes two times a day (BID) every 8h±1h for 1 week and then patients self-administered 1 drop of Lubricin 150 µg/ml in both eyes from two to six times a day as needed (PRN) during the second week of the study.

Results obtained from this clinical investigation allow claiming the efficacy, the safety and the tolerability of use of the test device. The investigation results demonstrated the similarity of lubricin 150 µg/mL eye drops versus the comparator sodium hyaluronate 0.18% eye drops used by patients with dry eye syndrome of moderate intensity thus confirming the use intended for

lubricin as ocular surface lubricant. No limitation in the use of lubricin 150 µg/mL eye drops, when used according to the recommendations provided, either as Investigational Medical Device (IMD) in future clinical investigations or as marketed medical device is envisaged as compared to sodium hyaluronate 0.18% eye drops.

RISK/BENEFITS

4.1. Anticipated Clinical Benefits

LUBRICIN EYE DROPS are intended to be used in subjects suffering from ocular discomfort following refractive surgery in order to contribute to normal hydrodynamic lubrication of the ocular surface by boundary lubrication.
Therefore the primary objective of this study is to evaluate the tolerability and safety of an eye drop treatment containing Lubricin 20µg/ml or 50µg/ml as compared with a standard sodium hyaluronate (HA) 0.18% eye drop solution in subjects suffering from ocular discomfort following refractive surgery.

4.2. Anticipated Adverse Device Effects

Based on preclinical studies (ISO 10993) there is no evidence of adverse events related to the use of the Lubricin eye drops.
Local or systemic adverse device effects after the use of Lubricin or sodium hyaluronate eye drop solutions are not described. However, it could be possible to observe local irritation and/or local hypersensitivity reaction to a component of the device.
Besides, immediately after ocular instillation a transient blurred vision could be experienced.

4.3. Residual Risks from Risk Analysis Report

The risk analysis according to ISO 14971 has been carried out by a team of experts and the results seem to be congruent, in particular 2 possible events located in the intolerable risk area and 6 possible events located in the Alarp 1 zone (defined between 6 and 11) have been identified and adequately commented and managed. For each risk Dompé has identified actions to reduce or eliminate the probability that risk is manifested. At the end of the analysis and with the actions involved, each risk is considered inside the area of risk broadly acceptable.

4.4. Risks Associated with the Participation in the CI

The subjects randomized in the CLINICAL INVESTIGATION (CI) are suffering from ocular discomfort following refractive surgery and no other associated ocular conditions. All procedures performed during the CI are not invasive and are not associated with risks for the patients. During Schirmer test the patient may experience minimal conjunctival discomfort due to the contact with the strip. However, these tests are currently performed during routine ocular examination in all the dry eye patients, with no concerns. The use of topical fluorescein, which is also routinely done in dry eye patients' visits, may cause transient irritation or allergic reactions, but does not carry any additional risk. Therefore no additional risks are expected apart those typical of eye drops administrations.

4.5. Risks Associated with Concomitant Medical Treatments

No risks are known for the concomitant use of Lubricin or sodium hyaluronate eye drop solutions and other medications.

4.6. Risk Control

The risks associated with the CI are those typical of eye drops instillations and will be minimized by the involvement of highly specialized medical staff who will specifically train the patients on the use of test ID/Control ID. All drug prescriptions and other medical intervention will be performed or approved by medical personnel.

4.7. Risk/Benefit Rationale

The subjects enrolled in this CI are in the need of dry eye symptoms relief.
Based on preclinical studies (ISO 10993), the Risk Assessment and the lubricant characteristics of Lubricin eye drops, it can be expected that benefit/risk for the investigational Medical Device is similar to the one associated to the control.

5. OBJECTIVES OF THE CLINICAL INVESTIGATION

5.1. Primary and Secondary Objectives

The primary objective of the study is to assess the tolerability and safety of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks in patients with ocular discomfort following refractive surgery.

Secondary objectives of the study are aimed at studying efficacy, including ocular surface permanence, of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks versus sodium hyaluronate (HA) 0.18% eye drops solution in patients with ocular discomfort following refractive surgery.

5.2. Claims and Intended Performances

Both IDs under study will improve temporarily lubrication of the ocular surface, reducing the symptoms, and increasing the tear film stability and ocular surface lubrication.
The Lubricin eye drops is expected to stabilize the lacrimal film, keeping the ocular surface protected and can be used with contact lenses.

5.3. Risks and Anticipated Adverse Device Events

Up to now, there are no known anticipated adverse events associated with the use of LUBRICIN EYE DROPS, anyway the occurrence of side effects cannot be excluded.
It must be considered that topical treatment with LUBRICIN EYE DROPS could cause local irritation or allergic reactions. There are no known contraindications to the use of LUBRICIN EYE DROPS.
All examinations and assessments that will be carried out during this study are non-invasive, are commonly used in the management of subjects with dry eye and pose no risk to the subjects. Subjects might feel a slight discomfort during the execution of Schirmer test and a local allergic reaction or irritation from the use of fluorescein may be observed. There are no known contraindications to the use of lubricin or sodium hyaluronate eye drops. No data are available about the embryo and fetal toxicity, therefore the experimental treatment will not be allowed to pregnant women or nursing mothers and women of childbearing potential not using appropriate birth control methods.
Local or systemic adverse device effects after the use of Lubricin or hyaluronic acid eye drop solutions are not described. However, it could be possible to observe local irritation and/or local hypersensitivity reaction to a component of the device.
Besides, immediately after ocular instillation a transient blurred vision could be experienced.

6. STUDY DESIGN

6.1. Clinical Study Design

6.1.1. Description and Justification of Study Design

This is a 2-week randomized (1:1:1), controlled, double-masked, parallel group study, to evaluate tolerability, safety permanence on the ocular surface and efficacy of two concentrations of Lubricin (20 and 50 µg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with ocular discomfort following refractive surgery.
Enrolled subjects will be randomized at inclusion, 1:1:1 ratio to receive Lubricin 20 µg/ml eye drops solution or Lubricin 50 µg/ml eye drops solution or sodium hyaluronate (HA) 0.18% eye drops solution. Upon randomization and until the end of the treatment period, subjects will be required to not use topical ophthalmic medications except of the study treatments.
On the Day 1 Visit (Baseline visit) subjects will be dispensed of the study medication and instructed to self-administer at home three times a day approximately every 6 hours for 2 weeks.
Subjects will be evaluated after 2 weeks of treatment and 1 week after end of treatment.

The subjects will be involved in the study for a maximum of 25 days from screening visit to last follow-up visit.

6.1.2 Primary and Secondary Endpoints

The primary endpoints of the study are:

1. Tolerability using a Visual analogue scale (VAS) for dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia
2. Treatment-emergent adverse events (TEAEs), assessed throughout the study

Secondary outcomes will include:

1. Ocular surface vital staining with Fluorescein (Oxford scale)
2. Schirmer-I test (without anaesthesia);
3. Permanence of Lubricin on the Ocular Surface Tear film break-up time (TBUT);
4. Best corrected distance visual acuity (BCVA);
5. SANDE questionnaire scores – discomfort improvement entity;
6. SANDE questionnaire scores – discomfort improvement speed;
7. Signs evaluated by Slit lamp examination (SLE) (blepharitis, eyelid hyoeremia/oedema, lashes, conjunctiva hyperemia)
8. Intraocular pressure (IOP)
9. Corneal sensitivity by Cochet-Bonnet aesthesiometry

Parameters will be evaluated at each visit as reported on par 1.2 – Study Flow Chart.
The safety of the Test ID/Control ID will be evaluated by reporting and evaluating the eventually occurred AE/ADE and SAE/SADE.

6.1.3. Duration and Timing of the Variable Recording

A written informed consent will be obtained before any study assessment or procedure. Maximum study duration will be 25 days, including all study visits.

Each study subject will undergo to 3 visits.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical site by the 1st enrolled subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical site (or the telephonic follow-up, if applicable) by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Interventional phase**
  - Visit 1 - Day 1
  - Visit 2 - Day 15 ± 2.

- **Follow-up phase**
  - Visit 3 - Final Visit follow-up - (Day 22±2) /ETV (Early Termination Visit) in case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV).

The procedures/assessments details are summarized hereafter.

	Day	Procedures/Assessments
Visit 1 – Day 1 – Baseline – Pre-Dose	*Day 1 pre-dose*	➢ Explanation to the patient of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S01, S02, etc.) ➢ Demographic data ➢ Medical and surgical history/current medical conditions ➢ Prior/concomitant medications ➢ External Ocular Examination ➢ AE monitoring ➢ Ocular examination in both eyes: 1. Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) 2. Assessment by SANDE questionnaire 3. Assessment of best corrected distance visual acuity 4. Slit lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid Erythema, Eyelid – Oedema, Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal transparency, Corneal neovascularization 5. Assessment of central corneal sensitivity by Cochet-Bonnet aesthesiometry 6. Tear collection for Lubricin dosing (both eyes) using tear wash technique with 40 µL of sterile saline solution **At least 10 minutes break** 7. Tear Film Break Up Time (TFBUT) 8. Corneal fluorescein staining (Oxford score) **At least 15 minutes break** 9. Schirmer's test (ST) I (without anaesthesia) 10. Intraocular pressure (IOP) ➢ Pregnancy test for female patients. ➢ Inclusion/exclusion criteria evaluation ➢ Patient eligibility confirmation and randomization number assignment ➢ At the completion of the pre-dose assessments, the investigator will administer the study product (morning dose) into the eligible eye(s)
Baseline - Visit 1	*Day 1 15 minutes post-dose*	The following procedures will be performed: ➢ Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ➢ Tear collection for Lubricin dosing in the right eye

	Day	Procedures/Assessments
Baseline - Visit 1	*Day 1 30 minutes post-dose*	The following procedures will be performed: ➢ Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ➢ Tear collection for Lubricin dosing in the left eye ➢ The Investigator will deliver to the patients the investigational medical device for the treatment period (15±2 days)
At home	*From Day 1 to Week 2± 2 Days Visit*	➢ Self-administration at home of the Investigational medical device TID approximately every 6h into the eligible eye(s)
Visit 2	*Week 2 ± 2 Days (prior the morning dose)*	The following procedures will be performed before receiving the first eye drop treatment of the day: ➢ Review of current medical conditions (ocular and systemic: including External Ocular Examination) ➢ AE and concomitant medications ➢ Ocular examination in both eyes, consisting of the assessments detailed for the baseline visit (points 1-10), in the same order and with the same intervals ➢ Urine Pregnancy test (only female) ➢ At the completion of the pre-dose assessments, the investigator will administer the study product (morning dose) into the eligible eye(s)
Visit 2	*Week 2 ± 2 Days 15 minutes post-dose*	The following procedures will be performed: ➢ Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ➢ Tear collection for Lubricin dosing in the right eye
Visit 2	*Week 2 ± 2 Days 30 minutes post-dose*	The following procedures will be performed: ➢ Assessment of ocular tolerability (Visual analogue scale, VAS: dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) Tear collection for Lubricin dosing in the left eye

	Day	Procedures/Assessments
Visit 3/ETV **Final Follow-Up Visit**	*Days 22±2*	The final visit is defined as the visit performed 7±2 days after last administration (day 21 ± 2). In case of study discontinuation subjects will undergo an early termination visit. The following procedures will be performed: ➢ Review of current medical conditions (ocular and systemic: including External Ocular Examination) ➢ AE and concomitant medications ➢ Ocular examination in both eyes, consisting of the assessments detailed for the baseline visit (points 1-10), in the same order and with the same intervals ➢ Patient discharge

6.1.4. Methods and Equipments for Endpoints Recordings

6.1.4.1. *Ocular evaluations*

Ocular evaluations will be performed on both eyes. The assessments must always be performed according the sequence (1 – 10) detailed in § 6.1.3 The assessment will be performed at visit 1 (day 1), 2 (day 15±2), 3 (day 22±2))/early termination visit.

The ophthalmological assessment will include:

1. **Visual analogue scale (VAS)**: Local ocular tolerability score: A global ocular discomfort score will be determined using a 100 mm VAS
2. **Symptom Assessment in Dry Eye (SANDE):** Subjects with SANDE overall score ≥ 30 mm are eligible for enrolment\randomization. The SANDE questionnaire is a short questionnaire to evaluate both dry eye intensity and frequency by using a 100 mm VAS.
3. **Best corrected distance visual acuity (BCDVA):** Subjects with best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units in both eyes are eligible for enrolment\randomization. Refraction and visual acuity measurements will be performed for all subjects by trained vision examiners only.

   Equipment: Refraction equipment required includes:
   - Retroilluminated Light box and ETDRS 4 meter distance acuity chart set
   - Trial lens frames
   - Trial lens set with plus or minus cylinder lenses
   - Jackson cross-cylinders of 0.25, 0.50, and 1.00 diopters
   - Pinhole occluder
   - Tissues or eye pads and tape
   - A 1 meter rigid measuring stick
4. **Slit lamp examination (SLE):** The slit lamp examination must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.

   The subject will be seated at the slit lamp while being examined. Grading of the eyelids, l lashes, conjunctiva, cornea, lens, iris and anterior chamber will be done.
5. **Central corneal sensitivity by Cochet-Bonnet aesthesiometry:** The Cochet-Bonnet aestheiometer contains a thin, retractable, nylon monofilament that extends up to 6 cm in length. Variable pressure can be applied to the cornea by adjusting the monofilament length. The monofilament length ranges from 6 to 0.5 cm. As the monofilament length is decreased the pressure increases from 11 mm/gm to 200 mm/gm.
   Corneal sensation will be measured in the affected eye(s) in the central area of the cornea using a Cochet Bonnet aesthesiometer before the instillation of any dilating or anesthetic eye drops.
   Start the procedure by testing the corneal sensitivity within the area (center) of the PED or corneal ulcer of the affected eye.

   Steps for using the Cochet Bonnet aesthesiometer:
   1. Extend the filament of the aestheiometer to full length of 6 cm. Slowly advance the monofilament towards the eye until the tip perpendicularly touches the corneal surface. Continue to exert a slight pressure until obtaining an inflection deviation of the filament of about 4% (i.e. the first visible inflection). If a positive reaction to the touch of cornea is illicited proceed to step 3. If a positive reaction is not achieved proceed to step 2. (NOTE:

A positive response is any action indicating corneal sensation whether communicated verbally or physically).

2. Retract the filament incrementally in 0.5 cm and repeat this step until the patient gives a positive reaction indicating that the contact of the monofilament on the cornea has been sensed. (NOTE: The shorter filament lengths indicate decreased corneal sensation).
3. Record the length of the filament in cm at which the patient sensed the contact with the cornea.
4. Repeat steps 1-3 in each of the 4 corneal quadrants (superior nasal, inferior nasal, superior temporal and inferior temporal) outside the area of the PED or corneal ulcer in the affected eye and in each of the 4 corneal quadrants of the non-affected eye.
5. To clean the instrument refer to your national standards for devices that contact the eye and tears or follow the suggested manufacturer's recommendations.

The length of the filament in cm at which the patient corneal sensation was observed for the tested area of the cornea will be entered into the eCRF.

6. **Tear collection for Lubricin dosing:** tear collection will be performed using tear wash technique with 40 µL of sterile saline solution. Dompé farmaceutici s.p.a. will be responsible for samples collection and dosing procedure.
7. **Tear Film Break Up Time (TFBUT):** TFBUT will be measured by determining the time to tear break-up. The TFBUT will be performed after instillation of sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye.
8. **Corneal fluorescein surface staining (Oxford score):** The corneal fluorescein staining will be graded by using the Oxford scheme to assess cornea and conjunctiva epithelium damage. It will be performed after instillation of sodium fluoresce in into the inferior conjunctival cul-de-sac of each eye with the aid of a slit lamp at 10X magnification using cobalt blue illumination.
9. **Schirmer's test (ST) I (without anaesthesia):** Schirmer strips (Manufacturer: Contactcare Ophthalmics &Diagnostics; distributor: Alfa Intes S.r.l., Via Fratelli Bandiera, n.c.c. - 80026 Casoria (NA), Campania ITALIA) will be used.

   This test will be performed to measure aqueous tear secretion prior to the instillation of any dilating or anesthetic eye drops. Both eyes may be tested at the same time.

   This test will be conducted in a dimly lit room.
10. **Intraocular pressure (IOP):** IOP may be performed using either Goldmann applanation tonometry after the instillation of a topical anesthetic.

    IOP should be measured in both eyes after completion of all other slit lamp examinations to avoid potential interference with the other evaluations.

All examinations and assessments that will be carried out during this study are non-invasive , are commonly used in the management of subjects with dry eye and pose no risk to the subjects. Subjects might feel a slight discomfort during the execution of the Schirmer test and a local allergic reaction or irritation from the use of fluorescein may be observed.

6.1.5. Subjects Replacement

Discontinued subjects will not be replaced. Any patient who exits early from the study must undergo all procedures outlined in Visit 3.

6.2. ID AND COMPARATORS

6.2.1. Description and Justification of ID/Comparator Exposure

During the 2 week (15±2 days) double-masked, randomized, controlled treatment period, (hereafter, also referred to as the controlled treatment period) enrolled subjects will be randomized at baseline in a 1:1:1 ratio to the experimental treatment arm (Lubricin 20 µg/ml or Lubricin 50µg/ml, one drop TID for two weeks) or the control arm Vismed® 0.18% (sodium hyaluronate eye drop solution, one drop TID for two weeks).

During the follow-up period at the discretion of the treating physician any ocular topical treatment is allowed, including other artificial tears/lubricants.

Investigational Medical Devices will be administered by ocular route according to 1:1:1 randomization. If the subject forgets to take the study drug, it should be taken as soon as the subject remembers.

The proposed duration of the treatment has been considered as adequate to support local tolerability, safety and efficacy of the product in comparison with the selected control.

6.2.2. Justification of the Choice of Comparator

HA 0.18% eye drops are one of the most used ocular lubricant for moderate dry eye patients.

The presentation of the control has been selected to ensure complete masking of the CI.

6.2.3. Number and Justification of the IDs Used

The tolerability, safety and efficacy profile of LUBRICIN EYE DROPS will be compared with HA 0.18% (Vismed® multidose) one of the most used eye drops in relieving eye dry symptoms.

During the follow-up period at the discretion of the treating physician any ocular topical treatment is allowed, including other artificial tears/lubricants.

Each subjects will receive enough quantity of IDs to complete the study, in case of loss of samples by the subject/s, and after an enquiry, Dompé will provide sufficient amount of samples in surplus over the minimum required for full treatment.

6.3. SUBJECTS

The subject selection criteria will be checked at the Day 1 baseline Visit (Visit 1).

6.3.1. Inclusion criteria for Subject Selection

1. Patients 18 years of age or older.
2. Patients undergone ocular refractive surgery within 6 months from Day 1 Visit.
3. Patients with ocular discomfort defined as SANDE score ≥ 30 at baseline.
4. Average VAS score (dryness, foreign body sensation, burning/stinging, itching, pain, stick feeling, blurred vision and photophobia) ≥ 25 mm;
5. Best corrected distance visual acuity (BCDVA) score ≥ 0.1 decimal units in both eyes at the time of study enrolment.
6. Only patients who satisfy all Informed Consent requirements may be included in the study. The patient and/or his/her legal representative must read, sign and date the Informed Consent document before any study-related procedures are performed. The Informed Consent form signed by patients and/or legal representative must have been approved by the IEC for the current study.

6.3.2. Exclusion criteria for Subject Selection

1. Patients with a severe Dry Eye condition (severity level 4 according to the Report of the International Dry Eye Workshop -DEWS, 2007)
2. Best corrected distance visual acuity (BCDVA) score of < 0.1 decimal units in either eye at the time of study enrolment
3. Evidence of an active ocular infection in either eye
4. History or presence of ocular surface disorders other than ocular discomfort in either eye
5. Use of any ocular topical medication other than the study medications for the treatment of ocular diseases including artificial tears during the study period
6. Use of topical cyclosporine, topical corticosteroids or any other topical medication for the treatment of dry eye in either eye within 30 days of study enrolment
7. History of any ocular surgery (excluding laser or refractive surgical procedures) in either eye within 30 days before study enrolment. Ocular surgery will not be allowed during the study treatment period and elective ocular surgery procedures should not be planned during the duration of the follow-up period
8. Known hypersensitivity to one of the components of the study or procedural medications
9. Participation in another clinical study at the same time as the present study or within 90 days of screening/baseline visit
10. History of drug, medication or alcohol abuse or addiction.
11. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:
    - **a.** are currently pregnant or,
    - **b.** have a positive result on the urine pregnancy test at the Screening/Baseline Visit or,
    - **c.** intend to become pregnant during the study treatment period or,
    - **d.** are breast-feeding or, not willing to use highly effective birth control measures, such as: Hormonal contraceptives – oral, implanted, transdermal, or injected and/or mechanical barrier methods – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD during the entire course of and 30 days after the study treatment periods.

6.3.3. Criteria and Procedure for Subject Withdrawal or Discontinuation

A subject should be withdrawn from the trial if, in the opinion of the Investigator, it is medically necessary or if it is the wish of the subject.

The study treatment will be discontinued at any time if any of the following events occur:

- **Adverse event**: Any significant adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 14.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a patient to follow-up
- **non-compliance with study ID**: an indication that a patient has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject

- **pregnancy**: pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by Sponsor**: an indication that a clinical study was stopped by its Sponsor
- **site terminated by Sponsor**: an indication that a clinical site was stopped by the study Sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

Any treatment discontinuation must be recorded on the case report form (CRF) by the Investigator, who will indicate date and reason(s) for treatment withdrawal. Unless the subject has withdrawn consent, the early termination visit assessments should be performed as detailed in Section 6.1.3.

6.3.4. Point of Enrolment

Subjects will receive the randomization number before enter in a 2 week double-masked, randomized, controlled treatment period, followed by 1 week follow-up.

6.3.5.Total Expected Duration of the Clinical Investigation

The study is expected to be completed within 3-4 months.
The study will be considered completed at the date of the last visit of the last subject or upon completion of any follow-up procedure described in the CIP. The investigator and the Sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately. In this event, no further subjects will receive doses of the IDs, and subjects already having received a dose of IDs will not receive any further doses of the study ID but will undergo all safety assessments scheduled after the last dose of ID, up to an including the end of study examination

6.3.6. Expected Duration for Each Subject

Treatment duration 14 days (2 weeks) ± 2 days (maximum total study duration 16 days) and 1 week (7± 2 days) of follow-up.

The total maximum duration is expected to be about 25 days.

6.3.7. Total Number of Randomized Subjects

30 subjects (10 per arm) will be randomized to 1:1:1 ratio.
Recruitment will proceed until the planned number of randomized subjects is achieved.

6.3.8. Total Enrolment Time

The best total enrolment time is estimated to be of 45 days.

6.4. PROCEDURES

6.4.1. Clinical Investigation Procedures

6.4.1.1. Efficacy

Ocular Evaluations

Ocular evaluations will be performed on both eyes. The assessments must always be performed according the sequence (1 – 10) detailed in § 6.1.3. The assessment will be performed at visit 1 (day 1), 2 (day 15±2), 3 (day 22±2) /early termination visit.

The ophthalmological assessment will include:

1. ***Symptom Assessment in Dry Eye (SANDE):*** Subjects with SANDE overall score ≥ 30 mm are eligible for enrolment.

   The SANDE questionnaire is a short questionnaire to evaluate both dry eye intensity and frequency by using a 100 mm VAS. The subject symptoms of ocular dryness and/or irritation will be quantified on the scale based on two questions that assess both severity and frequency of symptoms. A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of irritation that a subject feels ranges across a continuum from none to an extreme amount of irritation. From the subject's perspective this spectrum appears continuous (i.e. their irritation does not take discrete jumps, as a categorization of none, mild, moderate and severe would suggest). It was to capture this idea of an underlying continuum that the VAS was devised.
   For the assessment, the subjects mark on the 100 mm VAS line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the subject marks. The SANDE scores will be then evaluated for the 2 questions severity (0-100) and frequency (0-100).

2. ***Best corrected distance visual acuity (BCDVA*)**: Subjects with best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units in both eyes are eligible for enrolment. Refraction and visual acuity measurements will be performed for all subjects by trained vision examiners only. The name of the vision examiner should be documented in the subject's visual acuity (VA) worksheet (provided by the Sponsor) at each visit. Refraction should be conducted prior to visual acuity testing to obtain best-corrected vision as described below. Best-corrected visual acuity is measured at all trial visits using standard charts, lighting, and procedures. Best correction is determined by careful refraction at that visit according to the standard protocol for refraction as described below
   Equipment: Refraction equipment required includes:
   - Retroilluminated Light box and ETDRS 4 meter distance acuity chart set
   - Trial lens frames
   - Trial lens set with plus or minus cylinder lenses
   - Jackson cross-cylinders of 0.25, 0.50, and 1.00 diopters
   - Pinhole occluder
   - Tissues or eye pads and tape
   - A 1 meter rigid measuring stick

Visual acuity charts: Chart 1 is used for testing the visual acuity of the RIGHT eye; Chart 2 for testing the LEFT eye; and Chart R (or 3) for refraction only. Subjects should not be allowed to see any of the charts before the examination**.**

A distance of 4 meters is required between the subject's eyes and the visual acuity chart. With the box light off, not more than 15 foot-candles of light (161.4 Lux) should fall on the centre of the chart. To measure the amount of light, the room is set up for visual acuity testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one line available for testing visual acuity, the visual acuity of an individual subject should be measured in the same line at each visit, if possible. If different lines are used to test visual acuity, they must each meet the same standards.

Retroilluminated ETDRS charts are used in this trial. The illuminator box will be either wall-mounted or mounted on a stand. The light box should be mounted at a height such that the top of the third row letter is 49 + 2 inches from the floor.

The visual acuity light box is equipped with two General Electric 20-watt fluorescent tubes and ballast. Each tube is partly covered by a 14-inch fenestrated sleeve, which is centered on the tube and open in the back**.** This serves as a "baffle" to produce even illumination over the testing chart. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours, new tubes should be kept on for 4 days (96 hours) continuously, and should be replaced once a year

A sticker should be placed on the back of the light box, indicating the date when the present tubes were installed. A spare set of burned in bulbs should be available on site.

Detailed instructions for VA assessment As a reminder, Charts 1, 2 and R (or 3) are used for testing the right eye, left eye, and refraction, respectively. Subjects should not see the charts until the test begins. The lens correction from the subjective refraction should be in the trial frame worn by the subject.

All eyes must be tested at 4 meters first, even if the refraction was performed at 1 metre

The subject should be seated comfortably directly in front of the chart so that the eyes remain at the 4 meter distance. Testing always begins with the right eye. The fellow eye should be occluded with a folded tissue or eye pad lightly taped over the eye behind the trial frame serves as an effective occluder that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.

The subject is asked to read the letters slowly, approximately one letter per second. The subject should be told that only one chance is given to read each letter, but may change their mind before moving to the next letter. If the subject is unsure about the identity of the letter, then the subject should be encouraged to guess.

The subject should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. The subject should be encouraged to continue reading even if making mistakes. Each letter read is counted. The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the provided VA worksheet. An X is put through letters read incorrectly. Letters, for which no guess was attempted, are not marked. When a subject reaches a level where he/she cannot guess, the examiner may stop the test, provided that the subject has made errors on previous guesses, which is a clear indication that the best visual acuity has been obtained.

When a subject cannot read at least 20 letters on the chart at 4 meters, the subject is tested at 1 meter. The distance from the subject to the chart should be measured again using the rigid one meter stick. The distance is measured from the outer canthus to the center of the fourth letter (right eye) or the second letter (left eye) of the third line of the chart. The spherical correction

in the trial frame should be changed by adding +0.75 to correct for the closer test distance. The subject may fixate eccentrically or turn or shake his/her head to improve visual acuity. Particular care should be taken to make sure the subject does not move forward when testing at 1 metre. The subject should be reminded to blink.
The examiner should not tell the subject if a letter was identified correctly. The patient may be encouraged by neutral comments, such as "good", "next", and "OK".
The examiner should not stand close to the chart during testing. Attention should be focused on the patient and the VA worksheet. If the patient has difficulty locating the next line to read, the examiner may go up to the chart and point briefly to the next line to be read, but then must move away from the chart.
When 20 or more letters are read at 4 meters the visual acuity score for that eye is recorded as the number of letters correct at 4 meters plus 30 (refer to the VA worksheet). The patient gets credit for the 30 letters at 1 meter even though they did not have to read them. Otherwise, the visual acuity score is the number of letters read correctly at 1 meter plus the number, if any, read at 4 meters. If no letters are read correctly at either 4.0 meters or 1 meter, then the visual acuity score is recorded as "0".

3. ***Slit lamp examination (SLE):*** The slit lamp examination must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.
The subject will be seated at the slit lamp while being examined. Grading of the eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber will be done according to the following scales:
Eyelid - Meibomian glands (evaluation of the central ten Meibomian gland openings in the mid-portion of the upper eyelid):
0 = None (none are plugged).
1 = Mild (1 to 2 glands are plugged).
2 = Moderate (3 to 4 glands are plugged).
3 = Severe (All glands are plugged).
Eyelid - Erythema
0 = None (normal).
1 = Mild (redness localized to a small region of the lid(s) margin OR skin).
2 = Moderate (redness of most or all lid margin OR skin).
3 = Severe (redness of most or all lid margin AND skin).
4 = Very severe (marked diffuse redness of both lid margin AND skin).
Eyelid - Oedema
0 = None (normal).
1 = Mild (localized to a small region of the lid).
2 = Moderate (diffuse, most or all lid but not prominent/protruding).
3 = Severe (diffuse, most or all lid AND prominent/protruding).
4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).
Lashes
0 = Normal
1 = Abnormal (specify)
Conjunctiva – Erythema
0 = None (normal).
1 = Mild (a flush reddish color predominantly confined to the palpebral or bulbar conjunctiva).
2 = Moderate (more prominent red color of the palpebral or bulbar conjunctiva).
3 = Severe (definite redness of palpebral or bulbar conjunctiva).

Conjunctiva - Oedema
0 = None (normal).
1 = Mild (slight localized swelling).
2 = Moderate (moderate/medium localized swelling or mild diffuse swelling).
3 = Severe (severe diffuse swelling).
4 = Very severe (very prominent/protruding diffuse swelling).
Lens
0 = No opacification (normal lens).
1 = Mild lens opacification.
2 = Moderate lens opacification.
3 = Severe lens opacification.
N/A = Subject with artificial lens
Iris
0 = Normal
1 = Abnormal.
Anterior Chamber Inflammation (Slit beam = 0.3 mm wide, 1.0 mm long)
0 = None (no Tyndall effect).
1 = Mild (Tyndall effect barely discernible).
2 = Moderate (Tyndall beam in the anterior chamber is moderately intense).
3 = Severe (Tyndall beam in the anterior chamber is severely intense).
Cornea transparency
0= completely transparent
1= mild opacity
2= moderate opacity (iris details clearly visible)
3=severe opacity (iris details not clearly visible)
4=complete cornea opacity (anterior chamber structures not visible)
Cornea neovascularization
0= absence of neovascularization
1= neovascularization in less than 90°
2= neovascularization between 90° and 180°
3= neovascularization between 180° and 270°
4= neovascularization between 270° and 360°

Relevant findings of the SLE will be entered in the CRF.

4. ***Central corneal sensitivity by Cochet-Bonnet aesthesiometry:*** The Cochet-Bonnet aestheiometer contains a thin, retractable, nylon monofilament that extends up to 6 cm in length. Variable pressure can be applied to the cornea by adjusting the monofilament length. The monofilament length ranges from 6 to 0.5 cm. As the monofilament length is decreased the pressure increases from 11 mm/gm to 200 mm/gm.

Corneal sensation will be measured in the affected eye(s) in the central area of the cornea using a Cochet Bonnet aesthesiometer before the instillation of any dilating or anesthetic eye drops.

Start the procedure by testing the corneal sensitivity within the area (center) of the PED or corneal ulcer of the affected eye.

Steps for using the Cochet Bonnet aesthesiometer:

a) Extend the filament of the aestheiometer to full length of 6 cm. Slowly advance the monofilament towards the eye until the tip perpendicularly touches the corneal surface. Continue to exert a slight pressure until obtaining an inflection deviation of the filament of

about 4% (i.e. the first visible inflection). If a positive reaction to the touch of cornea is illicited proceed to step 3. If a positive reaction is not achieved proceed to step 2. (NOTE: A positive response is any action indicating corneal sensation whether communicated verbally or physically).

b) Retract the filament incrementally in 0.5 cm and repeat this step until the patient gives a positive reaction indicating that the contact of the monofilament on the cornea has been sensed. (NOTE: The shorter filament lengths indicate decreased corneal sensation).

c) Record the length of the filament in cm at which the patient sensed the contact with the cornea.

d) Repeat steps 1-3 in each of the 4 corneal quadrants (superior nasal, inferior nasal, superior temporal and inferior temporal) outside the area of the PED or corneal ulcer in the affected eye and in each of the 4 corneal quadrants of the non-affected eye.

e) To clean the instrument refer to your national standards for devices that contact the eye and tears or follow the suggested manufacturer's recommendations.

The length of the filament in cm at which the patient corneal sensation was observed for the tested area of the cornea will be entered into the eCRF.

5. ***Tear collection for Lubricin dosing:*** tear collection will be performed using tear wash technique with 40 µL of sterile saline solution. Dompé farmaceutici s.p.a. will be responsible for samples collection and dosing procedure. Samples will be shipped after LPLV

6. ***Tear Film Break Up Time (TFBUT):***

   TFBUT will be measured by determining the time to tear break-up. The TFBUT will be performed after instillation of fluorescein solution into the inferior conjunctival cul-de-sac of each eye. The subject will be instructed to blink several times to thoroughly mix the fluorescein with the tear film. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT. With the aid of a slit lamp at 10X magnification using cobalt blue illumination, the examiner will monitor the integrity of the tear film, noting the time it takes to form lacunae (clear spaces in the tear film) from the time that the eye is opened after the last blink. This measurement will be performed within 10 seconds maximum. The TFBUT will be measured twice during the first minute after the instillation of the fluorescein. If the 2 readings differ by more than 2 seconds a third reading is taken.
   The TFBUT value will be the average of the 2 or 3 measurements.
   Relevant TFBUT findings will be entered in the CRF.

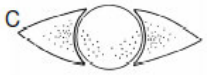
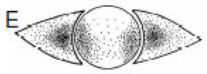
7. ***Schirmer's test (ST) I (without anaesthesia):***

   This test will be performed to measure aqueous tear secretion prior to the instillation of any dilating or anesthetic eye drops. Both eyes may be tested at the same time.
   This test will be conducted in a dimly lit room. While the subject looks upwards, the lower lid will be drawn gently downwards and temporally. The rounded bent end of a sterile strip will be inserted into the lower conjunctival sac over the temporal one-third of the lower eyelid margin. The test should be done without touching directly the Schirmer test strip with the fingers to avoid contamination of skin oils. The subjects will be instructed to close their eyes gently.
   After 5 minutes have elapsed, the Schirmer's test strip will be removed and the length of the tear absorption on the strip will be measured (millimeters/5 minutes).

The wetting distance at 5 minutes for each eye will be recorded in the CRF.

8. ***Corneal fluorescein surface staining (Oxford score):***

The corneal fluorescein staining will be graded by using the Oxford scheme to assess cornea and conjunctiva epithelium damage. It will be performed after instillation of sodium fluoresce in into the inferior conjunctival cul-de-sac of each eye with the aid of a slit lamp at 10X magnification using cobalt blue illumination.
Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale as follow:
Corneal fluorescein staining will be assessed after the Tear Film Break Up Time (TFBUT) examination and will also be graded according to the oxford scheme.

PANEL	GRADE	CRITERIA
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

9. ***Intraocular pressure (IOP):*** IOP may be performed using either Goldmann applanation tonometry after the instillation of a topical anesthetic.

IOP should be measured in both eyes after completion of all other slit lamp examinations to avoid potential interference with the other evaluations. The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining.
Both eyes will be tested, with the right eye preceding the left eye. The same equipment must be used throughout the course of the study.
IOP for each eye in mmHg will be recorded in the CRF.

6.4.1.2. Tolerability and Safety

Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in subject's medical conditions. Changes in any protocol-specific ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the subject's responses to any questionnaire utilized during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

***Visual analogue scale (*VAS)**: Local ocular tolerability score: A global ocular discomfort score will be determined using a 100 mm VAS on which 0 means no symptoms and 100 means the worst possible discomfort. This evaluation is to be performed before any ophthalmic assessment at a given study visit. Specific ocular symptoms to be assessed with the VAS include:

- dryness
- foreign body sensation,
- burning/stinging,
- itching,
- pain,
- sticky feeling
- blurred vision
- photophobia

VAS parameters that will be used for the evaluation of tolerability and safety are: .

The subjects will be instructed to place a vertical mark on the horizontal line indicating his/her level of discomfort for that symptom in the eyes. The VAS is expected to take the subject about 5 minutes to complete. A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.

6.4.1.3. General procedure

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's exclusion criteria.

Prior to enrolment in the clinical trial, female subjects of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the study treatment period ends and of the potential risks associated with an unintentional pregnancy. During the trial, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant; in the same way, male subjects who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately. The study Sponsor must be contacted immediately and a decision will be made regarding continuation of the pregnant woman in the study based upon the circumstances surrounding the pregnancy. Pregnancy is not reportable as an adverse event; however, complications may be reportable and will be decided on a case by case basis. A form

prepared by the Sponsor will be utilized to capture all pregnancy-related information until the birth of the child for both the subject and the partner during the study treatment period (2 weeks) and follow-up period (total 3 weeks).

Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRFs. He must also check that the data reported in the CRFs correspond to those in the subjects' source documents.

To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialed. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination.

The investigator must provide a reasonable explanation for all missing data.

The CRFs will be completed, signed by the investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the Sponsor.

Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier for study site consists of the Sponsor study code (i.e. LUB0116MD), the 3-digit screening number (e.g S01, S02, etc.) and, if applicable, the 2-digit subject study number (e.g. 01, 02, etc.).

Study code, screening number and subject study number are separated by slashes (e.g. "LUB0116MD/S01/01"). The last 5 digits of the unique subject identifier (randomized subjects), corresponding to the subject screening and subject study numbers separated by a slash, or the last 3 digits of the unique subject identifier (not randomized subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the subjects in in-text tables or wording (if applicable).

Coding dictionaries

Medical/surgical history and underlying diseases, physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).
Prior and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE). Version of coding dictionaries will be stated in the study report.

Concomitant Treatments

All concomitant therapies taken during the study from screening visit to the follow-up visit must be recorded in the specific section of the CRF.

Allowed/Disallowed treatments

Use of topical cyclosporine, topical corticosteroids or any other topical medication for the treatment of dry eye in either eye is not allowed during the treatment period.

During the study follow-up period (from day 15±2 to day 22±2), any ocular topical treatments allowed, including other artificial tears/lubricants as prescribed by the treating physician.

Hormonal contraceptives for females will be allowed.

6.4.2. CRO Activities

CRO shall prepare all the documents on the need for the CI which shall be approved by Sponsor/Investigator. CRO shall following and monitoring the entire conduction of the CI up to its conclusion. CRO shall prepare all the documents to implement the Technical File of ID (e.g. Clinical Investigational Report).

6.4.2.1. Database management

Data management of all data captured within the CRF will be performed by the CRO with the Clinical Data Management System (CDMS) according to a double data entry with total re-entry of data and discrepancy resolution by a third individual. CRO will update and verify the database and create the final SAS data sets. The tabulation datasets and analysis datasets created according to the standard CDISC (STDM and ADaM) will be provided to the Sponsor with all the other study documentation.

6.4.3. Foreseeable Bias

In order to minimize the bias the clinical study is design as randomized (1:1:1), controlled, double-masked. Subjects will enter in a 2 week double-masked, randomized, controlled treatment period. The double-masked technique is used to assure the double blind of the study.

6.4.4. Material supplied to the clinical centre

Besides the ID products, the following study material will be supplied to the clinical centre:

- CIP
- CRF for each subject plus some spare copies
- VAS forms and SANDE Questionnaires for each subjects
- copy of the investigator's brochure (IB) relative to the ID
- informed consent forms
- Urine Pregnancy Test

Moreover, before the start of the study, the investigator(s) will be provided with the following main documents: ICH guidelines, confidentiality agreement (if applicable), CIP amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form other documents will be provided by CRO.

6.5. Monitoring, Data and Quality Management

6.5.1. Monitoring

Quality assurance is under Dompé farmaceutici s.p.a.'s responsibility.

Monitoring activities and responsibilities will be described in detail in a monitoring plan

Monitoring of the present clinical trial is assigned to CRO that has the responsibility to adequately qualify the monitoring staff and assures that the conduct of the Clinical investigation complies with the approved CIP, subsequent amendment(s), ISO 14155-2012 and the GCP.

According to the ISO 14155-2012 and the GCP, a number of measures and procedures aimed to guarantee data quality and reliability are to be applied and followed in carrying out this clinical Investigation.

6.5.1.1. Clinical monitoring and identification of source data

The study will be monitored by regular monitoring visits in compliance with ISO 14155-2012, GCP and CRO Standard Operating Procedures (SOPs) to verify data entered and collected on the CRF(s). Monitoring will be performed by the CRO**.**

The Investigator should agree to receive periodic monitoring visits, based on subjects' enrolment rate or for other reasons, such as to verify SAEs.

At each visit, the Investigator or a designated member of the study personnel should be available to provide direct access to all study-related documentation, including the original subject notes, and to make any necessary corrections to the CRF and/or other study documents. Source documents should be available to support the data recorded in the CRF, apart from those data for which the CRF might be accepted as being the sole source document and that will be identified prior to study commencement (physical examination, vital signs biometric measures, pregnancy test, external ocular examination, slit lamp examination, TFBUT, corneal fluorescein surface staining, Schirmer's tests I, intraocular pressure). The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

The monitor will provide the Investigator with all the study materials before the study starts and, during the course of the study, will check at least the following:

- Full compliance with ISO 14155-2012, ICH-GCP, the study protocol and applicable regulatory requirements.
- Subject recruitment.
- Subject compliance.
- Drug accountability.
- Completeness and accuracy of the CRF data and their consistency with the source documents (appropriate source data verification will be conducted on all CRFs).
- Verification of the facilities.
- Investigator's Trial Master File.

The monitor will ensure completeness of CRFs on an ongoing basis.

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a CI necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

6.5.2. Audit

The Investigator/Institution must allow Dompé farmaceutici s.p.a. and/or independent bodies acting on behalf of the Sponsor and CRO to have the right to perform the audits as an integral part of the quality assurance system.. The audit is an independent verification, separate from the monitoring activity, of the activities and of the documents to ensure that the activities pertinent to

the study were duly carried out and that they were recorded, analyzed and transferred in compliance with the protocol, ISO 14155, GCP, relevant SOPs and with applicable legislation.

6.5.3. Inspections

The Investigator/Institution must allow national and foreign Regulatory Authorities to conduct inspections.

The Inspection on the part of one or more Regulatory Authorities consists of an official review of the documents, facilities, records and any other resource considered by the authorities to be connected with the study.

7. STATISTICS

7.1 Design, Methods and Analytical Procedures

7.1.1 Statistical Methods

The data documented in this study will be listed by subject, treatment, eye (enrolled eye(s), left and right) and evaluation time point, i.e Baseline or Day 1 (Visit 1), Day 15 ±2 (Visit 2) and follow-up (Visit 3).

Appropriate descriptive statistics will be used according to the nature of the variable.

Not available data will be evaluated as "missing values". The statistical analysis will be performed using SAS® version 9.3 (TS1M1) for Windows® **(19)** or higher.

7.1.2 Definitions

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A subject will be defined as randomized in the study if he/she is assigned to a treatment arm (Test 1 (20 µg/mL), Test 2 (50 µg/mL) or Control).

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics
- Full Analysis Set (FAS): all randomized subjects, who receive at least one dose of the ID. This analysis set will be used for the efficacy analysis
- Safety set: all subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for tolerability and safety analyses

Each subject will be coded by the CRO Biometry Unit as valid or not valid for the Enrolled set, FAS and Safety set. Subjects will be evaluated according to the treatment dose they will actually receive.

7.1.3 Demographic, Baseline and Background Characteristics

Standard continuous or categorical variable summaries will be used for demographic and population characteristics.Data will be presented for Baseline visit.

7.1.4 Tolerability and Safety Evaluation

AEs

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of the ID and not worsening after the first dose of the IMD
- TEAEs: all AEs occurring or worsening after the first dose of the ID

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarized by dose and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity.
A summary of adverse events leading to premature withdrawal will be provided, grouped by body system and preferred term.

Visual analogue scale (VAS)

Local ocular tolerability score will be performed before any ophthalmic assessment at a given study visit. Specific ocular symptoms to be assessed with the VAS include: dryness, foreign body sensation; burning/stinging; itching; pain; sticky feeling; blurred vision; photophobia. Time profile of treatments will be analized according to analysis of variance for repeated measure model.

7.1.5 Analysis of Ophthalmological Evaluations

Variables will be presented using descriptive statistics according to the nature of the variable, i.e. arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, proportions and frequencies for qualitative variables.

Considering the design of the study, data will be presented at Baseline, Day 15 and Follow-up periods separately. Changes from baseline and Day 15 will also be presented.

Inferential tests on changes from baseline will be used to estimate potential differences between treatments within Day 15 visits separately.

For the following variables Student t test will be considered:

Corneal fluorescein surface staining (Oxford score)

Schirmer's test (ST) I (without anaesthesia)

Tear Film Break Up Time (TFBUT)

Best corrected distance visual acuity (BCDVA)

Assessment of central corneal sensitivity by Cochet-Bonnet aesthesiometry

Symptom Assessment in Dry Eye (SANDE)

Intraocular pressure (IOP)

For Slit lamp examination (SLE), grading of the eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber will be processed separetely using Wilcoxon Rank Sum Test.

7.2 Sample Size

As the primary objective of this study is to evaluate the tolerability and safety of Lubricin (20 and 50 µg/mL) eye drops solution administered over 2 weeks in patients with ocular discomfort following ocular refractive surgery, sample size was calculated based on clinical feasibility and no formal sample size calculation has been performed.

7.3 Expected Drop-out Rate

An anticipated 10% drop-out of the randomized subjects will be expected

7.4 Interim Analysis

No formal interim analyses will be planned

7.5 Statistical criteria for CI Termination

Since no formal interim analysis is planned, statistical criteria for CI termination is not defined.

7.6 Statistical Plan Deviations

Full details and chages of statistical analyses will be reported and justified in the CIR

7.7 Subgroups

No subgroups are expected in this CI

7.8 Missing, Drop-out and All Data Analysis

Not available data will be evaluated as “missing values”. All data obtained will be used in the analysis and no imputation will be carried out for missing data to come from data not recorded in the CRF, from withdrawal of subjects from the study or from exclusion of subjects evaluated during the blind review meeting.

7.9 Exclusion of Particular Information

7.9.1. Reasons for Exclusion from the Full Analysis Set

Reasons for the exclusion from the Full Analysis Set are the following:

- failure to take at least one dose of the IDs
- lack of any efficacy data post enrolment
- failure to satisfy inclusion/exclusion criteria (eligibility violations). Subjects who fail to satisfy an inclusion/exclusion criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:
  - the inclusion/exclusion criterion was measured prior to enrolment
  - the detection of the relevant eligibility violations can be made completely objectively
  - all detected violations of the particular inclusion/exclusion criterion are excluded

8 DATA MANAGEMENT

8.1 Data Review, Cleaning and Data Queries

Data management of all data captured within the CRF will be performed by the CRO with the Clinical Data Management System (CDMS) according to a double data entry with total re-entry of data and discrepancy resolution by a third individual. CRO will update and verify the database and create the final SAS data sets. The tabulation datasets and analysis datasets created according to the standard CDISC (STDM and ADaM) will be provided to the Sponsor with all the other study documentation.
Missing data will not be entered in any format in the database. Queries will be issued and resolved directly between CRO staff personnel and the Investigators through the Monitors.

8.2 Electronic Data System

The statistical analysis will be performed using the qualified software SAS® version 9.3 (TS1M1)for Windows® **(19)** or higher.

8.3 Data Retention

Essential documents should be retained by Investigator's, until at least 15 years after study conclusion. Investigator's should maintain Site File (including signed Informed Consent forms and copy of Subject Information Sheet for all subjects), subject files, other source data (laboratory records, ECGs etc.) and CRF copies for the period of time for as long as possible but not less than 15 years.
Investigator must be also requested to inform Sponsor/CRO whenever he/she should leave the investigational study site after the termination of the study; this in order to allow undertaking measures for the maintenance of the essential documents relevant to the trial.
No documents related to the study will be destroyed without the prior written consent of Sponsor and the investigator/s.
The originals of all documents and copies of all documentation and correspondence related to the study will be added to the Clinical Investigation Master File (CIMF) and will be kept by CRO in a safe place in their offices until the end of the study and thereafter by the Sponsor throughout the product life. The CIR will be kept by the Sponsor, or any buyers, for at least 5 years after the recall of the product.

8.4 Data Retention Timing

No documents related to the study will be destroyed without the prior written consent of Sponsor and the investigator/s.

The investigator and the Sponsor should maintain the study documents as specified in the ISO 14155-2012 and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including ophthalmic assessments, insurance contracts, certificate of analysis of the ID(s), ID(s) accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the Sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the Sponsor as long as needed to comply with ISO & ICH-GCP, national and international regulations. By signing the protocol, the investigator and the Sponsor agree to adhere to these requirements.

8.4.1 Archiving

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The investigator must keep source documents for each subject in the study. All information on the CRFs must be traceable to these source documents.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the CI documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP, in the ISO 14155 – Annex E and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the CI and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects, insurance contracts, drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the CI, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP and ISO, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

8.5 Quality Assurance

Audit will be made by QAU of Dompé farmaceutici s.p.a. and/or by a delegated third party according to GCP and ISO 14155 and Dompé SOPs.

8.5.1. Confidentiality and data protection

By signing this protocol, the Investigator(s) agree to keep all the information provided by the Sponsor in strict confidentiality and to request similar confidentiality from his/her staff. Study documents provided by the Sponsor (protocols, Investigators' brochures, CRFs and other materials) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator and to the CRO cannot be disclosed to others without direct written authorization from the Sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected on the CRFs during the study will be documented in an anonymous way. If, as an exception, it becomes necessary to identify a subject for safety or regulatory reasons, the monitor, the Sponsor and the investigator will be bound to keep this information confidential.

9 AMENDMENTS TO THE CIP

In order to obtain interpretable results, neither the investigator nor the Sponsor will alter the study conditions agreed upon and set out in this CIP. Amendments should be made by mutual agreement between the investigator and the Sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the CIP.
All amendments will be sent to the EC and concerned Competent Authorities.

10 DEVIATIONS FROM THE CIP

10.1 Investigator Statements

As reported in page 4 of this CIP the Investigator's signed the agreement to conduct the study according to this CIP and to comply with its requirements and its ethical and safety considerations.

10.2 Deviation Procedures

The investigator/s as soon as possible informs the Sponsor/CRO in the case of repeated violations of CIP.
CIP deviations and their explanations should be provided on the CRF of competenceDeviations from the statistical plan will be included in the Final Report and adequately justified.

10.3 Notification and Timing

Any amendments to the CIP will be discussed and approved with the Dompé and, if necessary, submitted and approved by the Ethical Committee and Competent Authority (if appropriate).

10.4 Corrective/Preventive Actions and Investigator Disqualification Procedures

The Investigator's and the Centre/s has been qualified according to Dompé SOP, if during the monitoring/auditing visit arise repeated deviations to the CIP, Dompé might suspend or finish the CI (see also Statement agreement of page 4) and disqualify the Investigator's /Centre according to Dompé SOPs.

11 DEVICE ACCOUNTABILITY

The Test ID/Control ID will be supplied by Sponsor to Study Site in quantities sufficient to complete the treatment of subjects randomized.

11.1 Supply and Storage of the ID and Other Materials

The ID/Control ID will be sent to the Investigator/s in a quantity sufficient for the randomized subjects.

The Pharmacist and/or Investigator will be responsible for receipt, proper storage and usage of IDs.

Partially used or unused IDs should be destroyed on site (on request of Dompé, and documentation of destruction provided to Dompé farmaceutici s.p.a.) or returned to Dompé farmaceutici s.p.a., at the end of the study. Adequate record of receipt, use or loss of IDs will be retained.

11.2 Responsibilities

All product supplies that will be used in the CI must be stored and maintained securely under the responsibility of the Investigator/s, or the Hospital Pharmacist, or other trial staff personnel designated and authorized by the Investigator/s to store and dispense ID, according to the regulations in force.
IDs shall be dispensed in accordance with CIP requirements and Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of dispensed and returned compounds is maintained.
This will be possible with the regular completion of the CRF section about ID Dispensing and the ID Accountability Form which will be part of the IF.

11.3 Control of Occurred Treatment

e investigator/s will ensure that the subject has received the Test ID/Control ID at Visit 1; any deviations from the fixed dosing will be specifically asked to the subjects at each visit and deviations will be included in the CRF. The Investigator should accurately complete all the ID Accountability Forms at all visits and check treatment self-administration compliance.

Any new information about the IDs will be communicated to the subject and the consent modified and submitted to the EC for approval.

12 STATEMENTS OF COMPLIANCE

12.1 Declaration of Helsinki

The CRO/sponsor and the Investigator's ensure that all procedures described in this CIP, data evaluation and documentation will be produced strictly according to the current version of Declaration of Helsinki.

12.2 International Standard

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.

The present clinical study will be also carried out according to Attachments VIII and X del legislation decree 24 February 1997, n.46 and s.m.i., the standard ISO14155-2012 and the general principles of "ICH Topic E6, CPMP/ICH/135/95", July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002.

12.3 Ethic Committee and Regulatory Authority Approvals and Any Additional Requirements

The CIP and essential documents (CRF, ICF, Insurance, etc..) will be approved by the Ethics Committees. The approval of the CIP by the relevant Ethics Committee will be obtained before the start of the study.

Study notification to the Competent Authority will be performed according to the Italian current regulations on Medical Device.
It is understood that the study can begin only after full approval by the Ethics Committee, and by the Competent Authorities. Products will not be sent to Investigator/s before the Ethics Committee and Competent Authorities approvals.

12.4 Amendments and EC/CA Additional Requirements

Any amendment to this CIP will be sent to the EC/CA (if required), any amendments that may lead to increased risks and/or inconvenience to the subject must first be approved by the EC and Competent Authority, if appropriate, and such approval in writing addressed to the Sponsor.
Copies of all documents must be stored also by the Investigator/s. Any revision of the CIP shall be reported on the CRF, if applicable. Any additional EC/CA requirement will be followed as appropriate.

12.5 Insurance Policy

An insurance cover has been issued in favor of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities

12.5.1 Liability Statement

On behalf of the Sponsor, the investigational sites will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigators, the persons instructed by them and the hospital, practice or institute in which they are employed and the liability of the Sponsor in respect of financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the applicable local laws.
As a precautionary measure, the investigators, the persons instructed by them and the hospital, practice or institute are included in such cover in respect of work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance.

13 INFORMED CONSENT

13.1 General Procedures

Before being enrolled into the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by Dompé and must be approved by the EC and regulatory authorities. It will include all the elements required by law according to the ISO 14155-2012 and ICH-GCP recommendations.
In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organized
- the type of treatment
- any potential negative effects attributable to the study treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardizing their further course of medical treatment
- the existence of subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the subjects.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements.
The investigator will allow inspection/audit of the forms by authorized representatives of the Sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.
In case any new information regarding the IDs will be available during the study the subject will be contacted by the Investigator and if the case a new informed consent will be prepared, submitted to the EC/CA and after approval proposed to the subject.

13.2 Special Procedures

No vulnerable subjects are expected to be enrolled in this CI.

14 SAFETY EVALUATION AND REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND DEVICE DEFICIENCIES

14.1 Definitions

MEDDEV 2.7/3 (Rev 3, May 2015) attached to this CIP (Annex C), provides definitions for serious and non-serious Adverse Events (SAE and AE) and Adverse Device Effects (SADE and ADE) and for Device Deficiency (DD) and Unanticipated Serious Adverse Device Effect (USADE). All serious adverse events must be fully recorded and immediately notified to all Competent Authorities of the Member States in which the clinical investigation is being performed within the timeframe and format specified in the MEDDEV 2.7/3; all adverse events and device deficiencies (related to the identity, quality, durability, reliability, safety or performance of an investigational medical device) shall be documented and assessed.

The Flowchart for guidance of adverse event categorization is reported in figures F1 and F2 of ISO 14155:2011 (Annex D of this CIP).

The ISO 14155 Adverse Event Categorization is summarized hereafter.

ADVERSE EVENTS	Non-device-related	Device- or Procedure -Related	
Non-Serious	Adverse Event (AE)	Adverse Device Effects (ADE)	
Serious	Serious Adverse Event (SAE)	Serious Adverse Device Effects (SADE)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effects (ASADE)	Unanticipated Serious Adverse Device Effects (USADE)

14.2 Management of adverse event/adverse device effect

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination.
Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

When an **AE/ADE** occurs, the Investigator must fill in the appropriate section of the CRF recording at least the following information:
- description of the event
- subject's identification (initials, subject number)
- duration (start date and end date)
- intensity (mild/moderate/severe)
- action taken
- outcome
- assessment of relationship to investigational medical device(s)
  assessment of relationship to the procedure involved (any procedure in the clinical investigation plan)
- assessment of seriousness of the AE/ADE.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution or stabilization.

While filing in the AE information in the CRF, the Investigator shall assess the event and evaluate it for the following three criteria:
- Serious: yes/no
- Relationship with study treatment.

An AE shall be considered **serious** if:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or

- a permanent impairment of a body structure or a body function, or

- in-patient hospitalization or prolongation of existing hospitalization, or

- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

If the event is assessed as serious, the event shall be treated and processed as SAE/SADE as described in Paragraph 14.4.

The **relationship** between the use of the ID (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. Clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the Risk Analysis Report shall be consulted when assessing the causality. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

In line with the MEDDEV 2.7/3 (to be referred to for further information), each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;

- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application and reintroduction of its use do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that

    o the investigational device or procedures are applied to;

    o the investigational device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application and reintroduction of its use, impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The **Investigator** shall notify to the Sponsor and CRO (at the contacts reported at § 1.1) any AE/ADE within 30 calendar days from initial awareness. The page of the appropriate section in the CRF (AE – Adverse Event page) shall be sent to the Sponsor via e-mail or fax.

The **Sponsor Materiovigilance Department** shall review the Investigator's assessment of all AE/ADEs and determine and document in writing the evaluation of the seriousness and relationship to the ID. In case of disagreement between the Sponsor and the Investigator, the Sponsor shall communicate the discrepancy to the Investigator.

The Investigator shall refer to the Dompé medical Expert for any Clinical issue and question (see contact at § 1.1).

14.3 List of always serious adverse events and rescue procedure

The following adverse events are considered to be of special interest and by default shall be reported as SAEs (medically important criteria):

- Adverse Events that caused a decrease in visual acuity of >30 ETDRS letters or > +0.6 LogMAR (compared with the last assessment of visual acuity at the last visit) lasting >1 hour
- Adverse Events that caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour
- Adverse Events that required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- Adverse Events associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)
- Adverse Events that, in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight.

All AEs should be followed-up to determine outcome of the reaction. The Investigator should follow up the event until resolution or stabilization of the condition at least until 10 days after the final visit. It is the Investigator's responsibility to assure that the subjects experiencing an AE receive definite treatment for any AE, if required.

The **Investigator** shall refer to the Dompé Medical Expert for any Clinical issue and question (see contact at § 1.1)

14.4 Management of Serious adverse event/Serious adverse device effect

The **Investigator** must record all SAEs/SADEs, including sight-threatening events, occurring at any time during the study regardless of presumed causal relationship, on the Serious Adverse Event form.
Within 24 hours from first knowledge of the SAE, the Investigator shall send the filled in and signed SAE form to the Sponsor and the CRO, as described in Paragraph 14.6.
If assistance is needed with the reporting of a SAE, contact details for the Sponsor and the CRO are provided in § 1.1.
Samples of SAE Reporting forms to be sent to the Sponsor are provided among the study documentation.
The telephone, e-mail address and telefax numbers of the contact person(s) for reporting are listed also in the Investigator File provided to the site.
The investigator must complete the Serious Adverse Event Reporting Form in English.
If necessary a case narrative, as much exhaustive as possible, will be attached to the SAE Reporting Form. A photocopy of all relevant examinations which have been carried out for the event (ECG, lab tests…) will also be attached.
The original copy of the form must be kept with the study documentation at the site.

Depending on the nature and seriousness of the SAE, the Sponsor may request further information, including copies of appropriate medical records of the subject, as well as results of laboratory tests performed. If the subject was hospitalized, a copy of the discharge summary should be provided to the Sponsor as soon as it is available, if possible.
In any case, the Investigator shall further follow up each SAE to complete case information till resolution of the event, as appropriate, and provide the follow up information to the Sponsor.

Follow-up SAE information should be communicated through a new SAE form duly filled in and signed, within 24 hours from awareness, to the same contacts reported below for initial SAE reports, whenever becoming aware of new available information regarding the SAE, once the condition is resolved or stabilized and when no more information about the event is expected.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome.

Any SAE that occurs after the study period (defined as 10 days after Follow-up visit) and if considered to be possibly related to the study treatment or study participation should be recorded and reported immediately to the Sponsor.

SAE will be managed directly by the **Dompé Materiovigilance Department**, with the support of the Dompé Medical expert who will provide assessment of causality, expectedness and medical evaluation and may draft Follow Up requests.
SAE shall be notified to the Competent Authority by the Sponsor Materiovigilance Department (see Paragraph 14.7 for timing and procedure)
The **Investigator** will also accomplish to his/her obligations with respect to EC, as per local EC rules.

The Investigator shall refer to the Dompé medical Expert for any Clinical issue and question (see contact at § 1.1).

14.5 Process of Device Deficiencies Reporting

The Investigator shall inform the CRO/Sponsor as soon as possible of any Device Deficiencies found during the study.
Device deficiencies should be investigated by the Sponsor Quality Department and if related to safety should be assessed also by Sponsor Materiovigilance Department according to internal SOPs.
Device deficiencies that might have led to a SAE, if

a) suitable action had not been taken
b) intervention had not been made, or
c) circumstances had been less fortunate

shall be reported to the Regulatory Authority within the same timeframe and modalities for SAE (see Paragraph 14.7).

14.6 Timeframes and Contacts for Reporting from Investigator to the Sponsor/CRO

The Investigator shall report via e-mail or fax as per contact details reported in § 1.1:

	AE/ADE	**SAE/SADE**	**Device deficiencies**
Deadline from awareness	30 calendar days	24 hours	3 calendar days
Reporting tool	AE page from CRF	SAE form	Description using e-mail
Sponsor department	• Materiovigilance • Medical expert • Clinical Development	• Materiovigilance • Medical expert • Clinical Development	• Quality • Materiovigilance • Medical expert • Clinical Development
CRO	TBD	TBD	TBD

14.7 Regulatory Reporting

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of Directives 90/385/EEC and 93/42/EEC, as described in MEDDEV 2.7/3:

- any SAE,
- any Investigational Medical Device Deficiency that might have led to a SAE if:
  a) suitable action had not been taken or
  b) intervention had not been made or
  c) if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

In addition, any device deficiency that led to a SADE (therefore falling under the definition of SAE).

Dompé Materiovigilance Department shall submit reportable events to all National Competent Authority/ies (NCA) where the clinical investigation has commenced, using the summary tabulation as per MedDev Guideline (MEDDEV 2.7/3 – APPENDIX SUMMARY REPORTING FORM) attached to this CIP as Annex C.

Dompé must report to the NCAs where the clinical investigation has commenced:

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by the sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events as described above or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

Regulatory reporting is independent from causality assessment (also SAE unrelated to ID shall be reported to NCA).

The Investigator shall ensure reporting to his Ethic Committee of the reportable SAEs or Investigational Medical Device Deficiency, within the timeframes and with the form requested by the Ethic Committee.

Reporting Form for Regulatory reporting *(*SAE Reporting Form - MedDev 2.7/3 Rev 3)

The reporting form template for the summary SAE tabulation is given in the Appendix of MEDDEV 2.7/3 Rev 3 (the form will be taken in use from 1 September 2016 at the latest).

The table gives a cumulative overview of the reportable events per clinical investigation and shall be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual reporting form.

New/updated information shall be identified in the status column of the tabular form as:

a = added = new reportable event;

m = modified = new finding/update to an already reported event;

u = unchanged.

Changes in a line should be highlighted in bold and/or colour in the respective column.

The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan.

English is the recommended language for the reporting form.

The report should be sent by email in Excel to the participating NCAs, or an equivalent format which allows using the inserted filters.
Unblinding is not mandatory before regulatory submission of a reportable SAE/ Investigational Medical Device Deficiency

14.8 Data monitoring information

No DMC is expected for this CI due to the expected relatively low incidence of AE/SAE and ADE/SADE.

15 VULNERABLE POPULATION

15.1 General Description

No vulnerable population is expected see also § 13.2

15.2 Specific IC Procedures

No specific ICF are expected see also § 13.2

15.3 EC Procedures

No specific requirements are expected from EC due to what stated in the previous §15.1

15.4 Special Medical Care

No specific medical procedures are expected due to what stated in the previous §15.1

16 SUSPENSION AND PREMATURE TERMINATION OF CI

16.1 General Criteria and Site Criteria

According to the Declaration of Helsinki, each subject has the right withdraw from the study at any time without giving any justification.
In absence of relevant CIP violations or medical contraindications the Investigator shall make all reasonable efforts to keep the subject in the study. If, however, it becomes necessary to withdraw a subject from the study, a complete final evaluation must be performed. All the results of this evaluation, together with date of withdrawal and reason(s) for the subject's exclusion from the study, must be recorded in the CRF.

16.1.1 Removing Subjects from the Study

A subject should be withdrawn from the trial if, in the opinion of the Investigator, it is medically necessary or if it is the wish of the subject.
The study treatment will be discontinued at any time if any of the following events occur:

- Development of AE or unacceptable toxicity, precluding further therapy with the IDs. Severe protocol violations, such as an incorrect treatment administration, or a concomitant use of not permitted medications. Before removal, these cases should first be discussed with Dompé farmaceutici s.p.a.
- Severe protocol violations, such as an incorrect treatment administration, or a concomitant use of not permitted medications. Before removal, these cases should first be discussed with Dompé farmaceutici s.p.a.
- Subject request.
- Subject has been enrolled, but has not started study treatment e.g. due to onset of AE, consent withdrawal etc before treatment could be started.
- Subject becomes pregnant
- Treating physician decision in the subject's best interest.
- Onset of ocular conditions requiring additional topical treatments (e.g. onset of ocular inflammation, infection, hypertension etc) or surgery
- Request of Dompé farmaceutici s.p.a.

Any treatment discontinuation must be recorded on the case report form (CRF) by the Investigator, who will indicate date and reason(s) for treatment withdrawal. Unless the subject has withdrawn consent, the early termination visit assessments should be performed as detailed in § 6.1.3.

16.1.2 Discontinuation Criteria

The Investigator or Dompé farmaceutici s.p.a. may decide to terminate the study if in the opinion that continuing in the study poses unacceptable risks to the subjects. If such a decision is reached, no further subjects will receive study products and the study will stop. The decision will be based on an overall assessment of tolerability and safety.

16.1.2.1 Primary Reason for Discontinuation

- **Adverse event**: Any significant adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to **§ 14**.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a patient to follow-up
- **non-compliance with study ID**: an indication that a patient has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject

- **pregnancy**: pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by Sponsor**: an indication that a clinical study was stopped by its Sponsor
- **site terminated by** Sponsor: an indication that a clinical site was stopped by the study Sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

16.1.3 Discontinuation Procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)
- arrange for alternative medical care of the withdrawn subject, if necessary
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation
- record in the CRF any follow-up, if the subject is withdrawn for an AE

16.1.4 Withdrawal of Subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

16.2 Breaking Masked Criteria

The randomization list is held by CRO.
Individual envelopes identified with the subject assignment number have been prepared. Each one includes the identity of the treatment assigned to each subject. These envelopes, duly closed and sealed, are included into the IF.
During the study the integrity of the envelopes will be regularly checked by CRO Monitor during the visits at site. At the end of the study all the individual envelopes must be returned to Dompé.
The sealed envelope can only be opened in case of emergency, when knowledge of the ID is essential for treating the subject.
Only in case of real need the Investigator may open the sealed envelope. In case of opening, all the details (date, time, reasons….) must be specified into the CRF and the Sponsor must be informed within 24 hours.
If an envelope is opened before the end of the trial, the subject will be excluded from the trial.

A copy of the Individual envelopes identified with the subject assignment number will be also sent to the Dompé Materiovigilance Responsible. Dompé Materiovigilance will unblind a patient

treatment only for safety reason and will document envelope opening; unblinding is not mandatory before regulatory submission of a reportable SAE/ Investigational Medical Device Deficiency.

16.3 Follow-up

The CIP provides a follow-up visit and therefore throughout the study the Investigator should ensure the follow–up of all AEs, both serious and non-serious, until stable outcome of the event, i.e.: recovery, recovery with stable sequelae, death. “Stable” defines a clinical condition to be reasonably considered as not evolving, according to investigator’s judgement.For any follow-up information on SAEs, a new Serious Adverse Event Reporting form must be sent. Each re-occurrence, complication, relevant progression or sequelae of the original event should be reported as a follow-up to the first event.

Any SAE/SADE occurred within 10 days after conclusion of subject’s participation in the trial should be reported as well.
Subjects who drop-out from the study due to AE/ADE will be followed at least for the next 10 days, or until stable outcome of the event. Subjects who drop-out from the study due to a SAE/SADE will be followed in any case until stable outcome.

17 PUBLICATION POLICY

The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals; presenting results at scientific congresses; and posting information and results on internet-based public registers and databases.
In any case, study results will be communicated in full to the competent Health Authorities by the submission of a complete Clinical Investigational Report.
As the Sponsor agrees that the study results can be published by the Investigator(s), the Investigator agrees to submit any manuscript (abstract, publication, paper etc.) to the Sponsor before any public disclosure.
This will be done in order to ensure that clinical trial results are reported in an objective, accurate and balanced manner. The Sponsor reviews proposed manuscripts prior to submission within a reasonable period of time (30-90 business days in relation with the complexity of the work).
The Investigator(s) will also be provided by the Sponsor with the clinical investigational report and the results of any additional analysis, tables, figures etc undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).
On an exceptional basis, the Sponsor may temporarily delay registration of certain data elements (e.g. compound, name, outcome, measures etc.) to seek necessary intellectual property protection. This is because early disclosure of such a data could, in some circumstances, prevent or negatively impact patentability

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ANNEX A

LUBRICIN EYE DROPS SUBJECT'S INSTRUCTIONS (Italian version)

FOGLIO ILLUSTRATIVO

LUBRICIN GOCCE OCULARI

Questo documento contiene il testo proposto da Dompé per il foglio illustrativo da utilizzare con il dispositivo medico (DM) sperimentale “Lubricina gocce oculari”. Al termine della valutazione ai fini della sperimentazione clinica, tale testo potrebbe subire delle modifiche.

Si fa anche presente che il nome “Lubricina gocce oculari” non sarà quello proposto per la marcatura CE, ma sarà solo utilizzato per identificare il DM stesso durante la sperimentazione clinica.

ANNEX B

VISMED®
PATIENT'S INSTRUCTIONS
(Italian & English version)

VISMED® MULTI

D BENETZUNGSLÖSUNG FÜR DAS AUGE

Gebrauchsinformation

VISMED® MULTI
Natriumhyaluronat aus Fermentation 0,18 %.
Benetzungslösung für das Auge.
Steril, frei von Konservierungsstoffen.

Zusammensetzung: 1 ml Lösung enthält 1,8 mg Natriumhyaluronat sowie Natriumchlorid, Kaliumchlorid, Dinatriumhydrogenphosphat, Natriumcitrat, Magnesiumchlorid, Calciumchlorid und Wasser für Injektionszwecke. Die Lösung ist hypotone.

Anwendungsgebiete: Erscheinungen und Anzeichen eines trockenen Auges und/oder einer Schädigung der Augenoberfläche infolge mancher Erkrankungen, wie etwa superfizielle Keratitis, Sjögren Syndrom oder primäres Trockene-Augen-Syndrom. Zur Benetzung der Augen bei subjektiv empfundenem Trockenheitsgefühl sowie bei brennenden und müden Augen und anderen geringfügigen Befindlichkeitsstörungen ohne Krankheitswert, verursacht z. B. durch Staub, Rauch, trockene Hitze, klimatisierte Luft, Wind, Kälte, längerdauernde Bildschirmarbeit oder Kontaktlinsentragen (harte und weiche).

Gegenanzeigen: Überempfindlichkeit gegen einen der Inhaltsstoffe.

Wechselwirkungen: Nicht gleichzeitig mit Arzneimitteln oder anderen Produkten, welche auf das Auge aufgetragen werden, anwenden, da VISMED® MULTI deren Wirkung verändern kann.

Nebenwirkungen: In sehr seltenen Fällen können vorübergehende Befindlichkeitsstörungen auftreten, wie z.B. Bindehautreizung, Fremdkörpergefühl, Rötung oder Brennen der Augen sowie kurzzeitig verschwommene Sicht.

Dosierungsanleitung und Art der Anwendung: Vor der ersten Anwendung muss der Originalitätsverschluss an der Schutzkappe entfernt werden. Schutzkappe vom Behältnis abnehmen, den Kopf nach hinten neigen und die Tropföffnung über das zu behandelnde Auge halten. Mit dem Zeigefinger einer Hand das Unterlid des Auges nach unten ziehen. Durch leichtes Drücken des Fläschchens wird ein Tropfen der VISMED® MULTI Lösung freigesetzt (siehe Abbildungen). Soweit nicht anders empfohlen, nach Bedarf 1–2 Tropfen VISMED® MULTI in das Auge tropfen. Durch Lidschlag wird die Lösung verteilt und bildet eine transparente und haltbare Flüssigkeitsschicht auf der Oberfläche des Auges. VISMED® MULTI kann auch während des Tragens harter oder weicher Kontaktlinsen angewendet werden.

Vorsichtsmaßnahmen: Tropföffnung des geöffneten Behältnisses nicht berühren und nicht an das Auge bringen. Nach dem Gebrauch von VISMED® MULTI Schutzkappe wieder aufsetzen. Beschädigte Packungen von VISMED® MULTI nicht anwenden. VISMED® MULTI kann nach der ersten Anwendung für einen Zeitraum von 3 Monaten verwendet werden. Zwischen 2 °C und 25 °C lagern! VISMED® MULTI nach Ablauf des auf dem Behältnis und der Faltschachtel angegebenen Verfalldatums nicht mehr anwenden. Falls Ihre Beschwerden unter der Anwendung von VISMED® MULTI anhalten, suchen Sie sich ärztliche Behandlung begeben. Für Kinder unzugänglich aufbewahren.

Eigenschaften und Wirkungsweise: VISMED® MULTI enthält Natriumhyaluronat, ein natürliches Polymer, das auch in Strukturen des menschlichen Auges vorkommt. Die besonderen physikalischen Charakteristika von Natriumhyaluronat verleihen VISMED® MULTI seine wichtigen viskoelastischen und wasserbindenden Eigenschaften. VISMED® MULTI bildet eine stabile Schicht auf der Oberfläche des Auges, die nur allmählich durch den Lidschlag entfernt wird. VISMED® MULTI verbindet deshalb lang anhaltende Wirkung mit maximalem Komfort. VISMED® MULTI ist wegen seiner besonderen Zusammensetzung ausgezeichnet verträglich. VISMED® MULTI ist frei von Konservierungsmitteln.

Packungsgrößen: 10 ml Lösung in einem Multidosis-Behältnis.

Stand der Information: März 2011

Legende zu den Abbildungen 1–4:
1 Originalitätsverschluss entfernen.
2 Schutzkappe abnehmen.
3 Ein oder zwei Tropfen in das Auge träufeln.
4 Schutzkappe nach dem Gebrauch wieder aufsetzen.

GB LUBRICANT EYE DROPS

Instructions for use

VISMED® MULTI
Sodium hyaluronate from fermentation 0.18%.
Lubricant eye drops.
Sterile, free from preservatives.

Composition: 1 ml solution contains sodium hyaluronate 1.8 mg, sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride and water for injections. The solution is hypotonic.

Indications: Symptoms and signs of dry eye and/or ocular surface damage, due to diseases such as superficial keratitis, Sjögren syndrome or primary dry eye syndrome. For lubrication of the eyes in case of sensation of dryness, burning and ocular fatigue and other minor complaints of no pathological significance induced, for example, by dust, smoke, dry heat, air conditioning, wind, cold, extended computer screen use or contact lens wear (rigid or soft).

Contra-indications: Individual hypersensitivity to any constituent of the product.

Interactions: Do not use VISMED® MULTI at the same time as any drug or other product applied to the eye since it may modify their effects.

Undesirable effects: On very rare occasions transient disorders such as irritation of the conjunctiva, foreign body sensation, redness or burning sensation of the eye, short-term blurred vision may occur.

Dosage and administration: Tear off the tamper-evident seal before the first administration. Remove the protective cap. Tilt the head backwards and position the tip of the container above the eye to be treated. Move the lower eyelid down with the forefinger of one hand. Press the container and one drop of VISMED® MULTI will easily flow out (see illustrations). If not otherwise recommended, instill 1 or 2 drops of VISMED® MULTI onto the eye as often as needed. After blinking, the solution will disperse and form a transparent and long lasting coating on the surface of the eye. VISMED® MULTI may also be used while wearing contact lenses (rigid or soft).

Precautions: Do not touch the tip of the opened container and do not touch the surface of the eye with the tip of the container. Put the protective cap back on after using VISMED® MULTI. Do not use VISMED® MULTI if the container is damaged. VISMED® MULTI can be used up to 3 months after first use.
Store between 2 °C and 25 °C! Do not use VISMED® MULTI after the expiry date indicated on the container and the folding box. If discomfort persists while using VISMED® MULTI consult a physician. Keep out of reach of children.

Characteristics and mode of action: VISMED® MULTI contains sodium hyaluronate, a natural polymer, which is also present in the structures of the human eye. The particular physical characteristics of sodium hyaluronate confer to VISMED® MULTI its viscoelastic and water retaining properties. VISMED® MULTI provides a stable coating on the surface of the eye which is only slowly eliminated by blinking. Therefore VISMED® MULTI combines long lasting relief with maximum comfort. VISMED® MULTI is well tolerated due to its unique composition. VISMED® MULTI is free from preservatives.

Presentation: 10 ml solution in a multidose container.

Last revision date: March 2011

Legend to the illustrations 1–4:
1 Remove the tamper-evident seal.
2 Remove the protective cap.
3 Instill one or two drops onto the eye.
4 Put the protective cap back on after administration.

F LUBRIFIANT OCULAIRE

Notice d'emploi

VISMED® MULTI
Hyaluronate de sodium obtenu par fermentation 0,18 %.
Lubrifiant oculaire.
Stérile, sans agent conservateur.

Composition: 1 ml de solution contient 1,8 mg de hyaluronate de sodium, du chlorure de sodium, du chlorure de potassium, du phosphate disodique, du citrate de sodium, du chlorure de magnésium, du chlorure de calcium et de l'eau pour préparations injectables. La solution est hypotonique.

Indications: Signes et symptômes de sécheresse oculaire et/ou de lésion de la surface oculaire, dus à des maladies telles que la kératite superficielle, le syndrome de Sjögren ou le syndrome primaire de l'œil sec. Pour la lubrification des yeux en cas de sensation de sécheresse, de brûlure et de fatigue oculaire et d'autres troubles mineurs à caractère non pathologique induits, par exemple, par la poussière, la fumée, la chaleur sèche, la climatisation, le vent, le froid, le travail prolongé devant écran d'ordinateur ou le port de lentilles de contact (rigides ou souples).

Contre-indications: Hypersensibilité à l'un des constituants du produit.

Interactions: Ne pas administrer VISMED® MULTI en même temps que d'autres médicaments ou produits ophtalmiques car il peut en modifier les effets.

Effets indésirables: Dans de très rares cas, des troubles passagers tels qu'une irritation de la conjonctive, une sensation de corps étranger, une rougeur ou une sensation de brûlure de l'œil ainsi qu'une vision momentanément trouble peuvent apparaître.

Posologie et mode d'administration: Enlever la bague d'inviolabilité avant la première administration. Ôter le capuchon protecteur. Incliner la tête vers l'arrière et positionner l'embout du flacon au-dessus de l'œil à traiter. Tirer la paupière inférieure vers le bas avec l'index d'une main. Presser sur le corps du flacon et une goutte de VISMED® MULTI s'écoulera facilement (voir illustrations). Sauf recommandation contraire, instiller 1 à 2 gouttes de VISMED® MULTI dans l'œil aussi souvent que nécessaire. Quelques clignements des paupières assureront une répartition uniforme de la solution sur la surface oculaire en un film transparent et durable. VISMED® MULTI peut être utilisé pendant le port de lentilles de contact (rigides ou souples).

Dompé

Précautions: Ne pas toucher l'embout du flacon ouvert et ne pas toucher la surface de l'œil avec l'embout du flacon. Replacer le capuchon protecteur du VISMED® MULTI après usage. Ne pas utiliser VISMED® MULTI si le flacon est endommagé. VISMED® MULTI peut être utilisé jusqu'à 3 mois après la première utilisation.
À conserver entre 2 °C et 25 °C! Ne pas utiliser VISMED® MULTI après la date de péremption indiquée sur le flacon et la boîte. Si les troubles persistent pendant l'utilisation de VISMED® MULTI, consulter un médecin. Tenir hors de portée des enfants.

Propriétés et mode d'action: VISMED® MULTI contient du hyaluronate de sodium, un polymère naturel également présent dans les structures de l'œil humain. Les caractéristiques physiques particulières du hyaluronate de sodium confèrent à VISMED® MULTI ses propriétés viscoélastiques et de rétention d'eau. VISMED® MULTI forme ainsi un film stable à la surface de l'œil qui n'est que très lentement éliminé par le battement des paupières. VISMED® MULTI allie ainsi un effet prolongé à un confort maximal. En raison de sa composition particulière, VISMED® MULTI est très bien toléré. VISMED® MULTI ne contient pas d'agent conservateur.

Présentation: 10 ml de solution en flacon multidose.

Dernière révision: Mars 2011

Légende des illustrations 1–4:
1 Enlever la bague d'inviolabilité.
2 Ôter le capuchon protecteur.
3 Instiller une à deux gouttes dans l'œil.
4 Replacer le capuchon protecteur après usage.

E LUBRIFICANTE OCULAR

Instrucciones de uso

VISMED® MULTI
Hialuronato sódico obtenido por fermentación al 0,18 %.
Lubricante ocular.
Estéril, sin conservantes.

Composición: 1 ml de solución contiene 1,8 mg de hialuronato sódico, cloruro de sodio, cloruro de potasio, fosfato disódico, citrato de sodio, cloruro de magnesio, cloruro de calcio y agua para preparaciones inyectables. La disolución es hipotónica.

Indicaciones: Síntomas y signos de ojo seco y/o daños en la superficie ocular, debido a enfermedades como la queratitis superficial, el síndrome de Sjögren o el síndrome del ojo seco primario. Para la lubricación de los ojos en caso de sensación de sequedad, quemazón o fatiga ocular, u otras dolencias menores sin importancia patológica, inducidas, por ejemplo, por el polvo, el humo, el calor seco, el aire acondicionado, el viento, el frío, o el uso prolongado de la pantalla del ordenador o de lentes de contacto (duras o blandas).

Contraindicaciones: Hipersensibilidad individual a alguno de los componentes del producto.

Interacciones: No utilice VISMED® MULTI al mismo tiempo que otros medicamentos o productos aplicados al ojo dado que puede modificar sus efectos.

Reacciones adversas: En muy raras ocasiones pueden aparecer trastornos transitorios tales como irritación de la conjuntiva, sensación de cuerpo extraño, enrojecimiento o sensación de quemazón en los ojos, así como visión borrosa a corto plazo.

Posología y forma de administración: Abra el precinto de seguridad antes de la primera administración. Retire la tapa protectora. Incline la cabeza hacia atrás y coloque la punta del envase sobre el ojo que va a tratar. Tire hacia abajo el párpado inferior con uno de los dedos índices. Presione el envase y saldrá con facilidad una gota de VISMED® MULTI (véanse las ilustraciones). Si no se recomienda lo contrario, instile 1 o 2 gotas de VISMED® MULTI en el ojo tantas veces como sea necesario. Después de parpadear, la solución se dispersará formando una capa transparente y duradera en la superficie del ojo. VISMED® MULTI también puede usarse con lentes de contacto (duras o blandas).

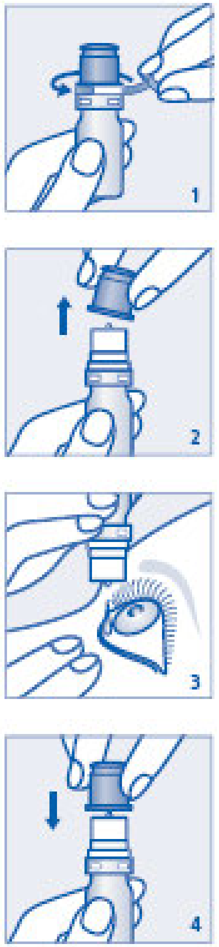
Precauciones: No toque la punta del envase abierto ni tampoco la superficie del ojo con la punta del envase abierto. Coloque de nuevo la tapa después de usar VISMED® MULTI. No use VISMED® MULTI si el envase está dañado. VISMED® MULTI puede ser utilizado hasta 3 meses después del primer uso.
Almacenar entre 2 °C y 25 °C. No usar VISMED® MULTI después de la fecha de caducidad indicada en el envase y en la caja. Consulte al médico si el malestar persiste con el uso de VISMED® MULTI. Manténgase fuera del alcance y de la vista de los niños.

Características y modo de acción: VISMED® MULTI contiene hialuronato sódico, un polímero natural que también está presente en las estructuras del ojo humano. Las características físicas particulares del hialuronato sódico le confieren a VISMED® MULTI sus propiedades viscoelásticas y de retención de agua. VISMED® MULTI crea una capa estable en la superficie del ojo que solamente se elimina lentamente al parpadear. Por lo tanto, VISMED® MULTI combina un alivio duradero con el máximo confort. VISMED® MULTI es bien tolerado debido a su composición única. VISMED® MULTI no contiene conservantes.

Presentación: 10 ml de solución en un envase multidosis.

Fecha de la última revisión del texto: Marzo 2011

Leyenda de las ilustraciones 1–4:
1 Abra el precinto de seguridad.
2 Retire la tapa protectora.
3 Instile una o dos gotas en el ojo.
4 Coloque de nuevo la tapa protectora después de su administración.



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VISMED® MULTI

NL BEVOCHTIGENDE OOGDRUPPELS

Gebruiksaanwijzing

VISMED® MULTI
Natriumhyaluronaat, kwaternair 0,18 %.
Bevochtigende oogdruppels.
Steriel, zonder conserveermiddelen.

Samenstelling: 1 ml oplossing bevat natriumhyaluronaat 1,8 mg, natriumchloride,kaliumchloride, natriumfosfaat, natriumcitraat, magnesiumchloride, calciumchloride en water voor injecties. De oplossing is hypotonisch.

Indicaties: Symptomen en tekenen van droogte en/of oppervlakkig letsel, door aandoeningen zoals oppervlakkige keratitis, syndromen van Sjögren of een primaire droge ogen. Voor lubrificatie van de ogen in geval van droog en branderig gevoel en oogvermoeidheid veroorzaakt door stof, rook, droge pathologische toestanden, bijvoorbeeld veroorzaakt door stof, rook, droge weersomstandigheden, airconditioning, wind, boulok, langdurig kijken naar computerschermen of contactlenzen (hard of zacht).

Contra-indicaties: Individuele overgevoeligheid voor een bestanddeel van dit product.

Wisselwerkingen: Gebruik VISMED® MULTI niet tegelijk met een geneesmiddel of ander product in het oog, moet worden toegepast, omdat de hun effect kan beïnvloeden.

Ongewenste effecten: In zeer zeldzame gevallen kunnen voorbijgaande steekpijnen optreden, zoals irritatie van het binnenlid, gevoel van vreemde voorwerpen, roodheid of branderig gevoel in het oog, kortstondige gezichtsvermoeidheid.

Dosering en wijze van gebruik: Verwijder de verzegelde sluiting voor de eerste toediening. Verwijder de beschermdop. Blijf het hoofd naar achteren en houd de tip van het flesje boven het te behandelen oog. Trek het onderste ooglid omlaag met de wijsvinger van één hand. Knijp in het flesje en zet één druppel van VISMED® MULTI uit vallen (zie afbeeldingen). Als niet eerder aanbevolen is, druppelt u zo vaak als nodig 1 of 2 druppels van VISMED® MULTI in het oog. Als u knippert, verspreidt de oplossing zich en vormt zo een doorzichtige en langhoudende laag op het oogoppervlak. VISMED® MULTI kan ook gebruikt worden tijdens het dragen van contactlenzen (hard of zacht).

Voorzorgsmaatregelen: Raak de tip van het gesprongde flesje niet aan. Raak ook de oppervlakte van het oog niet aan met de tip van het gesprongde flesje. Zet de dop na gebruik van VISMED® MULTI weer op het flesje. Gebruik VISMED® MULTI niet als het flesje beschadigd is. VISMED® MULTI kan gebruikt worden tot 3 maanden na het eerste gebruik.
Bewaren bij temperaturen tussen 2 en 25 °C! Gebruik VISMED® MULTI niet na de vervaldatum die vermeld staat op het flesje en de doos. Als de klachten aanhouden tijdens het gebruik van VISMED® MULTI, raadpleeg dan een arts. Buiten het bereik van kinderen houden.

Eigenschappen en werkingsmechanisme: VISMED® MULTI bevat natriumhyaluronaat, een natuurlijk polymeer dat van nature aanwezig is in de structuren van het menselijke oog. De bijzondere fysische kenmerken van natriumhyaluronaat verlenen VISMED® MULTI zijn visco-elastische en waterretentievermogen eigenschappen. VISMED® MULTI vormt een stabiele laag op het oogoppervlak die slechts traag verdwijnt met knipperen. Daarom combineert VISMED® MULTI langdurige werkzaamheid met maximaal comfort. VISMED® MULTI wordt goed verdragen door de unieke samenstelling. VISMED® MULTI is vrij van conserveermiddelen.

Verpakkingen: 10 ml oplossing in een multidosisrecipiënt.

Datum van laatste herziening: Maart 2011

Legende voor de afbeeldingen 1–4
1 Verwijder de verzegeling.
2 Verwijder de beschermdop.
3 **Druppel één of twee druppels in het oog.**
4 **Zet de beschermdop terug na toediening.**

I GOCCE OCULARI LUBRIFICANTI

Foglietto illustrativo

VISMED® MULTI
Sodio ialuronato ottenuto per fermentazione 0,18%.
Gocce oculari lubrificanti.
Sterile, senza conservanti.

Composizione: 1 ml di soluzione contiene 1,8 mg di sodio ialuronato, cloruro di sodio, cloruro di potassio, fosfato disodico, citrato di sodio, cloruro di magnesio, cloruro di calcio ed acqua per iniezioni. La soluzione è ipotonica.

Indicazioni: Sintomi e segni di secchezza oculare e/o di lesioni oculari superficiali, dovuti ad alcune malattie quali cheratite superficiale, sindrome di Sjögren o sindrome da secchezza oculare primaria. Per la lubrificazione oculare in caso di sensazione di secchezza, bruciore e affaticamento oculare e altri disturbi minori senza significato patologico indotti, ad esempio, da polveri, fumo, calore secco, aria condizionata, vento, freddo, lavoro prolungato allo schermo o uso di lenti a contatto (rigide o morbide).

Controindicazioni: Ipersensibilità individuale a qualsiasi componente del prodotto.

Interazioni: Non usare contemporaneamente ad altri farmaci o prodotti applicati sull'occhio; poiché VISMED® MULTI potrebbe modificarne gli effetti.

Effetti indesiderati: In rarissimi casi, possono comparire disordini transitori, quali irritazioni congiuntivali, sensazione di corpo estraneo, arrossamento o sensazione di bruciore oculare così come temporaneo offuscamento della visione.

Posologia e modo d'uso: Staccare il sigillo di garanzia prima della prima somministrazione. Togliere il cappuccio protettivo. Inclinare la testa all'indietro e posizionare la punta del flacone al di sopra dell'occhio da trattare. Con l'indice spostare la palpebra inferiore verso il basso. Premendo il flacone verrà fuoriuscire una goccia di VISMED® MULTI (vedere la figura). Se non percepito diversamente, instillare 1 o 2 gocce di VISMED® MULTI nell'occhio ogni volta che se ne sente la necessità. In seguito all'ammorbidimento delle palpebre, la soluzione si distribuirà e formerà un rivestimento trasparente e duraturo sulla superficie dell'occhio. VISMED® MULTI può essere usato anche con le lenti a contatto (rigide o morbide).

Precauzioni: Non toccare e non portare all'occhio la punta del flacone aperto. Riapplicare il cappuccio dopo l'uso di VISMED® MULTI. Non usare VISMED® MULTI se il flacone è danneggiato. VISMED® MULTI può essere usato fino a 3 mesi dopo il primo uso.
Conservare a temperature comprese tra 2 °C e 25 °C! Non usare VISMED® MULTI dopo la data di scadenza indicata sul flacone e sulla scatola polaghevole. Se il disturbo persiste durante l'uso di VISMED® MULTI, consultare un medico. Tenere fuori dalla portata dei bambini.

Caratteristiche e meccanismo d'azione: VISMED® MULTI contiene sodio ialuronato, un polimero naturale presente anche nelle strutture dell'occhio umano. Le particolari caratteristiche fisiche del sodio ialuronato conferiscono a VISMED® MULTI le sue proprietà viscoelastiche e idrotermiche. VISMED® MULTI crea un rivestimento stabile sulla superficie dell'occhio, che viene eliminato lentamente con l'ammiccamento palpebrale. In questo modo, VISMED® MULTI combina un sollievo di lunga durata con il massimo comfort. VISMED® MULTI è ben tollerato, grazie alla sua composizione unica. VISMED® MULTI non contiene conservanti.

Confezioni: 10 ml di soluzione in flacone multidose.

Data dell'ultima revisione: Marzo 2011

Leggenda delle figure 1–4:
1 **Togliere il sigillo di garanzia.**
2 **Togliere il cappuccio protettivo.**
3 **Instillare uno o due gocce nell'occhio.**
4 **Riapplicare il cappuccio protettivo dopo la somministrazione.**

P LUBRIFICANTE OFTÁLMICO

Folheto informativo

VISMED® MULTI
Hialuronato de sódio obtido por fermentação 0,18 %.
Lubrificante oftálmico.
Estéril, sem conservantes.

Composição: 1 ml da solução contém hialuronato de sódio 1,8 mg, cloreto de sódio, cloreto de potássio, fosfato dissódico, citrato de sódio, cloreto de magnésio, cloreto de cálcio e água para injetáveis. A solução é hipotónica.

Indicações: Sintomas e sinais de secura ocular e/ou lesões na superfície ocular devidas a doenças como queratite superficial, síndrome de Sjögren ou síndroma primário do olho seco. Para lubrificar os olhos em caso de sensação de secura, ardor e fadiga ocular e outras queixas menores sem significado patológico induzidas, por exemplo, por pó, fumo, calor seco, ar condicionado, vento, frio, utilização prolongada de monitores ou uso de lentes de contacto (rígidas ou não).

Contraindicações: Hipersensibilidade individual a algum dos constituintes do produto.

Interações: Não utilize VISMED® MULTI ao mesmo tempo que utiliza qualquer outro fármaco ou produto aplicado no olho, uma vez que pode alterar os seus efeitos.

Efeitos Indesejáveis: Em ocasiões muito raras, podem ocorrer distúrbios transitórios como irritação da conjuntiva, sensação de presença de corpo estranho, vermelhidão ou sensação de ardor no olho, visão enevoada de curta duração.

Posologia e modo de administração: Antes da primeira administração, rompa o selo que mostra que a embalagem não foi violada. Retire a tampa de proteção. Incline a cabeça para trás e posicione a extremidade da embalagem acima do olho a tratar. Puxe a pálpebra inferior para baixo com o indicador de uma das mãos. Aperte a embalagem e uma gota de VISMED® MULTI sairá facilmente (v. ilustrações). Caso não seja recomendado nada em contrário, instile 1 ou 2 gotas de VISMED® MULTI no olho tantas vezes quantas as necessárias. Depois de pestanejar, a solução dispersa e forma uma película transparente e duradoura sobre a superfície do olho. VISMED® MULTI também pode ser usado por pessoas portadoras de lentes de contacto (rígidas ou não).

Precauções: Não toque na extremidade da embalagem aberta nem na superfície do olho com a extremidade da embalagem. Volte a colocar a tampa depois de usar VISMED® MULTI. Não use VISMED® MULTI se a embalagem estiver danificada. VISMED® MULTI pode ser usado até 3 meses após a primeira utilização.
Conservar entre 2 °C e 25 °C! Não use VISMED® MULTI depois de expirar a data de validade indicada na embalagem e na caixa. Se o desconforto persistir durante a utilização de VISMED® MULTI, consulte um médico. Mantenha longe do alcance das crianças.

Propriedades e mecanismo de ação: VISMED® MULTI contém hialuronato de sódio, um polímero natural que também está presente nas estruturas do olho humano. As características físicas particulares do hialuronato de sódio conferem ao VISMED® MULTI as suas propriedades viscoelásticas e retentoras de água. VISMED® MULTI proporciona um revestimento estável na superfície do olho, o qual só vai sendo eliminado lentamente ao pestanejar. Por conseguinte, o VISMED® MULTI combina um alívio duradouro com o máximo conforto. VISMED® MULTI é bem tolerado graças à sua composição única. VISMED® MULTI não contém conservantes.

Apresentações: 10 ml da solução numa embalagem multidose.

Data da última revisão: Março 2011

Lenda das ilustrações 1–4:
1 Retire o selo que mostra que a embalagem não foi violada.
2 Retire a tampa de proteção.
3 Instile uma ou duas gotas dentro do olho.
4 Volte a colocar a tampa de proteção depois da administração.

GR ΥΓΡΑΝΤΙΚΟ ΔΙΑΛΥΜΑ ΜΑΤΙΩΝ

Οδηγίες χρήσεως

VISMED® MULTI
Υαλουρονικό νάτριο από ζύμωση 0,18 %.
Υγραντικό διάλυμα ματιών.
Αποστειρωμένο, χωρίς συντηρητικά.

Σύνθεση: 1 ml διαλύματος περιέχει 1,8 mg υαλουρονικού νάτριου καθώς και χλωριούχο νάτριο, χλωριούχο κάλιο, όξινο φωσφορικό νατρίου, κιτρικό νάτριο, χλωριούχο μαγνήσιο, χλωριούχο ασβέστιο και ύδωρ για ενέσιμα. Το διάλυμα είναι υποτονικό.

Ενδείξεις: Συμπτώματα και σημεία ξηροφθαλμίας και/ή βλάβης στην επιφάνεια του ματιού ως συνέπεια μερικών ασθενειών, όπως είναι η επιφανειακή κερατίτιδα, το σύνδρομο Sjögren ή το πρωτοπαθές σύνδρομο ξηροφθαλμίας. Ενδείκνυται για την ενύδατωση των ματιών όταν υπάρχει υποκειμενική αίσθηση ξηρότητας, όταν τα μάτια καίνε ή είναι κουρασμένα καθώς και άλλες τοπικές διαταραχές που δεν είναι επιβλαβείς για την υγεία, οι οποίες προξενήθηκαν π.χ. από σκόνη, καπνό, ξηρά θερμότητα, κλιματιζόμενο αέρα, αέρα, ψύχος, μεγάλης διάρκειας εργασία σε οθόνη οπτικής απεικόνισης ή χρήση φακών επαφής (σκληροί και μαλακοί).

Αντενδείξεις: Υπερευαισθησία σε ένα από τα συστατικά του προϊόντος.

Αλληλεπιδράσεις: Να μην χρησιμοποιείται ταυτόχρονα με φάρμακα ή άλλα προϊόντα, τα οποία είναι για τοπική χρήση μέσα στο μάτι, επειδή το VISMED® MULTI μπορεί να τροποποιήσει την δράση τους.

Ανεπιθύμητες ενέργειες: Σε πολύ σπάνιες περιπτώσεις μπορεί να παρουσιαστούν παροδικές τοπικές διαταραχές, όπως είναι π.χ. ερεθισμός του επιπεφυκότα, αίσθηση ξένου σώματος στους οφθαλμούς, ερυθρότητα ή αίσθηση καύσου των ματιών καθώς και θολή όραση για λίγη ώρα.

Δοσολογία και χρήση: Πριν από την πρώτη χρήση πρέπει να αφαιρείται η αρχική ασφάλεια στο προστατευτικό πώμα. Αφαιρείτε το προστατευτικό πώμα από το φιαλίδιο, γέρνετε το κεφάλι προς τα πίσω και κρατάτε το άνοιγμα της φιάλης πάνω από το πάσχον μάτι. Με τον δείκτη του ενός χεριού τραβάτε το κάτω βλέφαρο του ματιού προς τα κάτω ενώ ασκείτε ελαφριά πίεση στο φιαλίδιο και έτσι απελευθερώνεται μία σταγόνα του διαλύματος VISMED® MULTI (βλέπε απεικονίσεις). Εάν δεν συνιστάται κάτι διαφορετικό, σύμφωνα με τις ανάγκες ενσταλάξτε 1–2 σταγόνες VISMED® MULTI στο μάτι. Το διάλυμα κατανέμεται με τις ανοίξεις του βλεφάρου και σχηματίζει μία διαυγή και ανθεκτική στιβάδα υγρού στην επιφάνεια του ματιού. Το VISMED® MULTI μπορεί να χρησιμοποιηθεί και ενώ φοράτε σκληρούς ή μαλακούς φακούς επαφής.

Προφυλάξεις: Μην ακουμπάτε το σταγονομετρικό ρύγχος του ανοιγμένου φιαλιδίου και μην αγγίζετε το μάτι με αυτό. Επανατοποθετείτε το προστατευτικό πώμα μετά την χρήση του VISMED® MULTI. **Μην χρησιμοποιείτε φθαρμένες συσκευασίες του VISMED® MULTI.** Μετά την πρώτη χρήση, το VISMED® MULTI μπορεί να χρησιμοποιηθεί για ένα διάστημα 3 μηνών.
Να φυλάσσεται μεταξύ 2 °C και 25 °C! Μην χρησιμοποιείται το VISMED® MULTI μετά την πάροδο της ημερομηνίας λήξεως που αναγράφεται στο δοχείο και στο χαρτόνι συσκευασίας. Εάν τα συμπτώματά σας συνεχίζονται από την χρήση του VISMED® MULTI, θα πρέπει να αναζητήσετε θεραπευτική αγωγή από γιατρό. Να φυλάσσεται μακριά από παιδιά.

Χαρακτηριστικά και τρόπος δράσης: Το VISMED® MULTI περιέχει υαλουρονικό νάτριο, ένα φυσικό πολυμερές, το οποίο απαντάται και στις δομές του ανθρώπινου οφθαλμού. Τα ιδιαίτερα φυσικά χαρακτηριστικά του υαλουρονικού νάτριου προσδίδουν στο VISMED® MULTI τις σημαντικές του ελαστοϊξώδεις και υδρόφιλες ιδιότητες. Το VISMED® MULTI δημιουργεί μία σταθερή στιβάδα στην επιφάνεια του ματιού, η οποία απομακρύνεται μόνο σταδιακά με τις ανοίξεις του βλεφάρου. Για τον λόγο αυτό το VISMED® MULTI συνδυάζει δράση μεγάλης διάρκειας με μέγιστη άνεση. Το VISMED® MULTI έχει εξαιρετική συμβατότητα λόγω της ιδιαίτερης σύστασής του. Το VISMED® MULTI δεν περιέχει συντηρητικά.

Συσκευασία: 10 ml διαλύματος σε φιάλη πολλαπλών δόσεων.

Ημερομηνία του κειμένου: Μάρτιος 2011

Υπόμνημα για τις απεικονίσεις 1–4:
1 Αφαιρείτε την αρχική ασφάλεια.
2 Αφαιρείτε το προστατευτικό πώμα.
3 Ενσταλάζετε το διάλυμα στο μάτι.
4 Επανατοποθετείτε το προστατευτικό πώμα μετά την χρήση.

LOT
Chargenbezeichnung
Batch number
Numéro de lot
Número de lote
Charge nr.
Lotto n.
Αριθμός σειράς

Verwendbar bis ...
Expiry date
Date de péremption
Fecha de caducidad
Niet gebruiken na
Data di scadenza
Ημερομηνία λήξης

Gebrauchsanweisung beachten
Refer to instruction leaflet
Veuillez vous référer à la notice explicative
Consulte el prospecto de instrucciones
Raadpleeg bijsluiter
Vedere foglietto illustrativo
Διαβάστε τις οδηγίες χρήσης

STERILE A

2 °C – 25 °C

CE 0123

TRB CHEMEDICA
OPHTHALMIC LINE

TRB CHEMEDICA AG
Richard-Reitzner-Allee 1
85540 Haar/München, Germany

ANNEX C

MEDDEV 2.7/3 – Rev 3 - 2015

EUROPEAN COMMISSION
DG Internal Market, Industry, Entrepreneurship and SMEs
Consumer, Environmental and Health Technologies
Health technology and Cosmetics

MEDDEV 2.7/3 revision 3

May 2015

GUIDELINES ON MEDICAL DEVICES

CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC.

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector. These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC.

MEDICAL DEVICES DIRECTIVES
CLINICAL INVESTIGATION

GUIDELINES FOR ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC

Index

1. INTRODUCTION

This guidance defines Serious Adverse Event (SAE) reporting modalities and includes a summary tabulation reporting format. Individual reporting should be performed in accordance with national requirements. The objective of this guidance is to contribute to the notification of SAEs to all concerned National Competent Authorities (NCAs) [1] in the context of clinical investigations in line with the requirements of Annex 7 of Directive 90/385/EEC and Annex X of Directive 93/42/EEC, as amended by Directive 2007/47/EC. According to Annex 7 of Directive 90/385/EEC and to Annex X of Directive 93/42/EEC: ***"All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed."***

2. SCOPE

The reporting modalities and format set out in this guidance apply to pre-market [2] clinical investigations [3-4] conducted with:

a. Non-CE marked devices,

b. CE marked devices used outside the intended use(s) covered by the CE-marking.

The tabular format featured in the Appendix needs to be updated for each reportable event or for new findings/updates to already reported events. It shall be transmitted to all NCAs where the clinical investigation is being performed.

[1] For the purpose of this guidance," NCAs" encompasses the National Competent Authorities of the EU, the EEA and of Switzerland and Turkey.

[2] A specific guidance on Post Market Clinical Follow-Up Studies is available as MEDDEV 2.12/2 rev. 2: http://ec.europa.eu/health/medical-devices/files/meddev/2_12_2_ol_en.pdf .

[3] This includes pre-market clinical investigations:

- which started prior to 21 March 2010 and are continued after that date. [Note: reporting of SAE as covered in this guidance only started on 21 March 2010 with the implementation of Directive 2007/47/EC and is not retrospective.to SAEs that occurred prior to 21 March 2010].
- for pre-market clinical investigations involving CE marked comparator devices, SAEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported in accordance with these guidelines.

[4] Where the right to bear the CE marking has been obtained before the end of the clinical investigation, the SAE reporting continues until completion of the investigation, according to the clinical investigation plan.

3. DEFINITIONS (in line with EN ISO 14155)

Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation
NOTE: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
NOTE 1: This definition includes events related to the investigational device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.
b) led to a serious deterioration in health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

4. REPORTABLE EVENTS UNDER ANNEX 7 AND ANNEX X OF DIRECTIVES 90/385/EEC AND 93/42/EEC RESPECTIVELY

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of the above mentioned Directives [5] :

- any SAE,
- any Device Deficiency that might have led to a SAE if:
    a) suitable action had not been taken or

[5] The definition of the term SAE has changed over time. A distinction between SAE and device deficiencies was introduced with the adoption of standard ISO 14155 in 2011. While this MEDDEV document uses terminology according to the international standard, please be aware that the European medical device directives pre-date the split in the terminology. In order to fulfil reporting requirements under the European medical device directives, device deficiencies as well as SAE need to be documented during the course of the clinical investigation and reported to competent authorities as described in this chapter.

b) intervention had not been made or

c) if circumstances had been less fortunate

- new findings/updates in relation to already reported events.

Reportable events occurring in Third Countries [6] in which a clinical investigation is performed under the same clinical investigation plan have to be reported to the NCA(s) in accordance with this guidance. This includes events occurring in third Countries after European sites have closed.

5. REPORT BY WHOM.

Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer, the authorized representative or another person or entity [7-8].

6. REPORT TO WHOM.

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced [9-10] using the summary tabulation featured in the Appendix.

A list of clinical investigation contact points within the NCAs is published at the Commission's homepage.

7. REPORTING TIMELINES

7.1 Report by sponsor to NCAs.

[6] Countries other than Switzerland, Turkey and those belonging to the EU and the EEA.

[7] Note: Member States may also require separate reporting by clinical investigators/medical professionals.

[8] Note: SAEs concerning CE marked devices (e.g. comparators) which meet the vigilance reporting criteria may also need to be handled under the post-market surveillance/vigilance system.

[9] For the purpose of this guidance, an investigation is considered to have commenced in an individual Member State when the sponsor is authorized to start the investigation in accordance with the notification procedures in that Member State.

[10] Note: Member States may also require separate reporting to the Ethics Committee(s) and/or separate reporting to the other clinical investigators/study centers involved in the clinical investigation.

The sponsor must report to the NCAs where the clinical investigation has commenced:

- for all reportable events as described in section 4 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons [11] or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events as described in section 4 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

7.2 Report by the investigator to the sponsor

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events as defined under chapter 4 will be provided by the investigator to the sponsor immediately, but not later than 3 calendar days after investigational site study personnel's awareness of the event.

In some cases, a different periodicity or different modalities [12] may be agreed by the participating NCAs according to the investigational design and to the pathology under clinical investigation. This would allow adequate provision for clinical investigations (e.g. palliative oncology), in which SAE frequency is expected to be high due to progression of the disease. This needs to be agreed between the sponsor and relevant NCAs.

8. CAUSALITY ASSESSMENT

The relationship between the use of the medical device [13] (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and

[11] This includes:
A) events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, e.g. human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD). These concerns may be identified by either the NCA or the manufacturer.
B) the possibility of multiple deaths occurring at short intervals.
[12] In line with Annex 7.2.3.5 of Directive 90/385/EEC and Annex X.2.3.5 of Directive 93/42/EEC
[13] Intended as both medical device investigated in the investigation and comparator.

categorized.[14] During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

For the purpose of harmonising reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational [15] medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:
   - the event is not a known[16] side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has no temporal relationship with the use of the investigational device or the procedures;
   - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
   - the event involves a body-site or an organ not expected to be affected by the device or procedure;

[14] Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.
[15] Investigational device: any device object of the clinical investigation, including the comparators.
[16] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis [17], when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with investigational device use/application or procedures;
    - the event involves a body-site or organ that
        - the investigational device or procedures are applied to;

[17] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis [17], when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of

the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

9. REPORTING FORM

The reporting form template for the summary SAE tabulation is given in the Appendix of this document.

The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual reporting form. The sponsor shall identify the new/updated information in the status column of the tabular form featured in the Appendix as:
a = added = new reportable event;
m = modified = new finding/update to an already reported event;
u = unchanged.

Changes in a line should be highlighted in bold and/or colour in the respective column.
The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. English is the recommended language for the reporting form. The report should be sent by email in Excel to the participating NCAs, or an equivalent format which allows using the inserted filters.

Appendix – Summary Reporting Form

REFERENCES:

1. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, last amended by Directive 2007/47/EC.
2. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amended by Directive 2007/47/EC.
3. EN ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice

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MEDDEV 2.7/3 SAE Report Table v2

EUDAMED - ID:					
Title of Clinical Investigation:					
CIP Number:					
Contact person (Name, Address, E-Mail, Telephone Number)			Device type:		
MS+NCA Reference Numbers for all participating Countries:			Reference Member State:		
No. of Patients enrolled to date total:		No. of Patients enrolled to date (date of report) per country:	No. of Invest. Devices used to date total:		No. of Invest. Devices used to date per country:
Date of Report:	dd/mm/yyyy				

Status: A, M, U	Date Sponsor received Report of SAE (dd/mm/yyyy)	Countrycode	Study Center	Patient ID Code	SAE ID Code	Date of Procedure/ First Use (dd/mm/yyyy)	Date of Event Onset (dd/mm/yyyy)	SAE OR Dev. Def.	Description of event	action/ treatment/patient outcome	Relationship to Procedure: not related OR unlikely OR possible OR probable OR causal relationship	Relationship to Investigational Device: not related OR unlikely OR possible OR probable OR causal relationship	Unanticipated SADE: Yes OR No	Treatment Arm: Investigational Device/ Control Group/ blinded/ n.a.	Event Status: Resolved/ Resolved with Sequelae/ Ongoing/Death	Date of Event Resolution (dd/mm/yyyy)

Note 1: Submission of this report does not, in itself, represent a conclusion by the sponsor or the competent authority that the content of this report is complete or that the device(s) listed failed in any manner and/or that the device(s) caused or contributed to the alleged death or deterioration in the state of the health of any person.

Note 2: If additional columns are added to this form (for instance to include the opinion of the investigators), please add them next to the existing columns on the right. This form may be subjected to automatic analysis and addition of columns in between may interfere with automatic analysis. Widthening of columns can be applied without alteration of the order.

ANNEX D

Flowchart for guidance of adverse event and deficiencies categorization

Figures F.1 and F.2 of ISO 14155

Figures F.1 and F.2 provide guidance on questions that can be asked to categorize adverse events and device deficiencies but are not intended to show the interrelationship of categories.

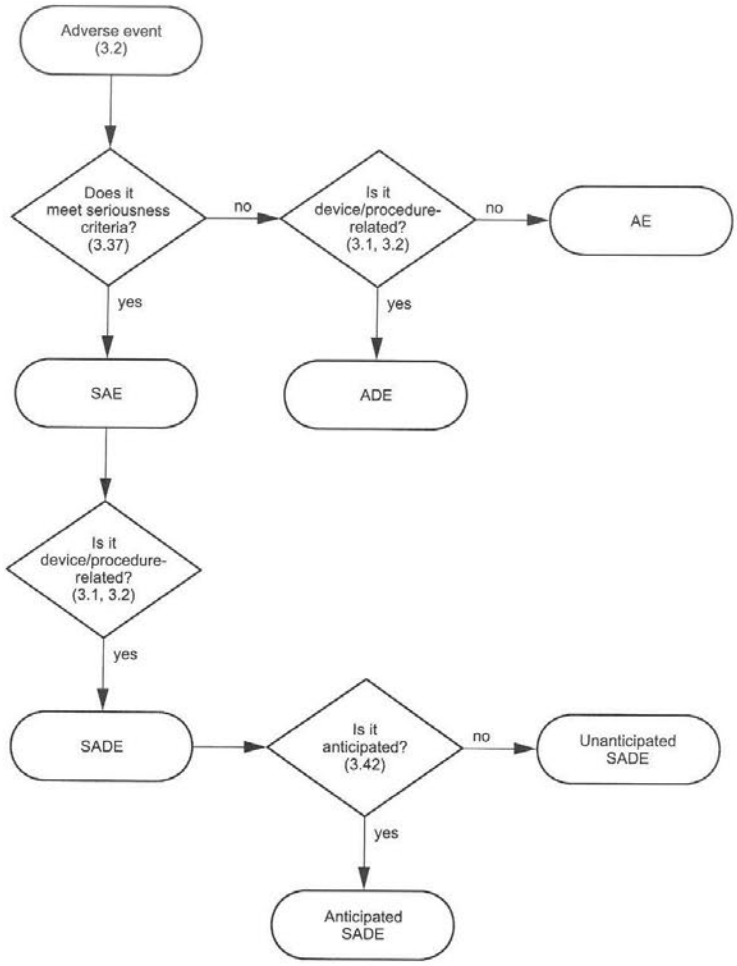

Figure F.1 — Adverse events categorization chart

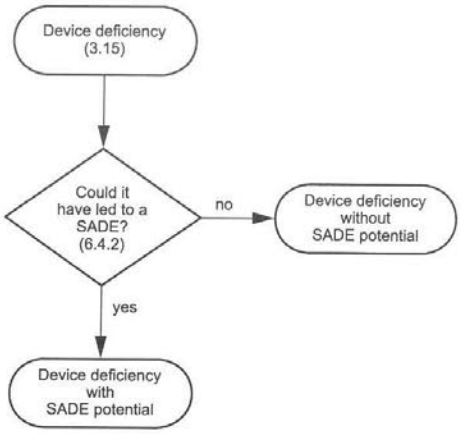

Figure F.2 — Device deficiency categorization chart