TITLE PAGE

A Study to Evaluate the Performance and Safety of CBL-102 versus Vismed® Multi Eye Drops in the Management of Dry Eye

PROTOCOL

STUDY # CBL-2017-01

Sponsor:

Laboratoire Chauvin

Affiliate of Bausch & Lomb Incorporated, a Valeant Pharmaceuticals International, Inc. company

This clinical investigation is being conducted in accordance with ISO 14155 (2011) Clinical Investigation of Medical Devices for Human Subjects, ICH GCPs, and applicable local regulations.

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SPONSOR APPROVAL PAGE

A Study to Evaluate the Performance and Safety of CBL-102 versus Vismed® Multi Eye Drops in the Management of Dry Eye

PROTOCOL

STUDY # CBL-2017-01

Author: [redacted]
Approved By:

[redacted]

10 - AUG - 2017
Date

27 July 2017
Date

09 August 2017
Date

The final document associated with this signature approval is maintained in the Trial Master File

INVESTIGATOR STATEMENT OF APPROVAL

A Study to Evaluate the Performance and Safety of CBL-102 versus Vismed® Multi Eye Drops in the Management of Dry Eye

PROTOCOL

STUDY # CBL-2017-01

I have read the attached document, concur that it contains all information necessary to conduct the study, and agree to abide by all provisions set forth therein.

I agree to conduct this study in accordance with ICH GCPs, ISO 14155 and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate IRB/EC and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent (and, if applicable, assent for children) from each study subject prior to performing any study specific procedures.

I understand that my signature on a case report form indicates that the data therein has been reviewed and accepted by me.

I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients when allowing the Sponsor of this clinical investigation, and/or relevant regulatory authorities and IRB/ECs, direct access to my medical records for study subjects.

_____

Principal Investigator, Printed Name

_____ _____

Principal Investigator, Signature Date

Upon signing, provide the original signed page to the Sponsor and retain a copy for your files.

PERSONNEL AND FACILITIES

NOTE: The information on this page is subject to change. All changes will be provided under separate cover.

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APPENDICES

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Term
AE	Adverse Event
ADE	Adverse Device Effect
ANCOVA	Analysis of Covariance
ART	Artificial Tears
ASADE	Anticipated Serious Device Adverse Events
ATC	Anatomical Therapeutic Classification
CFB	Change from Baseline
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
DD	Device Deficiency
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
EC	Ethics Committee
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
ITT	Intent-to-Treat
HRQoL	Health Related Quality of Life
LDPE	Low Density Polyethylene
MGD	Meibomian Gland Dysfunction
OSD-QoL	Ocular Surface Disease-Quality of Life
OTC	Over The Counter
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TID	Three Times Per Day
USADE	Unanticipated Serious Adverse Device Event
VA	Visual Acuity

NOTE: The first occurrence of some abbreviations is not spelled out in the document (eg, units of measure).

SYNOPSIS

CBL-102 Eye Drops Study # CBL-2017-01	
Title:	A Study to Evaluate the Performance and Safety of CBL-102 versus Vismed® Multi Eye drops in the Management of Dry Eye
Phase of study:	NA (Medical Device)
Number of study centers and subjects:	A total of approximately 84 subjects at approximately 14 clinical sites in France will be enrolled in this investigation.
Objective(s):	The primary objectives of this investigation are to show that the performance of CBL-102 Eye Drops is non-inferior to that of Vismed® Multi eye drops in subjects with moderate to severe keratoconjunctivitis sicca after 28 days, and to assess the safety of CBL-102 Eye Drops during a 90-day period with treatment administered 3 to 6 times per day.
Study design:	This is a multicenter, randomized, parallel group, investigator-masked, non-inferiority study. Approximately 84 subjects will be randomized in a 1:1 ratio to yield 33 subjects in each treatment group completing the study without major protocol deviations. Subjects will be randomized to one of the following treatment groups: • CBL-102 Eye Drops • Vismed® Multi Eye Drops Study duration will be approximately 15 weeks from screening to the last visit. Subjects will visit the clinic approximately 4 times. Visit 1 will be the Screening Visit and will occur 14 to 16 days prior to randomization. Subjects will be randomized to treatment on Visit 2 (Day 0). Visit 3 (Day 7 ± 1 day) will be a telephone visit, i.e. evaluation will be done on the phone for safety/compliance. After this interview, the investigator will determine whether the subject should come to the site or not. Then subjects will return to the clinic for assessment on Visit 4 (Day 28 ± 3 days), and Visit 5 (Day 90 ± 10 days). Subjects will begin artificial tear (ART) run-in on Day -14 (up to -16 days) and continue until Day 0. Subjects will begin investigational eye drop dosing on Day 0 and continue dosing for 90 days (± 10 days) of treatment. Subjects will be asked not to instill their tear substitute (if possible) within the hour before each visit.
Study endpoints:	**Primary Performance Endpoint** The primary performance endpoint for this study is mean change from baseline (CFB) in the study eye at Visit 4 (Day 28 ± 3 days) in ocular surface fluorescein staining score according to a scale from 0 to 15, combining corneal, nasal and temporal bulbar conjunctival fluorescein staining, each graded 0 to 5, according to the Oxford Scheme. The investigator will record the total score per eye (the maximum total score is 15 [maximum of 5 for each of the 3 areas]). The study eye will be the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye. **Secondary Performance Endpoints** The secondary endpoints will include the following: • Mean CFB in the study eye at Visit 5 in total ocular surface fluorescein staining score

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	□ Mean CFB in the study eye in fluorescein staining score for each area (cornea, nasal conjunctiva and temporal conjunctiva) at Visits 4 and 5 □ Mean CFB in the study eye in tear film break-up time (TFBUT) at Visits 4 and 5 □ Evolution from baseline of Ocular Surface Disease-Quality of Life (OSD-QoL®) questionnaire scores at Visit 5 for all 7 dimensions: Daily Activities, Handicap and Work Difficulties, Giving up Make-up, Acknowledgement, Acceptance, Fear for the Future and Emotional Well-Being,. □ Mean CFB in the global sum score of dry eye symptoms at Visits 4 and 5: sensation of dryness, foreign body, burning, stinging, itching, blurred vision, sensitivity to light, each graded from 0 to 4 □ Mean CFB in the study eye in volume of tear fluid secretion as assessed by the unanaesthetized Schirmer test at Visit 4 □ Frequency of investigational eye drop instillations, as reported in subject diary **Safety Endpoints** The safety endpoints for this study will include the following: □ Occurrence rates of ocular and non-ocular treatment emergent adverse events (TEAEs) □ Visual acuity (VA) measured with habitual correction, using Monoyer scale. **Tolerability and Ease-of use Endpoints** □ Assessment of investigational eye drop tolerability upon instillation as reported in subject diary □ Assessment of ease-of-use of the bottle as reported in subject diary
Criteria for inclusion:	1. Subjects must be of legal age (at least 18) on the date the Informed Consent Form (ICF) is signed and must be able to read, understand, and provide written voluntary informed consent on the Ethics Committee (EC) approved ICF 2. Subjects who are able and willing to comply with all treatment and follow-up/study procedures 3. Subjects who have been using tear substitutes for at least 2.5 months prior to inclusion, and who will use multidose preservative-free ART (Aqualarm® U.P. povidone 2% eye drops in 10 mL bottles) up to 6 times a day for at least 2 weeks immediately prior to randomization 4. Subjects with a score ≥ 1 for at least 2 out of the 7 following symptoms (rated 0 to 4): sensation of dryness, foreign body, burning, stinging, itching, blurred vision, sensitivity to light 5. Subjects with at least 1 eye with the following signs of keratoconjunctivitis sicca : □ Tear break-up time of □ 10sec (mean of 3 measurements) at both screening visit and inclusion visit □ Total ocular surface staining score ≥ 4 and ≤ 9 at both screening visit and inclusion visit. This assessment combines corneal, nasal and temporal bulbar conjunctival fluorescein staining, each graded 0-5 according to the Oxford Scheme 6. Subjects who have a decimal visual acuity (VA) with habitual correction equal to or better than 0.1 (Monoyer chart) in both eyes 7. Subjects with no systemic treatment or who are receiving stable

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	systemic treatment (unchanged for 1 month or longer) 8. For Female subjects, they must fall into 1 of the following categories: □ Post-menopausal □ Surgically sterile □ Using one of the following birth control methods throughout the duration of the study: o Intrauterine device (> 14 days) o Barrier method (condom or diaphragm) with spermicide (> 14 days) o Hormonal contraception (same dose and same formulation for at least 6 months) 9. For Female subjects who are of childbearing potential (i.e. who are not post-menopausal or not surgically sterile), they must have a negative urine pregnancy test result at screening
Criteria for exclusion:	**Ocular Exclusion Criteria** 1. Subjects with severe blepharitis defined by severe (a score of >2 from a range of 0 to 3) eyelid margin hyperemia or severe eyelid swelling or both and severe eyelid debris or severe plugging of meibomian glands or both. 2. Subjects who have severe ocular dryness accompanied by 1 of the following: □ Lid abnormality (except mild or moderate blepharitis) □ Corneal disease □ Ocular surface metaplasia □ Filamentary keratitis □ Corneal neovascularization 3. Subjects who currently wear contact lenses or have worn contact lenses within 90 days prior to study start 4. Subjects who have received ocular surgery, including laser surgery, in either eye within 180 days prior to study start 5. Subjects with a history of ocular trauma, non-dry eye ocular inflammation, or ocular infection within 90 days prior to study start 6. Subjects with a history of ocular allergic disease or ocular herpes within 1 year prior to study start 7. Subjects with a history of any inflammatory ulcerative keratitis, recurrent corneal erosion, or uveitis **Treatment Exclusion Criteria** 8. Subjects with known hypersensitivity or contraindications to any of the ingredients in the test or comparator products or ART (especially povidone, hyaluronic acid, boric acid, glycerol, Myritol and carbomer) 9. Subjects with initiation of, or changes to, concomitant medication that could affect dry eye within 30 days prior to Visit 1 (Screening) or with planned initiation or changes of such medications during the study 10. Subjects who have received ocular therapy (either eye) with any ophthalmic medication, except tear substitutes, within 2 weeks prior to study start 11. Subjects expected to receive ocular therapy during the study 12. Subjects treated with topical ocular steroidal or non-steroidal anti-

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	inflammatory medication within 30 days prior to study start 13. Subjects expected to receive ocular therapy with immunosuppressants (eg, cyclosporine) during the study or who have used ocular immunosuppressants within 90 days prior to study start 14. Subjects who have received occlusion therapy with non resorbable lacrimal or punctum plugs within 90 days prior to study start or subjects with resorbable plugs 15. Subjects who have received or who are planned to receive therapy such as LipiFlow® or BlephEx® **General Exclusion Criteria** 16. Females who are breastfeeding 17. Subjects participating in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation
Investigational product:	**Test Article:** The test article, CBL-102 Eye Drops, is a CE-marked medical device manufactured by Dr. Mann Pharma/Bausch & Lomb and containing 0.24% Hyaluronic acid salt, [redacted] Carbomer, [redacted] Medium chain triglycerides (Myritol), [redacted] Glycerol, [redacted] Sodium hydroxide and sterile water. The formula is unpreserved and presented in 10 mL bottles.
Comparator product and run-in therapy:	**Control Article:** The comparator product, Vismed® Multi ophthalmic solution (CE marked), contains 0.18% sodium hyaluronate, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, disodium hydrogen phosphate, sodium citrate, and water for injection. The formula is unpreserved and presented in 10 mL bottles. **Run-In Therapy:** Artificial tears will be dispensed as packaged for marketing. The run-in ART will be multidose preservative-free CE marked ART (Aqualarm® U.P. containing povidone 2%, sodium chloride, sodium hydroxide, boric acid and water for injections and presented in 10 mL bottles), manufactured by Dr. Gerhard Mann. The ART should be used no more than 6 times per day during the run-in period.
Study procedures:	**Visit 1 (Screening, Day -14 (up to -16 days))** Visit 1 will proceed as follows: ☐ Obtain written informed consent ☐ Determine if the subject meets preliminary eligibility criteria ☐ Collect demographic information ☐ Collect current and relevant medical and ophthalmic history ☐ Identify concomitant medications used ☐ Perform a urine pregnancy test, as applicable ☐ If the subject meets the preliminary eligibility criteria, perform the following: ☐ Symptoms assessment ☐ VA measurement ☐ Biomicroscopy assessments Biomicroscopy will be assessed for each of the following: o Lids o Ocular discharge o Conjunctiva (chemosis and hyperemia) o Cornea (erosion, edema, and infiltrates)

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	▯ TFBUT measurement ▯ Fluorescein staining ▯ If the subject meets the dry eye eligibility criteria on Visit 1, complete the following: ▯ Dispense a subject diary (Diary A) to record run-in ART instillation frequency per day ▯ Dispense run-in ART ▯ Remind the subject that both eyes should be treated as needed (not by habit) up to 6 times per day with run-in ART to relieve dry eye symptoms ▯ Instruct subject to bring run-in ART and subject diary (Diary A) to Visit 2 and that dry eye eligibility testing will be completed at Visit 2 **Visit 2 (Baseline, Day 0)** ▯ Collect adverse events (AEs) and changes in concomitant medications ▯ Collect subject diary (Diary A) and review for compliance ▯ Collect run-in ART ▯ Determine if the subject meets Visit 2 dry eye eligibility criteria by performing the following: ▯ Symptoms assessment ▯ VA measurement ▯ Biomicroscopy ▯ TFBUT measurement ▯ Fluorescein staining ▯ If the subject meets the dry eye eligibility criteria on Visit 2, proceed as follows: ▯ Perform the Schirmer test ▯ Have the OSD-QoL® questionnaire completed by the subject ▯ Dispense the investigational eye drops from the next sequential kit number to the subject ▯ Instruct the subject to instill 1 drop of the investigational eye drops in each eye 3 to 6 times per day ▯ Provide new subject diary (Diary B) to the subject to record investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the vial ▯ Instruct the subject to bring their subject diary with them to Visit 4 ▯ Instruct the subject to put their used and remaining unused bottles in the container (kit box provided at Visit 2) for retrieval at the end of the study **Visit 3 (Day 7, ± 1 day, Safety/compliance Telephone Assessment)** ▯ Assess treatment compliance ▯ Collect any adverse event since the previous visit and changes in concomitant medication

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	▯ Determine in the subject should come to the site for a visit or not If the subject comes to the site, proceed as follows: ▯ Confirm AEs and changes in concomitant medications ▯ Perform the following assessments: ▯ VA measurement ▯ Biomicroscopy ▯ Study personnel will review the subject diary (Diary B) for compliance and then return it to the patient For both the telephone assessment and the visit at site: ▯ Remind the subject to instill 1 drop of investigational eye drops in each eye 3 to 6 times per day ▯ Remind the subject to record investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the vial in the diary ▯ Instruct the subject to bring their subject diary with them to Visit 4 ▯ Remind the subject to continue to put their used and remaining unused bottles in the container (kit box provided at Visit 2) for retrieval at the end of the study **Visit 4 (Day 28, ± 3 days)** ▯ Collect AEs and changes in concomitant medications ▯ Perform the following assessments: ▯ Symptoms ▯ VA ▯ Biomicroscopy ▯ TFBUT measurement ▯ Fluorescein staining ▯ Schirmer test ▯ Collect subject diary (Diary B) and review for compliance ▯ Dispense new investigational eye drops kit ▯ Remind the subject to instill 1 drop of investigational eye drop in each eye 3 to 6 times per day ▯ Provide new subject diary (Diary C) to the subject ▯ Remind the subject to record in diary investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the vial ▯ Instruct the subject to bring their subject diary with them to Visit 5 ▯ Instruct the subject to put their used and remaining unused bottles in the container (kit box provided to them at Visit 4) and to bring the two kit boxes in a sealed container at Visit 5 **Visit 5 (Day 90, ± 10 days)** ▯ Collect AEs and changes in concomitant medications ▯ Perform the following assessments: ▯ Symptoms

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	☐ OSD-QoL® questionnaire ☐ VA ☐ Biomicroscopy ☐ TFBUT measurement ☐ Fluorescein staining ☐ Collect subject diary (Diary C) and review for compliance ☐ Collect the sealed container of investigational eye drops for accountability ☐ Exit the subject from the study ***NOTE: All investigational eye drops and subject diaries should be returned at this visit.***
Statistical methods:	A validated macro SAS v. 9.4 was used for sample size calculation. Assuming a unilateral α risk of 2.5%, a β risk of 10% (90% power), a non-inferiority margin of 2 and a standard deviation of 2.5 on the primary endpoint, a sample size of 33 evaluable subjects per treatment group is necessary to demonstrate non-inferiority of CBL-102 Eye Drops to Vismed® Multi. With a projected dropout rate of 10% and a protocol violation rate of 10%, a total of approximately 84 subjects with moderate to severe dry eye will be randomized in this clinical investigation. Summaries for continuous variables will include the sample size, mean, standard deviation (SD), median, minimum, and maximum. Calculations will be based on the number of subjects (or eyes) with non-missing values for the study population being summarized. Summaries for discrete variables will include the tabulation of frequencies and percentages. Percentages will be based on the number of subjects (eyes) with non-missing values. The denominator for percentage will be the number of subjects (eyes) from the study population being analyzed. The primary performance endpoint is the mean CFB to Day 28 in total ocular surface fluorescein staining score (corneal, nasal and temporal bulbar conjunctival fluorescein staining) with each area graded (0 to 5) according to the Oxford Scheme. The investigator will record the total score per eye (the maximum score is 15). The study eye will be the eligible eye with the highest total ocular surface staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye. An analysis of covariance (ANCOVA) model with main effects of treatment and baseline ocular surface staining score as covariates will be used to analyze the primary endpoint. Sensitivity analyses including investigator site as covariate will be performed. A 95% 2-sided confidence interval (CI) based on the ANCOVA model will be computed for the effect difference (CBL-102 Eye Drops minus Vismed® Multi). Non-inferiority will be demonstrated if the upper bound of the 95% CI is less than 2 grades in the per protocol (PP) analysis. Supportive analysis of the primary endpoint will be performed on the intent-to-treat (ITT) population. The same ANCOVA model will be used to analyze secondary continuous endpoints. Supportive analyses on secondary performance endpoints will be performed in the ITT and PP populations. Safety endpoints analysis will be performed on the safety population.

INTRODUCTION

Dry eye disease involves multiple physiological components and is a disease that is not completely understood. It is a common clinical problem, with surveys over the last 20 years estimating a prevalence of between 5% to more than 30% at various ages.[1] The 2007 Report of the International Dry Eye Workshop (DEWS) defines dry eye disease as "A multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".[2] Intrinsic factors such as aging, hormonal balance, autoimmune disease, or systemic medications, and extrinsic factors such as topical medications, environmental stresses, contact lens wear, or refractive surgery contribute to dry eye disease (DED).[2, 3]

Dry Eye Disease incidence increases significantly with age, (from 10.7% in subjects aged 48 to 59 years to 17.9% in those 80 years or older).[4]

The pathophysiology of DED involves multiple interacting mechanisms. Dysfunction of any lacrimal functional unit component can lead to DED by causing alterations in the volume, composition, distribution, and/or clearance of the tear film. Two mutually reinforcing global mechanisms, tear hyperosmolarity and tear film instability, have been identified[2].

Aqueous-deficient DED can be caused by either lacrimal alterations (including autoimmune disorders either primary or secondary to systemic autoimmune diseases such as rheumatoid arthritis) or blockade of reflex secretion or medications causes.[1]

Evaporative DED also has various causes, including meibomian gland disease, eyelid aperture disorders or lid/globe incongruity, blink disorders, and ocular surface disorders. The most common cause is meibomian gland dysfunction (MGD; also called posterior blepharitis), a condition of meibomian gland obstruction.[5]

Although these major categories seem clear-cut, in reality there is considerable overlap between them. Any form of dry eye may be associated with any other form.[6] Second, because of the interaction between the 2 global DED mechanisms, tear hyperosmolarity and tear film instability, the differentiation between aqueous deficient and evaporative DED is often unclear. Certain DED etiologies involve multiple mechanisms.

Patients with dry eye disease can suffer from ocular irritation and discomfort, photophobia, blurred vision and a host of other bothersome symptoms.

Tear substitutes represent the basis of dry eye treatment.[7] CBL-102 Eye Drops are a new CE marked multi-component tear substitute (i.e. medical device) designed to provide long-lasting moisturization of the eye by supporting the 3 layers of the tear film (lipid, aqueous and mucin) for the relief of dry eye. As a matter of fact, CBL-102 Eye Drops combine well known components used in the field of dry eye, i.e. 0.24% Hyaluronic acid salt, [redacted] Carbomer, [redacted] Medium chain triglycerides (Myritol); they also include [redacted] Glycerol, [redacted] Sodium hydroxide and [redacted] sterile water.

Hyaluronic acid, carbomer and glycerol are characterized by highly moisturizing properties and medium-chain triglycerides support the lipid layer of the tear film.

Hyaluronic acid is known for its properties of retention of water, slow release of moisture, tear film stabilization, lubrication and mucomimetic behaviour. It is a naturally occurring glycosaminoglycan that is present in the human eye structure and tear fluid, and it has been reported that hyaluronic acid concentrations were reduced in patients with dry eye.[8-9] Sodium hyaluronate eye drops have been shown to increase precorneal tear film stability and corneal wettability and reduce the healing time of corneal epithelium.[10-13] Clinically, sodium hyaluronate has been widely used in the management of dry eye[14-22] and it is a component of several tear substitutes approved for market in Europe.

Carbomer (carbopol 980) is a water soluble high molecular weight acrylic acid polymer that expand in aqueous media to form three-dimensional gel network, increasing tear stability and prolonging residence time.[23] Carbomer acts together with hyaluronic acid as viscosity modifier and protectant, providing relief to ocular symptoms and improvement of signs of dry eye.[24-26]

Medium chain triglycerides help restore the lipid layer and prevent evaporation of the aqueous phase[27-28].

The formula is free of buffer and unpreserved.

The main intended purpose of CBL-102 Eye Drops is to improve the lubrication and wetting of the ocular surface, and the tear film stability in both evaporative and aqueous-deficient dry eye.

CBL-102 Eye Drops are currently marketed in some European countries to provide relief and protection for dry eye caused by persistent tear dysfunction. They are not yet marketed in France.

1.0 OBJECTIVES

The primary objectives of this investigation are to show that the performance of CBL-102 Eye Drops is non-inferior to that of Vismed® Multi Eye Drops in subjects with moderate to severe keratoconjunctivitis sicca after 28 days, and to assess the safety of CBL-102 Eye Drops during a 90-day period with treatment administered 3 to 6 times per day.

2.0 STUDY DESIGN

2.1 Description of Study Design Including Choice of Control Groups

This is a multicenter, randomized, parallel group, investigator-masked, non-inferiority study to evaluate the performance and safety of CBL-102 Eye Drops in subjects with moderate to severe dry eye.

Subjects will visit the clinic approximately 4 times. Visit 1 will be the Screening Visit and will occur 14 to 16 days prior to randomization (Screening, Day -14 (up to -16 days). Subjects will be randomized to treatment on Visit 2 (Baseline, Day 0). Visit 3 (Follow-up Telephone call, Day 7 ± 1) will be done as a telephone call assessment for safety/compliance, and subjects will return to the clinic for assessment on Visit 4 (Follow-up, Day 28 ± 3), and Visit 5 (Study Exit, Day 90 ± 10). Subjects will be randomized on Visit 2 in a 1:1 ratio to 1 of the following investigational treatment groups:

- CBL-102 Eye Drops
- Vismed® Multi Eye Drops

Approximately 84 subjects of either gender, aged 18 or older, having a clinical diagnosis of moderate to severe dry eye disease in at least 1 eye at Visit 1 (Screening) and Visit 2 (Baseline) will be enrolled in the study.

The study will be conducted in a 90-day (± 10 days) treatment phase (assigned investigational eye drop, i.e. investigational medical device), preceded by a 2-week screening phase when subjects are limited to the use of run-in artificial tears (ART) only. The ART will be used up to 6 times a day as needed during the run-in period. In the treatment phase, subjects will instill 1 drop of investigational eye drops 3 to 6 times per day for 90 days (± 10 days).

2.2 Selection of Study Population

A total of up to approximately 84 subjects at approximately 14 clinical sites in France with a clinical diagnosis of moderate to severe keratoconjunctivitis sicca will be enrolled in this investigation.

2.2.1 Eligibility

2.2.1.1 Inclusion Criteria

1. Subjects must be of legal age (at least 18) on the date the Informed Consent Form (ICF) is signed and must be able to read, understand, and provide written voluntary informed consent on the Ethics Committee (EC) approved ICF
2. Subjects who are able and willing to comply with all treatment and follow-up/study procedures
3. Subjects who have been using tear substitutes for at least 2.5 months prior to inclusion, and who will use multidose preservative-free ART (Aqualarm® U.P. povidone 2% eye drops in 10 mL bottles) up to 6 times a day for at least 2 weeks immediately prior to randomization
4. Subjects with a score ≥ 1 for at least 2 out of the 7 following symptoms (rated 0 to 4): sensation of dryness, foreign body, burning, stinging, itching, blurred vision, sensitivity to light
5. Subjects with at least 1 eye with the following signs of keratoconjunctivitis sicca:
   - Tear break-up time of 10sec (mean of 3 measurements) at both screening visit and inclusion visit
   - Total ocular surface staining score ≥ 4 and ≤ 9 at both screening visit and inclusion visit. This assessment combines corneal, nasal and temporal bulbar conjunctival fluorescein staining, each graded 0-5 according to the Oxford Scheme
6. Subjects who have a decimal visual acuity (VA) with habitual correction equal to or better than 0.1 (Monoyer chart) in both eyes
7. Subjects with no systemic treatment or who are receiving stable systemic treatment (unchanged for 1 month or longer)

8. For female subjects, they must fall into 1 of the following categories:
   - Post-menopausal
   - Surgically sterile
   - Using one of the following birth control methods throughout the duration of the study:
     - Intrauterine device (> 14 days)
     - Barrier method (condom or diaphragm) with spermicide (> 14 days)
     - Hormonal contraception (same dose and same formulation for at least 6 months)
9. For female subjects who are of childbearing potential (i.e. who are not post-menopausal or not surgically sterile), they must have a negative urine pregnancy test result at screening

2.2.1.2 Exclusion Criteria

Ocular Exclusion Criteria

1. Subjects with severe blepharitis defined by severe (a score of >2 from a range of 0 to 3) eyelid margin hyperemia or severe eyelid swelling or both and severe eyelid debris or severe plugging of meibomian glands or both.
2. Subjects who have severe ocular dryness accompanied by 1 of the following:
   - Lid abnormality (except mild or moderate blepharitis)
   - Corneal disease
   - Ocular surface metaplasia
   - Filamentary keratitis
   - Corneal neovascularization
3. Subjects who currently wear contact lenses or have worn contact lenses within 90 days prior to study start
4. Subjects who have received ocular surgery, including laser surgery, in either eye within 180 days prior to study start
5. Subjects with a history of ocular trauma, non-dry eye ocular inflammation, or ocular infection within 90 days prior to study start
6. Subjects with a history of ocular allergic disease or ocular herpes within 1 year prior to study start
7. Subjects with a history of any inflammatory ulcerative keratitis, recurrent corneal erosion, or uveitis

Treatment Exclusion Criteria

8. Subjects with known hypersensitivity or contraindications to any of the ingredients in the test or comparator products or ART (especially povidone, hyaluronic acid, boric acid, glycerol, Myritol and carbomer)
9. Subjects with initiation of, or changes to, concomitant medication that could affect dry eye within 30 days prior to Visit 1 (Screening) or with planned initiation or changes of such medications during the study
10. Subjects who have received ocular therapy (either eye) with any ophthalmic medication, except tear substitutes, within 2 weeks prior to study start
11. Subjects expected to receive ocular therapy during the study
12. Subjects treated with topical ocular steroidal or non-steroidal anti-inflammatory medication within 30 days prior to study start
13. Subjects expected to receive ocular therapy with immunosuppressants (eg, cyclosporine) during the study or who have used ocular immunosuppressants within 90 days prior to study start
14. Subjects who have received occlusion therapy with non resorbable lacrimal or punctum plugs within 90 days prior to study start or subjects with resorbable plugs
15. Subjects who have received or who are planned to receive therapy such as LipiFlow® or BlephEx®

General Exclusion Criteria

16. Females who are breastfeeding
17. Subjects participating in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation

2.2.2 Subject Completion

A subject has completed the study after completion of Visit 5 (Study Exit, Day 90 ± 10). Subjects who require further follow-up for an AE will be followed according to Section 6.8.

2.2.3 Subject Discontinuation

A subject MAY be discontinued (at the discretion of the Investigator, the Sponsor, and/or the EC) prior to the final visit for several reasons, including, but not limited to:

- A serious adverse event (SAE) occurring during the course of the study, which precludes continued treatment or follow-up
- The subject not following required study procedures
- If a subject exhibits intolerable AEs (related or not related to the investigational medical device), or if a subject fails to show improvement or the clinical status worsens, the treating Investigator may opt to withdraw the subject from the study and implement necessary intervention.

A subject MUST be discontinued prior to the final visit for any of the following reasons:

- Voluntary withdrawal
- Death
- Investigator decision that it is not in the best medical interest of the subject to continue participation in the investigation. In case a subject administers more than 8 instillations per day for both eyes on a regularly continued basis (approximately 70 %) as assessed on Visit 4, the subject will be discontinued from the study and the investigator will prescribe an appropriate treatment.

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final visit, obtain as much follow-up data as possible, and to retrieve all investigational materials. Adverse events will be followed as described in Section 6.5 . Subject withdrawals will be documented clearly on the source document and applicable electronic case report form (eCRF). The assessments scheduled for Visit 5 should be performed at this early termination visit.

Notification of subject discontinuation will be made to the Sponsor Representative and will be clearly documented on the applicable eCRF. Any subject discontinued from the study will not be replaced.

2.2.4 Screening Failures

Subjects failing to meet eligibility criteria at Visit 1 (Screening) and Visit 2 (Baseline/Randomization) are considered screening failures.

2.2.5 Lost to Follow-up

Subjects who do not return for scheduled follow-up visits, as defined by the visit window and cannot be contacted, may be considered lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed.

2.3 Investigators

- The study will be conducted at approximately 14 investigative sites located in France.
- The study will be conducted by Investigators who are determined by the Sponsor or Sponsor Representative to be suitably qualified by training and experience to conduct this study in compliance with all applicable GCPs and local regulations.
- Each Investigator will enroll approximately 6 subjects. In the event that selected sites do not meet full enrollment, the Sponsor may decide to increase enrollment as needed at other currently active sites and additional sites may be added to satisfy the enrollment requirements of the study.

2.4 Study Duration

The duration of the study, including the time to enroll all subjects, will be approximately 10 months.

Study duration per subject will be approximately 15 weeks from screening to the last visit. Subjects will begin ART run-in on Day -14 (up to -16 days) and continue until Day 0. Subjects will begin investigational medical device dosing on Day 0 and continue

dosing for 90 days (± 10 days) of treatment. Last dose of investigational medical device will be administered on the day of the last visit.

2.5 Treatments

Approximately 84 subjects will be randomized in a 1:1 ratio to receive either CBL-102 Eye Drops or Vismed® Multi.

At least 1 eye in each subject must meet eligibility criteria at Visit 1 (Screening) and Visit 2 (Randomization), as indicated in the inclusion criteria. Both eyes will be treated with investigational eye drops starting at Visit 2.

Beginning with Visit 1, both eyes may be treated as needed (not by habit) up to 6 times per day with run-in ART to relieve symptoms of dry eye syndrome. The subject must record the frequency of run-in ART instillations daily on the diary provided.

Starting with Visit 2, subjects will begin dosing with investigational eye drops (i.e. investigational medical device) for total treatment duration of 90 days (± 10 days). The frequency of investigational eye drop instillations will be recorded on the diary provided to the subjects as well as the tolerability upon instillation and the assessment of the ease-of-use of the bottle.

3.0 STUDY MATERIALS

All study materials are CE marked devices and are being tested within the scope of their intended use.

To maintain a level of treatment masking, the outer carton of control article will be packaged identically to the test article, labeled with identical study-specific information.

3.1 Description of Test Article

The test article, CBL-102 Eye Drops, is a CE marked medical device containing 0.24% Hyaluronic acid salt, [redacted] Carbomer, [redacted] Medium chain triglycerides (Myritol), [redacted] Glycerol, [redacted] Sodium hydroxide and [redacted] sterile water. The formula is unpreserved and presented in bottles with a fill volume of 10 mL.

3.2 Description of Comparator Article

The comparator article, Vismed® Multi ophthalmic solution (CE marked), contains 0.18% sodium hyaluronate, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, disodium hydrogen phosphate, sodium citrate, and water for injection. The formula is presented in preservative-free bottles of 10 mL.

3.3 Description of run-in Article

The run-in therapy will be dispensed as packaged for marketing. The run-in ART will be multidose preservative-free CE marked ART (Aqualarm® U.P. eye drops in 10 mL bottles) containing povidone 2%, boric acid, sodium chloride, sodium hydroxide and water for injection.

3.4 Instructions for Use and Administration

The subject will be instructed by the site staff on the proper instillation of the topical eye drops as follows:

Preservative-free multidose bottles for the run-in period:

Before first use or after not having used it for a certain time, the pump should be primed: remove the cap and overturn the bottle down, press the device several times (around 20) until a drop appears. The device is ready for use.

1. Carefully wash your hands before using the device.
2. Remove the protective cap from the tip of the bottle before each use. Make sure that your fingers or any other surface do not touch the tip of the bottle so as to avoid any contamination of the solution.
3. Lean your head back slightly. Gently pull your lower eyelid down with a finger of your free hand, hold the bottle vertically above your eye and press the pump mechanism to apply one drop into your eye. Avoid touching the eye surface with the tip of the bottle to prevent any possible injury. Close your eye then roll it slowly in all directions to optimally spread the drop on the surface of your eye.
4. Immediately after use, shake the bottle to remove potential remaining drops and replace the protective cap on the dry tip of the bottle.

The ART will be used up to 6 times a day as needed during the run-in period.

After the run-in period, eligible subjects will be dispensed a kit at Visit 2 and resupplied with a kit at Visit 4. The kit dispensed at Visit 2 will contain investigational eye drops to dose for the first approximate 30 days of treatment. The kit dispensed at Visit 4 will contain investigational eye drops to dose for the remaining approximate 70 days of treatment.

For the treatment period, multidose bottles instructions for use are as follows:

1. Carefully wash your hands
2. If there is a tamper-evident seal, remove it before first use.
3. Turn up and remove the protective cap from the tip of the bottle before each use. Make sure that the tip of the bottle does not touch your fingers. Before first use, if there is a pump mechanism, lean the bottle downwards and squeeze the bottle several times until a drop appear.
4. Lean your head back slightly and gently pull your lower eyelid down with a finger of your free hand and hold the bottle vertically above your eye with the nozzle pointing downwards.
5. Make sure that the tip of the bottle does not touch your eye to prevent any possible injury or damage. Then, gently squeeze the bottle or the pump mechanism to apply 1 drop into the eye.
6. Close your eye afterwards and slowly roll it in order to optimally spread the drop on the surface of your eye.

7. Just after use, shake to remove potential remaining drops and replace the cap on the bottle.

Subjects will be instructed to instill 1 drop of their assigned investigational eye drops 3 to 6 times per day according to the kit instructions for 90 days (± 10 days) starting at Visit 2. The frequency of instillations must be recorded in the subject diary provided by the Sponsor. Subject instillation instructions will be provided.

Subjects will also be instructed to maintain whatever lid hygiene practices are employed at the time of randomization throughout the study. If lid hygiene practices (eg, warm compresses or lid scrubs or masks) have been prescribed for the subject, they should continue to do so prior to instillation of investigational eye drop; if not, subjects should not initiate these practices during the study.

Storage Requirements:

All investigational material must be stored in an upright position, in an area free from environmental extremes, at controlled temperatures between 2-25ºC in accordance with the conditions specified on the study label. The product should be kept away from sunlight. The storage location at the clinical site must have limited access, available to study personnel only and temperature must be controlled appropriately.

Should a temperature extreme occur, then the Study Manager should be contacted prior to further use of the material. The contact information is located on the Personnel and Facilities page of this protocol.

3.5 Other Materials

The Sponsor will supply the following additional study materials:

- Diaries
- OSD-QoL® questionnaires
- fluorescein strips
- Sterile saline single dose units
- Schirmer test strips (for unanesthetized testing)
- Yellow barrier filter for slit lamp
- Stopwatch
- Urine pregnancy test kits
- Temperature recorder

3.6 Packaging and Labeling

The test articles will be packaged and labeled in a manner consistent with the study design.

Investigational eye drop kits will be provided at Visits 2 and 4. The kit dispensed at Visit 2 will contain 7 bottles of investigational eye drops to dose for the first approximate 30 days of treatment. The kit dispensed at Visit 4 will contain 16 bottles of investigational eye drops to dose for the remaining approximate 70 days of treatment. Within each kit will be 10mL bottles of investigational eye drops.

Supply labeling will minimally include the protocol number, kit identification (ID) number, product description, directions for use, storage conditions, caution statement and Sponsor information. The labeling may also contain additional information as required by local regulations.

Each kit will be labeled with a 2-part tear-off label. Upon dispensing, the site designee will remove the tear-off portion and affix it to a printed form (label page) provided by the Sponsor. The printed form must be placed in a binder maintained by the Investigator or designee.

3.7 Accountability

During the course of the study, the Investigator will be responsible for keeping current and accurate records of the amount of study boxes received and dispensed, and its disposition. All study kits must be stored under the appropriate conditions in a secure area and are to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. The Investigator must maintain an inventory of kits dispensed to the subject, including subject identifiers. At time points throughout the study and/or upon completion of the study, the Sponsor's representative will review and verify the Investigative Site inventory.

To maintain Investigator masking, an unmasked designee will be responsible for investigational eye drops accountability.

Upon completion of the study, the unmasked Sponsor's representative will review and verify the test articles accountability. Following verification, and as directed by the Sponsor, study articles must be returned to the designated Contract Development and Manufacturing Organization at the address on the Personnel and Facilities page.

3.8 Masking/Unmasking

The Investigator and Sponsor personnel involved in the monitoring or conduct of the study will be masked to the investigational eye drop codes. Investigational eye drops kits will be packaged in a sealed outer carton to maintain treatment masking upon dispensation. Subjects will be instructed to put their used and remaining unused bottles in the containers (kit boxes provided to them at Visits 2 and 4) and to bring the sealed containers at Visit 5. An unmasked designee, who is responsible for collecting returned investigational eye drops for accountability at study end, may not be masked to the investigational eye drop codes.

The randomization list will be produced prior to study enrollment.
Investigational eye drop codes will not be available to the above personnel until after the study is completed and the database is finalized. If unmasking is necessary, sealed unmasking envelopes will be unsealed by the Investigator to reveal the treatment assigned to the subject.

The Investigator must notify the Sponsor as soon as possible after unmasking. In addition, the Investigator must record the date, time, and reason for unmasking the investigational medical device in the source documentation.

3.9 Methods of Assigning Subjects to Treatment Groups

3.9.1 Treatment Allocation

During Visit 1 (Screening) subjects who fulfill all inclusion criteria and none of the exclusion criteria will receive Aqualarm® U.P. for run-in ART.

During Visit 2 (Baseline/Randomization), subjects who fulfill all inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive either CBL-102 Eye Drops or Vismed® Multi.

3.9.2 Randomization Method

The randomization list will be produced prior to study enrollment by an unmasked statistician who is not otherwise involved in the study. Each randomization number will correspond to a treatment group assignment. Investigational eye drop kits will be dispensed in consecutive order from the lowest sequential kit number available at the site.

3.9.3 Treatment Replacement

In the event that a subject's original kit is lost, damaged, or consumed prior to the end of treatment, the Investigator will contact the Sponsor's Representative as soon as he/she is made aware of the need of a replacement kit. The Sponsor's Representative will ask the Contract Development and Manufacturing Organization to provide a replacement kit corresponding to the subject treatment straight away.

4.0 PERFORMANCE AND SAFETY VARIABLES

4.1 Primary Performance Variables

Clinical assessments of ocular surface fluorescein staining will be performed according to the schedule in Appendix A and graded according to the 0 to 5 scale in Appendix C. The primary performance variable is the mean change from baseline (CFB) in ocular surface fluorescein staining score according to a scale from 0 to 15 in the study eye at Visit 4. The ocular surface staining score is the combination of corneal, nasal and temporal bulbar conjunctival fluorescein staining (each graded from 0 to 5). These evaluations will be performed by the same ophthalmologist for the same patient at all visits.

4.2 Secondary Performance Variables

Each performance variable will be performed according to the schedule in Appendix A.

Individual clinical assessments of fluorescein staining (cornea, nasal and temporal bulbar conjunctiva) each graded according to the 0 to 5 scale in Appendix C will be determined. Mean CFB for each individual staining score and for the total ocular surface staining score will be determined.

Clinical assessment of tear film break-up time (TFBUT) will be performed as defined in Appendix B. Mean CFB in TFBUT will be determined.

Clinical assessment of tear fluid secretion will be measured by the unanaesthetized Schirmer test according to Appendix B. Mean CFB in volume of tear fluid secretion will be determined.

Discomfort linked to dry eye disease will be evaluated through 7 items: sensation of dryness, foreign body, burning, stinging, pruritus, blurred vision and sensitivity to light, each graded from 0 to 4 as defined in Appendix B.

Impact of dry eye disease symptoms on patients' health-related quality of life (HRQoL) will be evaluated using the ocular surface disease quality of life (OSD-QoL®) questionnaire. Subjects will be instructed to complete the questionnaire according to Appendix B. OSD-QoL® scores will be calculated.

The frequency of investigational eye drop instillation will be captured every day in subject diaries.

4.3 Safety Variables

The incidence and type of ocular and non-ocular treatment-emergent adverse events (TEAEs) will be assessed. All adverse events reported by the subject or observed by the investigator at each visit, will be collected from the time the subject signs the ICF until study exit.

Visual acuity (VA) testing will be performed at each visit. Visual acuity will be measured with habitual correction at each visit using a Monoyer chart. The same VA testing method is to be employed for all visits for each subject.

Biomicroscopy assessments will be performed at each visit. Biomicroscopy variables will be evaluated using the grading scales defined in Appendix B.

4.4 Tolerability and Ease-of-Use Variables

Investigational eye drop tolerability (eye drop sensation upon instillation), as reported by each subject, will be captured in subject diaries as defined in Appendix B.

Ease-of-use of the bottle will be also assessed by each subject and captured in the diary according to Appendix B.

4.5 Appropriateness of Variables

In this study, all assessments and variables to assess the performance and safety of CBL-102 Eye Drops are considered standard practice in the field of ophthalmology for diagnosis and management of subjects with dry eye[29-33].

Ocular surface staining has been chosen as the primary endpoint as it assesses the protective properties of the tear substitutes on the cornea and conjunctiva in dry eye[13]. The Oxford Scheme provides a logarithmic scale for grading of the ocular surface staining and is considered valuable for distinguishing changes[29-30].

4.6 Risk Assessment

In rare cases Aqualarm® U.P., CBL-102 Eye Drops, and Vismed® Multi can cause hypersensitive reactions such as local allergic reactions. Refer to the patient information leaflet for approved product information for Aqualarm® U.P., CBL-102 Eye Drops, and Vismed® Multi which will be provided with the ICF.
The subjects will be informed of any known risks in the ICF. If additional risks are identified, the Sponsor will notify the Investigators.

5.0 STUDY METHODS

5.1 Study Visits

Refer to Appendix A for a schedule of visits and parameters and Appendix B for methods of clinical evaluation.

Subjects will be asked not to instill their tear substitute (if possible) within the hour before each visit.

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent will sign and date the EC-approved ICF, at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject. In addition, the applicable privacy regulation requirements must be met. An ICF must be signed prior to the start of any study-related procedures/assessments.

5.1.1 Visit 1 (Screening, Day -14 (up to -16 days))

- After obtaining written informed consent, prospective subjects will be screened to determine whether they meet the preliminary eligibility criteria for the study as follows:
  - Collect demographic information
  - Collect current and relevant medical and ophthalmic history
  - Identify concomitant medications used
  - Perform a urine pregnancy test, as applicable
- If the subject meets the preliminary eligibility criteria, perform the following:
  - Symptoms assessment
  - VA measurement
  - Biomicroscopy assessments

  Biomicroscopy will be assessed for each of the following:
    - Lids
    - Ocular discharge
    - Conjunctiva (chemosis and hyperemia)
    - Cornea (erosion, edema, and infiltrates)
  - TFBUT measurement
  - Fluorescein staining
- If the subject meets the dry eye eligibility criteria on Visit 1, complete the following:

- Dispense a subject diary (Diary A) to record run-in ART instillation frequency per day
- Dispense run-in ART
- Remind the subject that both eyes should be treated as needed (not by habit) up to 6 times per day with run-in ART to relieve dry eye symptoms
- Instruct subject to bring run-in ART and subject diary (Diary A) to Visit 2 and that dry eye eligibility testing will be completed at Visit 2

5.1.2 Visit 2 (Baseline/Randomization, Day 0)

- Collect AEs and changes in concomitant medications
- Collect subject diary (Diary A) and review for compliance
- Collect run-in ART
- Determine if the subject meets Visit 2 dry eye eligibility criteria by performing the following:
  - Symptoms assessment
  - VA measurement
  - Biomicroscopy
  - TFBUT measurement
  - Fluorescein staining
- If the subject meets the dry eye eligibility criteria on Visit 2, proceed as follows:
  - Perform the Schirmer test
  - Have the OSD-QoL® questionnaire completed by the subject
  - Dispense the investigational eye drops from the next sequential kit number to the subject
  - Instruct the subject to instill 1 drop of investigational eye drops in each eye 3 to 6 times per day
  - Provide new subject diary (Diary B) to the subject to record investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the bottle
  - Instruct the subject to bring their diary (Diary B) with them to Visit 4
  - Instruct the subject to put their used and remaining unused bottles in the container (kit box provided at Visit 2) for retrieval at the end of the study

5.1.3 Visit 3 (Day 7 ± 1 day, Safety/compliance Telephone Assessment)

- Assess treatment compliance
- Collect any adverse event since the previous visit and changes in concomitant medication

- Determine in the subject should come to the site for a visit or not

If the subject comes to the site, proceed as follows:

- Confirm AEs and changes in concomitant medications
- Perform the following assessments:
  - VA measurement
  - Biomicroscopy
- Study personnel will review the subject diary (Diary B) for compliance and then return it to the patient

For both the telephone assessment and the visit at site:

- Remind the subject to instill 1 drop of investigational eye drops in each eye 3 to 6 times per day
- Remind the subject to record investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the bottle in diary
- Instruct the subject to bring their subject diary with them to Visit 4
- Remind the subject to continue to put their used and remaining unused bottles in the container (kit box provided at Visit 2) for retrieval at the end of the study

5.1.4 Visit 4 (Day 28 ± 3 days)

- Collect AEs and changes in concomitant medications
- Perform the following assessments:
  - Symptoms
  - VA
  - Biomicroscopy
  - TFBUT measurement
  - Fluorescein staining
  - Schirmer test
- Collect subject diary (Diary B) and review for compliance
- Dispense new investigational eye drops kit
- Remind the subject to instill 1 drop of investigational eye drop in each eye 3 to 6 times per day
- Provide new subject diary (Diary C) to the subject

- Remind the subject to record in diary investigational eye drop instillation frequency, investigational eye drop tolerability upon instillation and ease-of-use of the bottle
- Instruct the subject to bring their subject diary with them to Visit 5
- Instruct the subject to put their used and remaining unused bottles in the box (kit box provided at Visit 4) and to bring the two kit boxes in a sealed container at Visit 5

5.1.5 Visit 5 (Study Exit, Day 90 ± 10 days)

- Collect AEs and changes in concomitant medications
- Perform the following assessments:
  - Symptoms
  - OSD-QoL® questionnaire
  - VA
  - Biomicroscopy
  - TFBUT measurement
  - Fluorescein staining
- Collect subject diary (Diary C) and review for compliance
- Collect the sealed container of investigational eye drops for accountability
- Exit the subject from the study

NOTE: All investigational eye drops and subject diaries should be returned at this visit.

5.1.6 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

If a subject is seen for multiple visits during a given visit time frame, the data from the visit that is intended to meet the protocol requirements for the scheduled visit should be captured on the visit eCRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol required scheduled visit eCRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit eCRF.

5.1.7 Missed Visits

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

5.2 Post-study Follow-up

If a subject requires further follow-up on AEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Refer to Sections 6.0 for follow-up of AEs following study exit.

5.3 Study Completion

The Sponsor Representative will contact the EC to inform them that the study is completed.

5.3.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, then the study will be terminated and appropriate notification will be given to the Investigator(s), EC, and Local Health Authority, as applicable. The Sponsor will instruct the Investigators to stop dispensing study materials/treatment and to arrange for study closeout at each site.

5.4 Concomitant Medications/Therapy

Administration of all medications used up to 30 days prior (immunosuppressants up to 90 days prior) to study entry (date ICF signed) through study exit must be reported in the source and appropriate section of the Concomitant Medications eCRF.

5.4.1 Permitted Therapy

- With the exception of the disallowed medications in Section 5.4.2, any medications that, in the Investigator's judgment, will not interfere with the study parameters are allowed to be used concurrently.
- Concomitant systemic medication that could affect dry eye (Section 5.4.2) but whose condition is stable for at least 1 month prior to Visit 1 will be continued, provided that it is not intended to alter the type, dose, and regimen of the medication during the trial.

5.4.2 Disallowed Therapy

No other ocular medications (with the exception of run-in ART) may be used during the study. A disallowed medication may be administered in an emergency if the subject's safety is in jeopardy. Disallowed medications include the following:

- Ocular therapy (either eye) with any ophthalmic solutions, including tear substitutes except the run-in ART provided.
- Systemic medication prescribed during the study and that could affect dry eye: antiparkinsonians, antidepressants, anxiolytics, neuroleptics, beta-blockers, clonidine, amiodarone, thiazide diuretics, anticholinergics, antihistamines, tetracyclines, anti-androgens, hormone replacement therapy, oral retinoids, anti-inflammatories, antineoplastic agents and immunomodulators [1,31].
- Any medication that the Investigator feels may interfere with study parameters.

5.5 Treatment Compliance

To document treatment compliance, subjects will be provided with diaries and instructed to record the frequency of instillations of investigational eye drops and the frequency of run-in ART instillations. Subjects will also be instructed to bring the diary to each visit.

Any subject who does not follow instructions to a degree that, in the Sponsor or Investigator's opinion, jeopardizes the subject's well-being or the validity of the study, must be discontinued.

5.6 Protocol Deviations

The date of and reason for protocol deviations will be documented in all cases.

Protocol assessments will continue until the end of the study, unless the protocol deviations put the subject at risk or the subject's condition requires that he/she be discontinued from the study.

6.0 ADVERSE EVENTS[34]

6.1 Definition of Adverse Events

Information about every adverse event (AE) will be collected and recorded.

- 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.

A treatment-emergent AE (TEAE) is defined as an AE that meets either of the following conditions:

- Begins on or after the first instillation of investigational medical device on Visit 2 (Day 0).
- Begins before Visit 2 (Day 0), and worsens in severity on or after the first instillation of investigational medical device on Visit 2 (Day 0).

6.2 Definition of Adverse Device Effect

Information about every adverse device effect (ADE) will be collected and recorded.

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.

The Investigator is obliged to determine the severity of the event and evaluate the causal relationship of the event to the investigational medical device.

6.3 Definition of Serious Adverse Events

Information about every serious adverse event (SAE) will be collected and recorded.

Adverse event that:

- led to a death, injury or permanent impairment to a body structure or a body function
- 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 (e.g., blindness), or
- in-patient hospitalization or prolongation of existing hospitalization, or
- medical or surgical intervention to prevent life threatening illness

- Led to foetal distress, foetal death or 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.

A medically significant event that does not result in any of the above, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize a subject condition and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.4 Definition of Serious Adverse Device Effect

Information about every serious adverse device effect (SADE) will be collected and recorded.

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

6.5 Definition of Unanticipated Serious Adverse Device Effect and Anticipated Serious Adverse Device Effect

Information about every Unanticipated Serious Adverse Device Effect and Anticipated Serious Adverse Device Effect (ASADE) will be collected and recorded.

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 is considered as an unanticipated serious adverse device effect (USADE).

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

6.6 Definition of Device Deficiency (DD)

Information about Device Deficiency (DD) will be collected and recorded.

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.

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) circumstances had been less fortunate

6.7 Causality assessment

The relationship between the use of the investigational medical device (including the procedure) and the occurrence of each adverse event shall be assessed and categorized as follows:

1) 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 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 event;

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

- the 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 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 where 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 (Certain): the 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;
  . the investigational device or procedures have an effect on;

- the 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 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 event.

Related adverse events (including serious adverse events) are AEs with at least a possible relationship to the investigational medical device or procedure.

6.8 Reporting Adverse Events and Follow-up

Throughout the course of the study, efforts will be made by the Investigator to remain alert to possible AEs that are either systemic or ocular in nature. The period of observation for collection of AEs extends from the time the subject gives informed consent until the last study visit, Visit 5 (Day 90 ± 10 days). The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports of AEs from the subject at each study visit and record all AEs. An assessment of each event will be made by the Investigator as to severity and causal relationship to investigational medical device, as well as, start and end dates.

The subject will be instructed to contact the Investigator immediately if any unusual systemic or ocular AEs occur between visits.

Additional assessments/visits may be scheduled, as necessary, to ensure the safety of the subject, during the study period. A subject who discontinues due to an AE should be seen for post-study follow-up visits as necessary.

Non-serious AEs that are ongoing at the study exit visit will be followed by the Investigator up to 30 days after the subject exits the study.

6.9 Reporting Serious Adverse Events and Follow-up

Any SAE must be reported to the Sponsor, independent of the circumstance or suspected cause, **within 24 hours** from the time the event was reported to the Investigator.

All SAEs (whether or not considered related) experienced from consent through 30 days from the last dose of the investigational medical device must be reported to the Sponsor regardless of the causal relationship to the investigational medical device. Following Visit 5 (Study Exit, Day 90 ± 10 days) + 30 days or early discontinuation from the study+30 days, only SAEs considered related to the study should be reported within 24 hours to the Sponsor (cf Personnel and Facilities page).

Within 24 hours of notification the Investigator will fax or send by e-mail using contact details provided in Personnel and Facilities page completed Serious Adverse Event Report to the Sponsor contact. For SAEs with fatal outcomes, a summary of available autopsy findings should be submitted within 24 hours from the time the document was reported to the Investigator.

The Sponsor / Sponsor Representative will notify the EC in writing of any SAE in accordance with the EC requirements.

The Sponsor will be responsible for submitting SAE reports to regulatory authorities based on applicable regulations. The Sponsor / Sponsor Representative will also send notifications to all participating Investigators of any SAE that is unanticipated and associated with the study. It is important that the Principal Investigator reviews these expedited reports, as they contain safety information that may be relevant to each of the participating subjects. For related SAEs that resulted in death, life-threatening events, imminent risk of death, or serious injury/illness that requires prompt remedial action, SAEs will be submitted to the applicable regulatory authorities within 2 calendar days from the time the Sponsor becomes aware of the event. All other related SAEs and investigational medical device deficiency that might have led to an SAE will be submitted within 7 calendar days.

If the Investigator becomes aware of any new information regarding an SAE (ie, resolution, change in condition, or new treatment), a new Serious Adverse Event Form must be completed and faxed or e-mailed to the Sponsor using contact details provided in Personnel and Facilities page within 24 hours. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

Serious adverse events that have previously been reported and continue after the subject’s discontinuation or completion of the study will be followed until their medical endpoints are determined or until no further change in the conditions is expected. The events and endpoints will be reported in writing by the Investigator to the Sponsor (cf Personnel and Facilities page).

Following the subject's discontinuation or completion of the study, for any timeframe afterward deemed medically significant, any SAEs, which are assessed as causally related to the investigational medical device, should also be reported to the Sponsor (cf Personnel and Facilities page).

6.10 Reporting Pregnancies and Follow-up

In the event that a study subject becomes pregnant, a notification will be sent to the Sponsor (cf Personnel and Facilities page), regardless of whether an AE/SAE was reported. All pregnancies will be followed to term. Every effort will be made to obtain

the health status of the mother and infant or the fetus (in cases of miscarriage or therapeutic abortion).

6.11 Reporting Complaints for Ancillary Marketed Bausch & Lomb Products

For Bausch & Lomb marketed products used as ancillary products in the study, the Investigator should report any complaints, malfunctions, or similar events related to these products as they would in their normal clinical practice.

6.12 Submitting an Expedited Safety Report to Competent Authorities

All SAE must be fully recorded and notified to all competent authorities of member States in which the clinical investigation is being performed within the required timeframe (whether or not the event is unanticipated or anticipated) In addition, any unanticipated SAE related to a subject's participation in the study (or conduct of study), regardless if the investigational product was administered, will be evaluated by Materiovigilance to determine if expedited reporting is required. For example, an unanticipated, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting.

The Sponsor will compile the report and submit the expedited safety report to the EC and competent authority within the required reporting timeframe.

7.0 STATISTICAL METHODS

7.1 Study Endpoints

7.1.1 Primary Performance Endpoints

The primary performance endpoint for this study is mean change from baseline (CFB) in the study eye at Visit 4 (Day 28 ± 3 days) in ocular surface fluorescein staining score, combining corneal, nasal and temporal bulbar conjunctival fluorescein staining, each graded 0 to 5, according to the Oxford Scheme. The investigator will record the total score per eye (the maximum score is 15 [maximum of 5 for each of the 3 areas]).

The study eye will be the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye.

7.1.2 Secondary Performance Endpoints

The secondary performance endpoints include the following:

- Mean CFB in the study eye at Visit 5 in total ocular surface fluorescein staining score
- Mean CFB in the study eye in fluorescein staining score for each area (cornea, nasal conjunctiva and temporal conjunctiva) at Visits 4 and 5
- Mean CFB in the study eye in TFBUT at Visits 4 and 5
- Evolution from baseline of Ocular Surface Disease-Quality of Life (OSD-QoL®) questionnaire scores at Visit 5 for all 7 dimensions: Daily Activities, Handicap

and Work Difficulties, Giving up Make-up, Acknowledgement, Acceptance, Fear for the Future, and Emotional Well-Being.

- Mean CFB in the global sum score of dry eye symptoms at Visits 4 and 5: sensation of dryness, foreign body, burning, stinging, itching, blurred vision, sensitivity to light, each graded from 0 to 4
- Mean CFB in the study eye in volume of tear fluid secretion as assessed by the unanaesthetized Schirmer test at Visit 4
- Frequency of investigational eye drop instillations, as reported in subject diary

7.1.3 Safety Endpoints

The safety endpoints include the following:

- Occurrence rates of ocular and non-ocular TEAEs.
- Visual Acuity measured with habitual correction, using Monoyer chart.

7.1.4 Tolerability and Ease-of-Use Endpoints

The tolerability endpoints are as follows:

- Assessment of investigational eye drop tolerability upon instillation as reported in subject diary
- Assessment of ease-of-use of the bottle as reported in subject diary

7.2 Hypotheses

$H_{0:}$ ($\mu_{CBL\text{-}102\ Eye\ Drops} - \mu_{Vismed} \geq 2$)

versus

$H_{1:}$ ($\mu_{CBL\text{-}102\ Eye\ Drops} - \mu_{Vismed} < 2$)

Where μ= mean CFB in the study eye at Visit 4 (Day 28 ± 3 days) in total ocular surface staining score.

7.3 Sample Size

A validated macro SAS v. 9.4 was used for sample size calculation. Assuming a unilateral α risk of 2.5%, a β risk of 10% (90% power), a non-inferiority margin of 2 and a standard deviation of 2.5 on the primary endpoint[22], a sample size of 33 evaluable subjects per treatment group is necessary to demonstrate non-inferiority of CBL-102 Eye Drops to Vismed® Multi.
With a projected dropout rate of 10% and a protocol violation rate of 10%, a total of approximately 84 subjects with moderate to severe dry eye will be randomized in this clinical investigation.

7.4 Randomization

A total of 84 subjects will be randomized to receive CBL-102 Eye Drops or Vismed® Multi in a 1:1 ratio.

7.5 Analysis Sets

The analysis sets that will be used in this study are:

- **Intent-to-Treat (ITT) Population**: includes all subjects who were randomized, who received at least 1 eye drop instillation and have a baseline and at least 1 post-baseline assessment. The ITT population will be used to analyze all performance endpoints. Subjects will be analyzed according to the treatment to which they were randomized. It is expected that subjects will be dispensed a correct investigational medical device. However, if a subject does receive incorrect investigational medical device, the impact to the study results will be investigated using ad hoc analyses.
- **Per Protocol (PP) Population**: includes all of the subjects in the ITT population who remained in the study through Visit 4 (Day 28) and who did not have any major protocol deviations. The PP population will be used for the primary performance analysis and for secondary performance endpoints.
- **Safety Population**: includes all subjects who received at least 1 dose of investigational eye drops.

7.6 Statistical Analysis

7.6.1 Methods of Analysis

Summaries for continuous variables will include the sample size (n), mean, standard deviation (SD), median, minimum, and maximum. Calculations will be based on the number of subjects (or eyes) with non-missing values for the study population being summarized.

Summaries for discrete variables will include frequencies and percentages. Percentages will be based on the number of subjects (eyes) with non-missing values. The denominator for percents will be the number of subjects (eyes) from the study population being analyzed. For each subject, baseline will be defined as the last non-missing measure prior to initiation of investigational treatment and endpoint will be defined as the measure of any follow-up scheduled visit. Change from baseline will be defined as (follow-up measure – baseline measure) and will be calculated if both baseline and follow-up endpoint are not missing.
The study eye will be the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye.
For each subject, the number of investigational eye drops used per day and for how many days during the course of study will be evaluated. It is expected that most subjects will not perform more than 6 applications per day on a continued regularly basis during the study.

The primary performance endpoint (mean change from baseline in total ocular surface fluorescein staining score) will be analyzed using analysis of covariance (ANCOVA) model. The model will include terms of treatment and baseline ocular surface staining score as covariates. Sensitivity analyses including investigator site as covariate will be performed. A 2-sided 95% confidence interval (CI) based on the ANCOVA model will be computed for the effect difference (CBL-102 Eye Drops *minus* Vismed® Multi). Non-

inferiority will be demonstrated if the upper bound of the 95% CI is less than 2 grades in the PP analysis. Supportive analysis of the primary endpoint will be performed on ITT population. The same ANCOVA model used to analyze the primary endpoint will be employed to analyze secondary continuous performance endpoints. Supportive analyses on secondary performance endpoints will be performed in the ITT and PP populations.

Ocular biomicroscopic assessment will be summarized at each visit using discrete summary statistics and presented by treatment.

Treatment-emergent systemic AEs will be summarized using discrete summary statistics at the subject and event level by system organ class and preferred term for each treatment group. Treatment-emergent ocular AEs will be summarized for treated eyes and fellow eyes separately. Similarly, TEAEs will be summarized by severity and relationship separately.

Categorical endpoints will be analyzed using Fisher's exact test or chi-square test where it is appropriate.

All the statistical tests will be performed at significance level $\alpha=0.05$.

The details of the analysis will be documented in the Statistical Analysis Plan (SAP) which will be reviewed at the masked data review and finalized before breaking the treatment codes.

7.6.2 Subject Demographics and Baseline Characteristics

Subject demographics of gender and age will be summarized using discrete summary statistics and presented by treatment group. Age will also be summarized using continuous summary statistics. Total ocular surface staining score at baseline will be summarized using continuous summary statistics.

7.6.3 Medical History

Non-ocular and ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by system organ class and preferred term. Ocular medical history will be similarly summarized separately at the subject level for study and fellow eyes separately. If a subject reports the same preferred term multiple times within the same system organ class, then that preferred term will only be reported once within that system organ class. As with the preferred term, if a subject reports multiple conditions within the same system organ class, then that system organ class will only be reported once.

7.6.4 Prior and Concomitant Medications

Ocular and non-ocular prior and concomitant medications will be summarized in separate tables, by Anatomical Therapeutic Classification (ATC) text and preferred term using discrete summary statistics and presented by treatment group. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group.

7.6.5 Subject Discontinuation

A disposition of subjects includes the number and percentage of subjects in each of the following categories:

- Subjects in the ITT population
- Subjects in the Safety population
- Subjects in the PP population

For each population, the number and percentage of subjects who completed and discontinued from the study will be summarized using discrete summary statistics and presented by treatment group. The primary reason for study discontinuation described in Section 2.2.3 will also be summarized for each treatment group.

7.6.6 Protocol Deviations

The number of subjects within each type of protocol deviations will be presented using listings and discrete summary statistics as appropriate. Protocol deviations will include, but are not limited to:

- Non-compliance with any scheduled study visit
- Non-compliance with investigational medical device treatment
- Disallowed concomitant medications
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

Deviations with a significant impact on the primary endpoint will be assessed as major deviations.

7.6.7 Treatment Compliance

Subject treatment compliance rate will be calculated by dividing the total frequency of drop instillations recorded in the diary for a subject across the entire treatment period by the total number of days times the expected frequency of drop instillations per day and then multiplying by 100. e.g., ([total frequency of drop instillations recorded in the diary across the entire treatment period] / [(the total number of days of exposure) x (the expected frequency of drop instillations per day)]) x 100.

Overall investigational medical device treatment compliance will be summarized using continuous summary statistics and presented by treatment group. Treatment compliance will also be presented using discrete summary statistics in the following categories: (< 80%, 80-120%, and > 120%). Percentages will be calculated out of the number of subjects who returned diaries from that dosing period. The number and percentage of subjects in each compliance rate category will be presented by treatment group.

7.6.8 Treatment Exposure

Extent of exposure is defined as the total number of days from the first dose date to the last dose date, as recorded at the randomization study visit and the study exit eCRF page. For subjects who are lost to follow-up, extent of exposure will be calculated based on the

last study visit attended. The extent of exposure will be summarized using continuous summary statistics and presented by treatment group.

7.6.9 Missing Data

For subjects who discontinue the study early, analyses of change from baseline to endpoint for continuous variables will be based on the last non-missing post-baseline data (last observation carried forward data imputation methodology).

8.0 DATA QUALITY ASSURANCE

8.1 Study Monitoring

The Sponsor Representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Sponsor Representatives.

Prior to the start of the study the Sponsor Representatives will review the protocol, eCRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub-Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur per the monitoring plan during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, ISO 14155, and EC requirements
- The integrity of the data, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remains qualified and able to conduct the study
- Test article accountability

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor, in cooperation with the Sponsor Representatives, will take action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions.

8.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Subject completed forms and diaries are considered source data. Designated site personnel will pre-record appropriate start dates of run-in ART or investigational eye drop administration and subject identifiers (year of birth and/or subject study number) on the diary. With this exception, only subjects are to record information in subject diaries. In no instance, should an Investigator or study site personnel record any data or make

changes to subject completed forms. The Investigator or designee should review diary entries during study visits. If an entry is found to be illegible or a mistake is found (eg, incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, and adding the date and year of birth next to the change.

8.3 Case Report Forms and Data Verification

Subject data required by this protocol are to be recorded on eCRFs. With the exception of subject diaries, the Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification and date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents. Subject diaries will be handled as described in Section 5.5, Treatment Compliance. Diaries will be sent to Sponsor Representative's Data Management for data capture in the database. A copy of the diary will be left at site as source document.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to the Sponsor Representative for quality assurance review, and statistical analysis.

A copy of the eCRFs (on CD or DVD) will be retained by the Investigator, who must ensure that it is stored in a secure place.

8.4 Recording of Data and Retention of Documents

Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by year of birth, if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by the Sponsor. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include but are not limited to the following:

- EC and /or Competent Authority approvals for the study protocol, all amendments, ICF(s), and advertisements
- EC correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- eCRFs (on CD or DVD)
- Subject's signed ICF
- Accountability records for the test article(s)

- Correspondence from and to the Sponsor
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement, relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator, site IRB/EC). The Investigator will provide notice of such transfer in writing to the Sponsor.

8.5 Auditing Procedures

Audits of clinical research activities may take place. A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority and/or IRB/EC, the Investigator must inform the Sponsor immediately that this request has been made.

8.6 Institutional Review Board/Ethics Committee Approval

The Investigator should ensure that his/her participation in the study, in addition to the protocol, subject recruitment materials (written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by their institution IRB/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to the Sponsor prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/EC has provided approval for any protocol amendments prior to implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor and the IRB/EC prior to implementation.

8.7 Publication of Results

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Bausch & Lomb Incorporated products and activities receive fair, accurate, and reasonable presentation.

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APPENDIX A: SCHEDULE OF VISITS AND PARAMETERS

All study tasks should be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. Furthermore, all ocular signs must be evaluated by an ophthalmologist.

PROCEDURE/ASSESSMENTS	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Inclusion	Follow-up Telephone call[d]	Follow-up	Study Exit
	ART run in	Baseline			
	Day -14 (up to -16 days)	Day 0	Day 7 (± 1 day)	Day 28 (± 3 days)	Day 90 (± 10 days)
Informed Consent	X				
Demographic data	X				
Current and relevant medical and ocular history	X				
Pregnancy test, if applicable	X				
Concomitant medication	X	X	X	X	X
Dry eye symptoms	X	X		X	X
OSD-QoL® questionnaire		X			X
Visual acuity	X	X	X[e]	X	X
Biomicroscopy	X	X	X[e]	X	X
TFBUT	X	X		X	X
Fluorescein staining	X	X		X	X
Schirmer test		X		X	
Eligibility determination	X	X			
Randomization		X			
Dispense run-in ART	X				

PROCEDURE/ASSESSMENTS	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Inclusion	Follow-up Telephone call[d]	Follow-up	Study Exit
	ART run in	Baseline			
	Day -14 (up to -16 days)	Day 0	Day 7 (± 1 day)	Day 28 (± 3 days)	Day 90 (± 10 days)
Collect run-in ART		X			
Dispense diary [a]	X	X		X	
Collect diary [b]		X		X	X
Dispense investigational eye drops		X		X	
Collect investigational eye drops in a sealed container					X
Review subject diary for compliance		X	X[e]	X	X
Adverse events [c]	X	X	X	X	X
Exit subject					X

Abbreviations: ART = artificial tears; OSD-QoL = Ocular Surface Disease-Quality of Life; TFBUT = tear film break-up time

[a] Diary A will be dispensed at Visit 1, Diary B will be dispensed at Visit 2, and Diary C will be dispensed at Visit 4

[b] Diary A will be collected at Visit 2, Diary B will be collected at Visit 4, and Diary C will be collected at Visit 5

[c] Adverse events will be collected from the time the subject signs the ICF to study exit

[d] Telephone call assessment for compliance and collection of adverse events by the Investigator or designee The Investigator should determine whether subject should come for a visit or not

[e] If visit performed

APPENDIX B: METHODS OF CLINICAL EVALUATION

Any changes to the procedures described in this appendix will be provided under separate cover.

1. OCULAR SURFACE DISEASE-QUALITY of LIFE (OSD-QoL®) QUESTIONNAIRE

Subjects will be instructed to complete the OSD-QoL® questionnaire at Visits 2 and 5 or, in case of premature study discontinuation, at the time of withdrawal.

OSD-QoL® is a specific questionnaire for evaluating OSD symptoms impact on patients' health-related quality of life (HRQoL)[26]. The Sponsor will provide OSD-QoL® to designated personnel at the site as part of the source documents, who will provide it to the subject for completion. The questionnaire includes 28 items divided into seven dimensions: "Daily activities," "Difficulties with work and handicap," "Giving up make-up," "Acknowledgement of the disease," "Acceptance of the disease," "Fear for the future" and "Emotional well-being."

OSD-QoL® is a validated and reliable instrument for measuring dry eye disease severity and impairment in HRQoL.

2. SYMPTOMS OF DRY EYE

Discomfort linked to dry eye will be evaluated through 7 items: sensation of dryness, foreign body, burning, stinging, pruritus, blurred vision and sensitivity to light, each graded from 0 to 4[2]:

0 = Absent
1 = Mild and/or episodic; occurs under environmental stress
2 = Moderate, episodic or chronic, stress or no stress
3 = Severe, frequent or constant without stress
4 = Severe and/or disabling and constant

3. VISUAL ACUITY

Visual acuity through historical correction will be measured for both eyes at each visit using a Monoyer chart. The same VA testing method is to be employed for all study visits for each subject. Visual acuity will be entered in the eCRF in decimal format.

4. BIOMICROSCOPY

Slit lamp examination of lids, conjunctiva and cornea will be performed without pupil dilation at all study visits for each eye.

Using a high power field slit beam of 1 mm x 1 mm, perform the following assessments:

<u>At Visits 1 and 2 only:</u>

Eyelid Margin Hyperemia: Assess degree of eyelid margin hyperemia[35].

0 = Absent: no or slight redness in lid margin conjunctiva and no telangiectasia crossing meibomian gland orifices

1 = Mild: redness in lid margin conjunctiva and no telangiectasia crossing meibomian gland orifices

2 = Moderate: redness in lid margin conjunctiva and telangiectasia crossing meibomian gland orifices with a distribution of less than half of the full length of the lid

3 = Severe: redness in lid margin conjunctiva and telangiectasia crossing meibomian gland orifices with a distribution of half or more of the full length of the lid

Eyelid Debris: Assess degree of eyelid debris.

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Plugging of Meibomian Glands: Assess degree of plugging of meibomian glands[35].

0 = Absent: no plugging of gland orifices

1 = Mild: fewer than 3 pluggings of gland orifices

2 = Moderate: three or more pluggings of gland orifices with a distribution of less than half of the full length of the lid

3 = Severe: three or more pluggings of gland orifices with a distribution of half or more of the full length of the lid

<u>At all Visits (Visits 1 – 5):</u>

Eyelid Erythema: Assess upper and lower eyelids and surrounding tissues for abnormal skin redness.

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Eyelid Swelling: Assess degree of eyelid swelling.

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Ocular Discharge: Assess degree of ocular discharge

0 = Absent

1 = Mild Small amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. No true matting of the eyelids in the morning upon awakening.

2 = Moderate Moderate amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. Frank matting together of the eyelids in the morning upon awakening.

3 = Severe Profuse amount of mucopurulent or purulent discharge noted in the lower cul-de-sac and in the marginal tear strip. Eyelids tightly matted together in the morning upon awakening, requiring warm soaks to pry the lids apart.

Conjunctival Chemosis: Assess swelling of the conjunctiva.

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Conjunctival Hyperemia: Assess degree of redness and inflammation of bulbar and eyelid conjunctival tissue.

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

Corneal Erosion, Edema, Infiltrates: Assess degree of corneal erosion, edema and infiltrates.

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

5. TEAR FILM BREAK-UP TIME (TFBUT) AND OCULAR SURFACE FLUORESCEIN STAINING

Tear film break-up time will be measured first and then ocular surface fluorescein staining will be assessed. For eligibility determination on Visit 1 and Visit 2, both tests will be conducted on the right eye first, and then both tests will be performed on the left eye. For subsequent visits, only the study eye will be assessed. The study eye will be the eligible eye with the highest total ocular surface fluorescein staining score at baseline or, if both eyes are eligible and have the same score, the study eye will be the right eye.

The TFBUT measurement will be performed in conjunction with ocular surface fluorescein staining using fluorescein strips previously wetted with 1 drop of sterile saline (supplied by the Sponsor). As soon as the tip is fully wetted, the excess will be shaken off briskly and the drop delivered quickly to the lower tarsal plate. The Investigator will ask the subject to blink freely several times to distribute the fluorescein and then to keep the eyelids open. The subject is asked to look straight ahead and the Investigator uses the x10 setting on the slit lamp with cobalt blue light viewed through the supplied yellow filter.

The endpoint is the time it takes from the final blink until the first appearance of a dry spot or a disruption of the tear film (micelles). The TFBUT will be measured with a stopwatch. The TFBUT will be conducted at least 3 times and the endpoints of 3 consecutive tests will be reported.

The yellow barrier filter supplied by the Sponsor must be used to assess ocular surface staining, which will be performed at approximately 2 minutes after instillation of the fluorescein.

To observe and grade staining over the entire corneal surface, it is important for the examiner to raise the subject's upper eyelid slightly. The temporal conjunctiva is to be observed with the subject looking nasally along the horizontal plane and the nasal conjunctiva is observed with the subject looking temporally.

The staining in each area will be graded using the Oxford Scheme which consists of a series of panels labeled A-E in order of increasing severity, A corresponding to grade 0 and more than in picture E corresponding to grade 5. In each chart, staining is represented by punctate dots as shown in Appendix C.

6. SCHIRMER TEST

A Schirmer test without anesthesia will be performed **at Visit 2 and at Visit 4 on the study eye** for each subject 5 minutes after the fluorescein staining test.

The strips supplied by the Sponsor will be carefully inserted over the lower eyelid margin of the eye approximately 2/3 temporal to the nasal canthus (to avoid irritating the cornea). The subject will be asked to close both eyes. The strips are removed after 5 minutes and the amount of tear fluid secretion is read to the nearest mm from the graduated strip markings.

7. SUBJECT DIARY

The subject will be asked to fill in a diary.

a. **Diary Card A for Run-In ART (Visit 1):** This diary will be provided to each subject on the day of Visit 1 (Screening, Day -14) and will be used for 2 weeks until Visit 2 (Day 0, baseline).

   This diary will capture the frequency per day of run-in ART instillations.

b. **Diary Card B and C for Investigational Eye Drops (Visits 2-5):** Diary Card B will be provided to each subject at Visit 2 (Baseline) and will be used through Visit 4 (Day 28 ± 3 days). Diary Card C will be provided to each subject at Visit 4 (Day 28 ± 3 days) and will be used through Visit 5 (Day 90 ± 10 days).

   This diary will capture the following information:

   - Daily: frequency per day of investigational eye drop instillations
   - At the end of the first week and then at the end of each month: investigational eye drop tolerability just after the first instillation of the day. The subject will be asked to provide information on:
     - Investigational eye drop sensation : "upon instillation these eye drops are comfortable in my eyes" (strongly agree/agree/disagree/strongly disagree)
   - At the end of Diary Cards B and C: ease-of-use. The subject will be asked to grade the following sentences:

- "The bottle is easy to use" (strongly agree/agree/disagree/strongly disagree)
- "With this bottle I can dispense exactly one drop" (strongly agree/agree/disagree/strongly disagree)

APPENDIX C: **GRADING OF CORNEAL AND CONJUNCTIVAL STAINING**

Oxford Scheme [24]