

Clinical Trial Protocol

A randomized, controlled study with a closed sequential design to compare the efficacy, safety and patient satisfaction of Blephapad Combo vs. standard treatment for eyelid cleansing in patients affected by bilateral posterior blepharitis.

STUDY NUMBER: BLEPHA 01-2017

VERSION: 1.0

DATE: January 19, 2017

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1 CLINICAL TRIAL SUMMARY

Title	A randomized, controlled study with a closed sequential design to compare the efficacy, safety and patient-satisfaction of Blephapad Combo vs. standard treatment for eyelid cleansing in patients affected by bilateral posterior blepharitis.
Investigational site	Unità Operativa di Oculistica, Università Magna Grecia – Catanzaro Principal Investigator: Prof. Vincenzo Scoria
Rationale	<p>Blepharitis is the most common condition in patients seeking an eye examination due to discomfort or eye irritation.</p> <p>Posterior blepharitis may be difficult to manage and is characterized by inflamed and thickened eyelid margins, the presence of eyelid crusts and foamy tear film. Meibomian blepharitis also causes or greatly exacerbates most cases of dry eye, and these two diagnoses are frequently found in the same patients. If an older patient presents with blepharitis, especially a patient with rosacea, Demodex mite infestation may be the cause.</p> <p>Treatment of blepharitis is recommended even in mild cases as chronic inflammation may cause permanent damage to the Meibomian glands.</p> <p>The purpose of this study is to evaluate the efficacy of, and patient satisfaction with Blephapad Combo in the treatment of posterior blepharitis.</p>
Study objectives	<ul style="list-style-type: none">• The main objective of this study is to evaluate the change vs baseline of clinical features in patients with posterior blepharitis following treatment with Blephapad Combo compared to standard treatment. Clinical features will be evaluated through the use of “Grading Scales for Meibomian Gland Dysfunction” applied to photographic images of the eyelids taken during visits.• The secondary objective is to evaluate the following parameters in patients with posterior blepharitis treated with Blephapad Combo compared to standard treatment:<ul style="list-style-type: none">– change from baseline of Ocular Surface Disease Index (OSDI)– patient preference respect to standard therapy– study treatment compliance– safety
Type of study	This is an open label, randomized, controlled study with a closed sequential design. The control is standard treatment.
Duration of the study	The duration of the study, for each patient, is of approximately 6 weeks.
Number of patients	The sequential design does not require a fixed sample size; patient enrollment is stopped as soon as one of the stopping boundaries defined by

	<p>the planned design is reached.</p> <p>The diagram is designed to detect a “medium-sized” difference between treatments and fixes the type 1 error α at 10%.</p>
Inclusion criteria	<p>Each patient must meet all of the following inclusion criteria:</p> <ul style="list-style-type: none"> • Age > 40 years • Male or female • Diagnosis of bilateral posterior blepharitis • Written informed consent of patient
Exclusion criteria	<p>Each patient must meet none of the following exclusion criteria:</p> <ul style="list-style-type: none"> • Treatment with topical ophthalmic drugs (artificial tears allowed) • Ocular surgery in the previous 6 months • Pregnant or breastfeeding women • Alcohol abuse • Psychiatric disorders • Cognitive impairment that could affect evaluation of preferences • Participation in other clinical studies in the last month • Hypersensitivity to one or more components of the study product
Investigational product	<p>Blephapad Combo twice daily for one month.</p> <p>Blephapad is a disposable wet wipe containing Hy-Ter[®] solution (sodium hyaluronate acid and 4-terpineol), aloe, natural anti-inflammatories and antiseptics. The product is used to cleanse, soften, soothe and decongest inflamed eyelids and cilia.</p> <p>The combo also presents an applicator with a heatable tablet that is applied to the eyelid in order to clean and open occluded Meibomian glands, thereby allowing the production of lipids necessary for a healthy tear film. The heatable tablet is to be used prior to cleansing with Blephapad wipes.</p>
Comparator	<p>Standard treatment, twice daily for one month, consisting in eyelid hygiene using wet, warm gauze.</p>
Study design	<p>Each eye of each patient represents an experimental unit. Each patient will apply study treatment to one eye and standard therapy to the other eye in accordance with the randomization procedure.</p> <p>At baseline and at the end of treatment, the photographs of both eyelids will be evaluated clinically using the “Grading Scales for Meibomian Gland Dysfunction.” Based on the percentage change from baseline to week 4 of the total score of the Grading Scales, the Investigator will choose which of the two eyes had a better change of clinical features.</p> <p>The closed sequential design is implemented by means of a diagram that</p>

traces the preferences of treatment A or B against the overall number of changes and is to be filled out sequentially as successive pairs of experimental units are evaluated. Tracing preferences on this diagram will eventually lead to one of the following conclusions:

- Study treatment is more effective than standard treatment
- Standard treatment is more effective than study treatment
- There is no evidence of a treatment difference

In order to implement the sequential design correctly, the evaluation of the experimental units of each patient must be performed sequentially according to patient number.

The study is made up of three visits and the total study duration, for each patient, will be of approximately 6 weeks:

Visit 1: During a 2-week run-in period starting at Visit 1, and after the patient has provided informed consent, the Investigator will collect demographic data and medical history and perform a physical examination of the patient.

Visit 2 (Baseline – week 0): If the patient is considered eligible for the study, each of his or her eyes will be assigned to one of two treatments according to a predefined randomization list that considers the following associations:

Left eye	Right eye
Blephapad Combo	Standard
Standard	Blephapad Combo

The patient will be provided with the two treatments (one for each eye) and asked to treat both eyes, twice a day, for 4 weeks. The patient will be given a diary on which to record the application of all morning and evening treatments, as well as any adverse events occurred. The diary is to be returned at Visit 3 for review.

Visit 3 (Post-treatment – week 4): The patient will be asked to come to this visit for post-treatment assessments and to return any unused product.

At Visit 2 and Visit 3, the patient will undergo a physical examination, photographs of the patient's eyelids will be taken, and clinical features will be evaluated using the Grading Scales for Meibomian Gland Dysfunction. The Investigator will complete the Ocular Surface Disease Index (OSDI) questionnaire based on the answers elicited from the patient.

At Visit 3, the patient will be asked which of the two treatments he or she preferred.

Monitoring of adverse events will take place throughout the study.

Evaluation criteria	<p><u>Primary efficacy variable</u></p> <p>The primary endpoint is the percentage change from baseline to week 4 of the total score of Grading Scales for Meibomian Gland Dysfunction applied to photographic images of the following aspects of each experimental unit:</p> <ul style="list-style-type: none">• Lid margin findings of vascularity (score 0-3)• Plugging of gland orifices (score 0-3)• Lid margin irregularity (score 0-2)• Lid margin thickening (score 0-2)• Partial glands (score 0-3)• Gland dropout (score 0-2) <p>Based on the percentage change from baseline to week 4 of the total score of Grading Scales for Meibomian Gland Dysfunction, investigators will choose which of the two eyes had a better change of clinical features.</p> <p><u>Secondary efficacy variables</u></p> <ul style="list-style-type: none">• Change from baseline to Visit 3, for each eye, of the total score of the Grading Scales for Meibomian Gland Dysfunction, expressed as one the following four possible outcomes: <table><tr><th>Possible outcome</th><th>Outcome of eye on Blephapad Combo</th><th>Outcome of eye on Standard</th></tr><tr><td>1</td><td>Improved</td><td>Improved</td></tr><tr><td>2</td><td>Improved</td><td>NOT improved</td></tr><tr><td>3</td><td>NOT improved</td><td>Improved</td></tr><tr><td>4</td><td>NOT improved</td><td>NOT improved</td></tr></table> <ul style="list-style-type: none">• Changes from baseline of the Ocular Surface Disease Index (OSDI), calculated as follows: OSDI = (sum of scores) * 25/(number of answers)• Patient preference of one of the two treatments. <p><u>Compliance</u></p> <p>Adherence to treatment will be evaluated by counting the applications of treatment (wet wipes) to each eye and by reviewing the data entered in the patient diary.</p>	Possible outcome	Outcome of eye on Blephapad Combo	Outcome of eye on Standard	1	Improved	Improved	2	Improved	NOT improved	3	NOT improved	Improved	4	NOT improved	NOT improved
Possible outcome	Outcome of eye on Blephapad Combo	Outcome of eye on Standard														
1	Improved	Improved														
2	Improved	NOT improved														
3	NOT improved	Improved														
4	NOT improved	NOT improved														

	<p><u>Safety</u></p> <p>A targeted physical examination will be performed at all visits and monitoring for ocular and systemic adverse events will occur throughout the study.</p>
Statistical considerations	<p><u>Analysis populations</u></p> <p>Patients without a valid or adequately obtained Informed Consent Form (ICF) will be excluded from any analysis population.</p> <p>The following analysis populations will be defined for statistical analyses:</p> <ul style="list-style-type: none"> • Randomized set: all randomized patients. • Safety set: all randomized patients that apply treatment at least once. • Intention to treat (ITT) set: all randomized patients that apply treatment at least once in one eye and have a baseline evaluation of the primary efficacy endpoint. The experimental units that interrupt treatment will be considered as “failures” for qualitative variables and their missing quantitative data will be replaced according to the LOCF method (Last Observation Carried Forward). • Per protocol (PP): all randomized patients that complete the study and were not affected by significant protocol violations concerning inclusion/exclusion criteria or that could condition efficacy evaluations. <p>The efficacy analysis will be performed on the ITT set whereas safety will be evaluated on the safety set.</p> <p><u>Methodology</u></p> <p>Continuous data will be summarized by means of common descriptive statistics: mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.</p> <p>Patients will be included in each analysis based on available assessments. Unless stated otherwise, two-sided p-values <0.05 will be considered statistically significant.</p> <p>All statistical tables, listings, figures and analyses will be generated using SAS® release 9.4 or later (SAS Institute Inc., Cary NC, USA).</p> <p>Further details about data analysis will be provided in the Statistical Analysis Plan document.</p> <p>All data about patient demographics and baseline characteristics will be summarized on the ITT set, overall, by means of summary descriptive</p>

	<p>statistics.</p> <p>Medical history data will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).</p> <p>Concomitant medications and significant non-drug therapies will be presented by WHO Drug Dictionary ATC class and preferred term.</p> <p>➤ Primary efficacy analysis</p> <p>The sequential design graphically leads to a conclusion without statistical analysis.</p> <p>➤ Secondary efficacy analysis</p> <ul style="list-style-type: none">• Summary statistics of raw data and percent change from baseline to Visit 3 for the total score of Grading Scales for Meibomian Gland Dysfunction will be presented by treatment group• Summary statistics of raw data and change from baseline to Visit 3 for the OSDI will be presented by treatment group. Between-group differences will also be analyzed.• Patient preference for one of the two treatments at Visit 3 will be presented in terms of number and percentage of patients preferring the standard or the study treatment.• Overall study treatment compliance will be summarized by means of descriptive statistics. <p>➤ Safety</p> <p>Results of the physical examination at each assessment time point will be presented overall.</p> <p>The incidence of ocular and systemic Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded throughout the study will be presented by MedDRA system organ class (SOC) and preferred term (PT).</p>
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2 ASSESSMENT CHART

Study period	Run in		Treatment
Visit	V1	V2	V3*
Time (weeks)	-2	0	4
Informed consent	X		
Inclusion/Exclusion criteria	X		
Demography/Medical history	X		
Physical examination	X	X	X
Randomization		X	
Dispensation of study product		X	
Photographic images		X	X
Grading Scales for Meibomian Gland Dysfunction [#]		X	X
Ocular Surface Disease Index (OSDI)		X	X
Treatment preference			X
Concomitant treatment		X	X
Adverse Event monitoring		X	X
Provide (V2) / review (V3) patient diary		X	X
Compliance			X

* If Visit 3 cannot be performed on the established date, the Investigator may fix an alternative one considering the clinical and practical aspects related to protocol procedures.

[#] The evaluation of the experimental units of each patient must be performed sequentially according to patient number.

3 TABLE OF CONTENTS

1	CLINICAL TRIAL SUMMARY	3
2	ASSESSMENT CHART	9
3	TABLE OF CONTENTS	10
4	LIST OF ABBREVIATIONS.....	14
5	INTRODUCTION AND RATIONALE	15
6	STUDY OBJECTIVES	16
6.1	PRIMARY	16
6.2	SECONDARY	16
7	STUDY DESIGN	16
7.1	DESCRIPTION OF THE PROTOCOL.....	16
7.2	DURATION OF STUDY PARTICIPATION	19
7.2.1	Duration of study participation for each patient.....	19
7.2.2	Determination of end of clinical trial (all patients).....	19
8	SELECTION OF PATIENTS	19
8.1	INCLUSION CRITERIA	19
8.2	EXCLUSION CRITERIA	19
9	STUDY TREATMENTS.....	20
9.1	INVESTIGATIONAL PRODUCT	20

9.2	STANDARD TREATMENT	21
9.3	METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP	21
9.4	PACKAGING AND LABELING	21
9.5	STORAGE CONDITIONS.....	21
9.6	RESPONSIBILITIES	21
9.7	TREATMENT ACCOUNTABILITY AND COMPLIANCE.....	21
9.8	BLINDING PROCEDURES	22
10	ASSESSMENTS	22
10.1	PRIMARY EFFICACY VARIABLE.....	22
10.2	SECONDARY EFFICACY VARIABLES	22
10.2.1	Change from baseline for each treatment.....	22
10.2.2	Ocular Surface Disease Index (OSDI).....	23
10.2.3	Patient treatment preference	23
10.3	SAFETY	23
10.4	COMPLIANCE	24
11	STUDY PROCEDURES	24
11.1	VISIT SCHEDULE	24
11.2	TEMPORARY OR PERMANENT TREATMENT/STUDY DISCONTINUATION	25
11.2.1	Temporary treatment discontinuation.....	25
11.2.2	Permanent treatment discontinuation	25

11.2.3	Handling of patients after permanent treatment discontinuation.....	25
12	DATA MANAGEMENT	26
12.1	DATA COLLECTION	26
12.2	DATA MANAGEMENT AND QUALITY CONTROL.....	26
13	STATISTICAL CONSIDERATIONS	27
13.1	DETERMINATION OF SAMPLE SIZE.....	27
13.2	STATISTICAL METHODS	29
13.2.1	Analysis populations.....	29
13.2.2	Statistical Analysis	29
14	ETHICAL AND REGULATORY CONSIDERATIONS	31
14.1	ETHICAL AND REGULATORY STANDARDS	31
14.2	INFORMED CONSENT	31
14.3	INDEPENDENT ETHICS COMMITTEE (EC).....	31
15	STUDY MONITORING	32
15.1	RESPONSIBILITIES OF THE INVESTIGATOR	32
15.2	RESPONSIBILITIES OF THE SPONSOR	32
15.3	SOURCE DOCUMENT REQUIREMENTS	32
16	ADDITIONAL REQUIREMENTS	32
16.1	CURRICULUM VITAE	32

16.2	RECORD RETENTION IN STUDY SITES.....	33
16.3	CONFIDENTIALITY	33
16.4	PROPERTY RIGHTS.....	33
16.5	DATA PROTECTION.....	33
16.6	INSURANCE COMPENSATION.....	33
16.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES.....	34
16.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE	34
16.9	PUBLICATIONS AND COMMUNICATIONS.....	34
17	CLINICAL TRIAL PROTOCOL AMENDMENTS.....	34
18	BIBLIOGRAPHIC REFERENCES	36

4 LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OSDI	Ocular Surface Disease Index
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class
TTO	Tee Tree Oil
WHO	World Health Organization

5 INTRODUCTION AND RATIONALE

Blepharitis is the most common condition in patients seeking an eye examination due to discomfort or eye irritation. A study conducted by American specialists found that 37% to 47% of patients seen during routine practice were affected by chronic blepharitis. In 2014, 700,000 specialized medical visits in the U.S.A. were related to blepharitis (1).

Posterior blepharitis (also called Meibomian blepharitis) is characterized by a dysfunction of the Meibomian glands. The ducts of these glands open on the inside margin of the eyelid and the oils produced by the glands help to prevent the evaporation of tears. Meibomian blepharitis leads to a decrease and/or altered secretion of the glands. Posterior blepharitis may be difficult to manage and is characterized by inflamed and thickened eyelid margins, the presence of eyelid crusts and foamy tear film. Meibomian blepharitis also causes or greatly exacerbates most cases of dry eye, and these two diagnoses are frequently found in the same patients.

If an older patient presents with blepharitis, especially an older patient with rosacea, Demodex mite infestation may be the cause. The incidence of Demodex infestation increases with age, occurring in 84 percent of the population at age 60. Two different Demodex species have been found to cause blepharitis: *Demodex folliculorum* can cause anterior blepharitis associated with disorders of the eyelashes, and *Demodex brevis* can cause posterior blepharitis with Meibomian gland dysfunction and keratoconjunctivitis (2).

Treatment of blepharitis is recommended even in asymptomatic or mild cases, as chronic inflammation may cause permanent damage to the Meibomian glands. Daily cleansing of eyelids and cilia is important as it removes debris, softens thickened secretions, removes ciliary dandruff and cleans the eyelid margin.

For Demodex infestations, lid scrub with tea tree oil has been found to clean dandruff from the lash root and also to stimulate embedded Demodex mites to migrate out of the skin. Typically, a daily lid scrub with 50% tea tree oil (TTO) and lid massage with 5% tea tree oil ointment will resolve ocular Demodex infestation. Respect to TTO, the use of Terpinen-4-ol increases efficacy against Demodex mites while avoiding the antagonistic effects of the other TTO components. Terpinen-4-ol is therefore particularly promising for treating skin and ocular pathologies caused by Demodex mites (3).

Other treatment options vary from just warm moist compresses and massage to oral doxycycline or tetracycline antibiotics, oral nutritional supplements with fish oil and other anti-inflammatory polyunsaturated fats. Topical treatments with steroids and azithromycin are also sometimes recommended.

Blephapad Combo

Blephapad is a disposable wet wipe containing Hy-Ter[®] solution (hyaluronic acid and 4-terpineol), aloe, natural anti-inflammatories and antiseptics. The product is used to cleanse, soften, soothe and decongest inflamed eyelids and cilia. The combo also presents an applicator with a

heatable tablet that is applied to the eyelid in order to clean and open occluded Meibomian glands, thereby allowing the production of lipids necessary for a healthy tear film. No known adverse effects or risks have been associated with the use of this medical device.

The purpose of this study is to evaluate the efficacy of, and patient satisfaction with Blephapad Combo in the treatment of posterior blepharitis.

6 STUDY OBJECTIVES

6.1 PRIMARY

- The main objective of this study is to evaluate the change from baseline of clinical features in patients with posterior blepharitis following treatment with Blephapad Combo compared to standard treatment. Clinical features will be evaluated through the use of “Grading Scales for Meibomian Gland Dysfunction” applied to photographic images of the eyelids taken during visits.

6.2 SECONDARY

The secondary objective is to evaluate the following parameters in patients with posterior blepharitis treated with Blephapad Combo compared to standard treatment:

- Change from baseline of Ocular Surface Disease Index (OSDI)
- Patient preference respect to standard therapy
- Study treatment compliance
- Safety

7 STUDY DESIGN

7.1 DESCRIPTION OF THE PROTOCOL

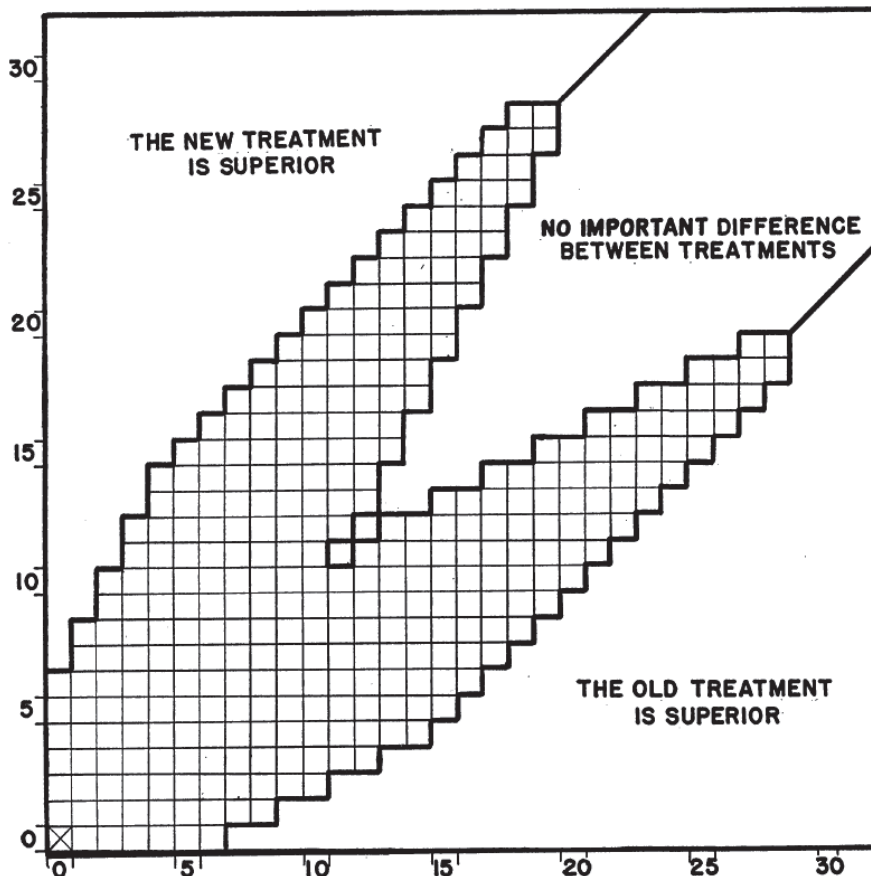
This is an open label, randomized, standard-treatment controlled study with a closed sequential design.

Each eye of each patient represents an experimental unit. Each patient will apply study treatment to one eye and standard therapy to the other (eyelid hygiene with wet, warm gauze) twice a day for one month in accordance with the randomization procedure.

At baseline and at the end of treatment, photographs of both eyelids will be evaluated clinically using the “Grading Scales for Meibomian Gland Dysfunction.” Based on the percentage change

from baseline to week 4 of the total score of the Grading Scales, investigators will choose which of the two eyes had a better change of clinical features.

The closed sequential design is implemented by means of the following diagram (4), which traces the preferences of treatment A or B and is to be filled out sequentially as successive pairs of experimental units are evaluated.



The diagram is designed to detect “medium-sized” differences between treatments and fixes the type 1 error α at 10%.

The experiment begins in the square marked with an “X” in the bottom-left corner of the chart, and then the outcome of each patient (i.e. pairs of experimental units/eyes) is plotted as soon as the results are known, according to the following rule (4):

- If the standard (i.e. labeled as “old” in the chart) and the study (i.e. labeled as “new” in the chart) treatments lead to the same outcome (same percentage change vs. baseline of clinical features) then neither treatment is superior and nothing is plotted on the chart.
- If the standard treatment causes a better percentage change of clinical features than the study treatment, then an “x” will be marked in the square to the right of the last entry on the chart.

- If the study treatment causes a better percentage change of clinical features than the standard treatment, then an "x" will be marked in the square above the last entry on the chart.

The diagram has upper, lower and middle boundaries. The study will end as soon as the plot of the trial results reaches one of these boundaries, at which point one of the following conclusions will be drawn:

- Study treatment is more effective than standard treatment if the superior margin is reached first.
- Standard treatment is more effective than study treatment if the inferior margin is reached first.
- There is no evidence of a treatment difference if the middle boundary is reached first.

A sequential design offers the following advantages:

- Ongoing analysis of data.
- Reduction of amount of data (and therefore of patients) to reach statistically valid conclusions.

In order to implement the sequential design correctly, the evaluation of the experimental units of each patient must be performed sequentially according to patient number.

The study is made up of three visits and the total study duration, for each patient, will be of approximately 6 weeks:

Visit 1: During a 2-week run-in period starting at Visit 1, and after the patient has provided informed consent, the Investigator will collect demographic data and medical history and perform a physical examination of the patients.

Visit 2 (Baseline – week 0): If the patient is considered eligible for the study, each of his or her eyes will be assigned to one of two treatments according to a predefined randomization list that considers the following associations:

Left eye	Right eye
Blephapad Combo	Standard
Standard	Blephapad Combo

The patient will be provided with the two treatments (one for each eye) and asked to treat both eyes, twice a day, for 4 weeks. The patient will be given a diary on which to record the application of all morning and evening treatments, as well as any adverse events occurred. The diary is to be returned at Visit 3.

Visit 3 (Post-treatment – week 4): The patient will be asked to come to this visit for post-treatment assessments and to return any unused product.

At Visit 2 and Visit 3 the patient will undergo a physical examination, photographs of the patient's eyelids will be taken, and clinical features will be evaluated using the Grading Scales for Meibomian Gland Dysfunction. The Investigator will complete the Ocular Surface Disease Index (OSDI) questionnaire based on the answers elicited from the patient.

At Visit 3, the patient will be asked which of the two treatments he or she preferred.

Monitoring of adverse events will take place throughout the study.

See [Section 2](#) for a table of the study assessments.

7.2 DURATION OF STUDY PARTICIPATION

7.2.1 Duration of study participation for each patient

The study for each participant will last approximately 6 weeks.

7.2.2 Determination of end of clinical trial (all patients)

The study will end as soon as the plot of the trial results reaches one of its boundaries ([see Section 7.1](#)).

8 SELECTION OF PATIENTS

The population will be made up of adult patients with bilateral posterior blepharitis.

8.1 INCLUSION CRITERIA

Each patient must meet all of the following inclusion criteria:

- Age > 40 years
- Male or female
- Diagnosis of bilateral posterior blepharitis
- Written informed consent of patient

8.2 EXCLUSION CRITERIA

Each patient must meet none of the following exclusion criteria:

- Treatment with topical ophthalmic drugs (artificial tears allowed)
- Ocular surgery in the previous 6 months
- Pregnant or breastfeeding women
- Alcohol abuse

- Psychiatric disorders
- Cognitive impairment that could affect evaluation of preferences
- Participation in other clinical studies in the last month
- Hypersensitivity to one or more components of the study products

9 STUDY TREATMENTS

9.1 INVESTIGATIONAL PRODUCT

Blephapad Combo

Blephapad is a disposable wet wipe containing Hy-Ter[®] solution (hyaluronic acid and 4-terpineol), aloe, natural anti-inflammatories and antiseptics. The product is used to cleanse, soften, soothe and decongest inflamed eyelids and cilia.

The combo also presents an applicator with a heatable tablet that is applied to the eyelid in order to clean and open occluded Meibomian glands, thereby allowing the production of lipids necessary for a healthy tear film. The heatable tablet is to be used prior to cleansing with Blephapad.

Blephapad wipes contain the following ingredients:

- water
- PEG /PPG - 20/15 dimethicone
- aloe barbadensis leaf juice powder
- HY-TER: sodium hyaluronate + 4-terpineol
- ammonium glycyrrhizate
- caprylyl / capryl glucoside
- sodium cocoyl wheat amino acids
- ethylhexylglycerin
- phenethyl alcohol
- sodium chloride
- sodium phosphate
- disodium phosphate
- PPG-26 Buteth-26
- PEG-40 hydrogenated castor oil

9.2 STANDARD TREATMENT

Standard treatment, twice daily for one month, consisting of eyelid hygiene using wet, warm gauze.

9.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Each eye of each patient will be assigned to one of two treatments according to a predefined computer-generated randomization list that considers the following associations:

Left eye	Right eye
Blephapad Combo	Standard
Standard	Blephapad Combo

9.4 PACKAGING AND LABELING

Each package of study treatment contains 28 Blephapad wipes and one heatable tablet.

Blephapad Combo and standard treatment will be provided free of charge. The content of the labeling will be in accordance with local regulatory specifications and requirements.

9.5 STORAGE CONDITIONS

The Principal Investigator or other authorized persons (pharmacists) are responsible for storing the product in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

9.6 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the product will be responsible for ensuring that it is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

Any quality issue detected upon receipt of the product (condition, appearance, documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor.

9.7 TREATMENT ACCOUNTABILITY AND COMPLIANCE

An adequate supply of product with shelf life adequate to reach the next visit will be ensured. Patients will be asked to return any unused wipes at Visit 3 (week 4). Compliance will be assessed at Visit 3 by counting unused wipes and by reviewing data entered in the patient diary. A subject Treatment Accountability Log for dispensed and returned treatment will be kept for each patient.

The Investigator will be responsible for ensuring that an accurate record of the treatment issued and returned is maintained through a Site Treatment Accountability Log.

9.8 BLINDING PROCEDURES

Not applicable; this is an open label study.

10 ASSESSMENTS

10.1 PRIMARY EFFICACY VARIABLE

The primary endpoint is the percentage change from baseline to week 4 of the total score of Grading Scales for Meibomian Gland Dysfunction (5) applied to photographic images of the following aspects of each experimental unit:

- Lid margin findings of vascularity (score 0-3)
- Plugging of gland orifices (score 0-3)
- Lid margin irregularity (score 0-2)
- Lid margin thickening (score 0-2)
- Partial glands (score 0-3)
- Gland dropout (score 0-2)

Based on the percentage change from baseline to week 4 of the total score of Grading Scales for Meibomian Gland Dysfunction, Investigators will choose which of the two eyes had a better change of clinical features.

10.2 SECONDARY EFFICACY VARIABLES

10.2.1 Change from baseline for each treatment

Change from baseline to Visit 3, for each eye, of the total score of the Grading Scales for Meibomian Gland Dysfunction, expressed as one the following four possible outcomes:

Possible outcome	Outcome of eye on Blephapad Combo	Outcome of eye on Standard
1	Improved	Improved
2	Improved	NOT improved
3	NOT improved	Improved
4	NOT improved	NOT improved

10.2.2 Ocular Surface Disease Index (OSDI)

The Ocular Surface Disease Index (OSDI) is a 12-item scale for the assessment of symptoms related to dry eye disease and their effect on vision. The index is to be completed by the Investigator based on the answers elicited from the patient. The index possesses the necessary psychometric properties to be used as an endpoint in clinical trials (6). Changes from baseline of the OSDI are calculated as follows: $OSDI = (\text{sum of scores}) * 25 / (\text{number of answers})$.

10.2.3 Patient treatment preference

The patient will be asked which of the two treatments he or she prefers (Blephapad vs. standard treatment).

10.3 SAFETY

Safety will be assessed based on targeted physical examinations and on the incidence of adverse events for each treatment. Adverse events will be classified as systemic and ocular.

An adverse event (AE) is as any untoward medical occurrence in a patient administered the product and which does not necessarily have to have a causal relationship with the treatment.

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event.

Should an SAE occur, the Investigator or designee must complete and send the SAE form signed and dated by fax within 24 hours following awareness to the CRO Pharmacovigilance Officer whose fax number and e-mail address appear below.

The Investigator should take appropriate measures to follow all AEs (both serious and not serious) until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up.

Any follow-up information of SAEs should be transmitted by fax or email as described above.

CRO Pharmacovigilance Officer: OPIS s.r.l. - Dr Riccardo Chisci Email: all_phv@opis.it Fax: +39 0362 633622 Tel: +39 0362 633312

Mobile: +39 348 6440813

Pregnancy

The Investigator is expected to record any case of pregnancy exposure occurring in a female patient during the study on the pregnancy form and send it by fax to the address indicated above.

The Investigator is requested to follow each case of pregnancy exposure until the outcome.

10.4 COMPLIANCE

Patients will be asked to return any unused wipes at Visit 3. Study treatment compliance is defined as the actual number of used wipes/study treatment applications compared to the planned treatment applications. Compliance with standard treatment will be evaluated through review of the patient diary.

11 STUDY PROCEDURES

11.1 VISIT SCHEDULE

The visit schedule consists of three visits: V1, V2 and V3.

At V1, after having obtained signed informed consent from the patient, the Investigator will gather demographic and medical history data. The Investigator will perform a physical examination and evaluate the patient's eligibility for the study according to the inclusion/exclusion criteria indicated in [Section 8](#).

At V2, each eye of each patient will be randomized to one of two treatments (Blephapad Combo or standard treatment) according to the scheme indicated in [Section 9.3](#) and will be provided with enough product to last until Visit 3. The Investigator will perform a physical examination, take a photograph of the patient's eyes, evaluate clinical features using the Grading Scales for Meibomian Gland Dysfunction, and enquire about any adverse events the patient may have experienced and about any concomitant medication the patient may have taken since Visit 1. The OSDI questionnaire will be completed by the Investigator according to the answers provided by the patient. The patient will be given a diary on which to record the application of all morning and evening treatments, as well as any adverse events occurred. The diary is to be returned at Visit 3 for review.

Visit 3 will take place approximately 4 weeks after Visit 2. If Visit 3 cannot be performed on the established date, the Investigator may fix an alternative one considering the clinical and practical aspects related to protocol procedures.

The same assessments described for Visit 2 will be performed at Visit 3 (physical examination, OSDI, photographs, Grading Scales for Meibomian Gland Dysfunction, adverse events,

concomitant medication). The patient will also be asked which of the two treatments he/she preferred.

See the assessment chart in [Section 2](#) for details regarding the visit schedule and assessments and [Section 7](#) for information concerning study design.

11.2 TEMPORARY OR PERMANENT TREATMENT/STUDY DISCONTINUATION

Patients should continue using the product whenever possible and permanent discontinuation should be only a last resort. Any treatment discontinuation should be fully documented on the Electronic Case Report Form (eCRF).

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.2.1 Temporary treatment discontinuation

Temporary treatment discontinuation may be considered by the Investigator because of a suspected AE. Treatment can be resumed under close clinical monitoring once the Investigator has considered an association of the treatment with the occurrence of the event unlikely and if the selection criteria for the study are still met (refer to [Section 8](#)).

The duration of all temporary treatment discontinuations should be recorded by the Investigator in the CRF.

11.2.2 Permanent treatment discontinuation

The patients may withdraw from treatment at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation on the eCRF.

11.2.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the last visit.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the CRF when considered confirmed.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient. Attempts to contact such patients must be documented in the patient's records.

12 DATA MANAGEMENT

12.1 DATA COLLECTION

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they are trained.

Web-based software will be used and no installation procedure is needed. . Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring Username and Password and may read, modify and update only the information reported at his/her site. Each page reports site code and patient code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the Contract Research Organization (CRO) working on behalf of the Sponsor. The Investigator will certify that the data entered into the eCRF is complete and accurate.

After database lock, the investigator will receive a CD-ROM of patient data for archiving at the investigational site.

12.2 DATA MANAGEMENT AND QUALITY CONTROL

The CRO working on behalf of the Sponsor will review the data entered into the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. If clarifications are needed, the Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows as well as the on-line and off-line checks are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA).

Randomization codes and data about the study treatment are tracked using the eCRF. The system is supplied by OPIS, who also manages the database.

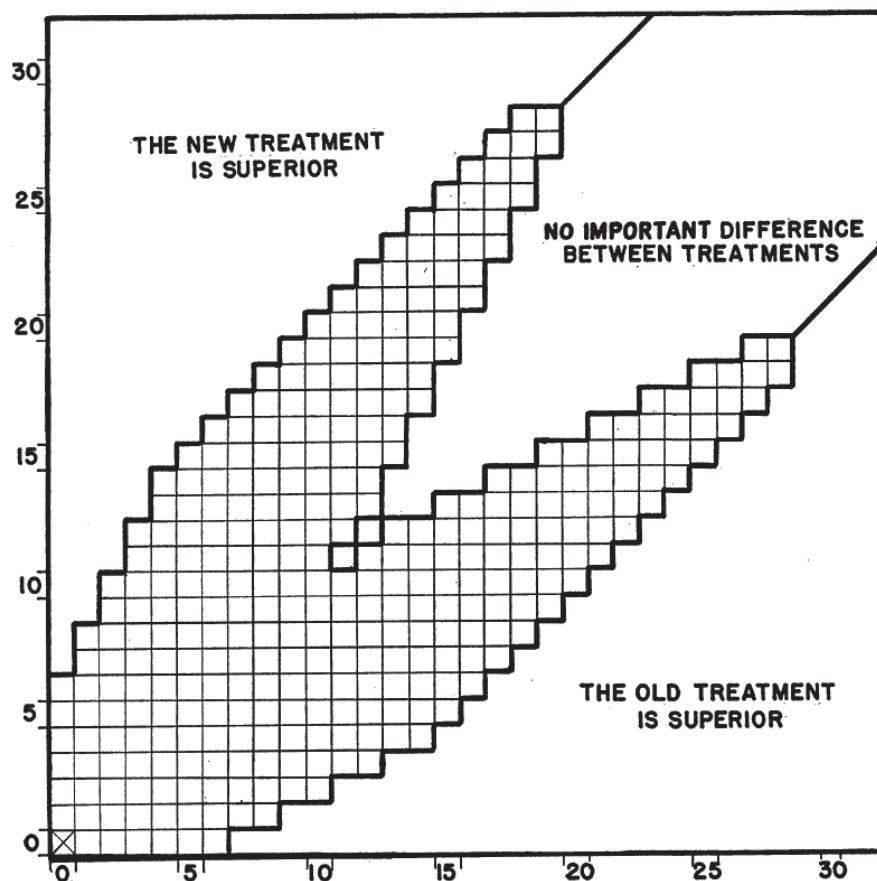
The occurrence of any protocol deviations will be checked and the database will be locked and made available for data analysis after the actions mentioned above have been completed and the database has been declared complete and accurate.

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

The sequential design does not require a fixed sample size; patient enrollment is stopped as soon as one of the stopping boundaries defined by the planned design is reached.

The closed sequential design planned for this study is based on the method described by I. Bross (4). The following plan, designed to detect "medium-sized" difference between treatments at the 10% type 1 error α , will be applied.



Considering the following formula:

$p^* = p_1(1 - p_2) / [p_1(1 - p_2) + p_2(1 - p_1)]$ where p_1 is the proportion of successes (i.e. clinical improvement in the total score of Grading Scales for Meibomian Gland Dysfunction from

baseline to week 4) with the standard treatment and p_2 is the proportion of successes with the study treatment

If:

- two treatments are equal $\rightarrow p_1 = p_2 \rightarrow p^* = 0.5$;
- the study treatment is more effective than the standard treatment $\rightarrow p_2 > p_1 \rightarrow p^* > 0.5$;

Assuming a value of $p^* = 0.7$ as clinically significant, the table below shows the proportion of successes with the study treatment p_2 , given a proportion of successes with standard treatment p_1 :

Standard treatment (p_1)	Study treatment (p_2)
10%	21%
20%	37%
30%	50%
40%	61%
50%	70%
60%	78%
70%	84%
80%	90%
90%	95%

With this design, and in the presence of a relevant difference between treatments (i.e. $p^*=0.7$), the median number of experimental units is given by the following formula

$$2 * k * (\text{median length of path}),$$

Therefore, the median number of patients is obtained as $k * (\text{median length of path})$, where

- $k = 1 / [p_1(1-p_2) + p_2(1-p_1)]$
- the median length of path for the applied plan is 23 in case of an important difference (i.e. $p^*=0.7$)

The following table shows the median number of patients for different values of p_1 and p_2 in case of $p^*=0.7$

Standard treatment (p_1)	Study treatment (p_2)	k	Median number of patients
10%	21%	3,7	85
20%	37%	2,4	55
30%	50%	2	46
40%	61%	1,9	44
50%	70%	2	46

Standard treatment (p ₁)	Study treatment (p ₂)	k	Median number of patients
60%	78%	2,3	53
70%	84%	2,7	62
80%	90%	3,8	87
90%	95%	7,1	163

13.2 STATISTICAL METHODS

13.2.1 Analysis populations

Patients without a valid or adequately obtained Informed Consent Form (ICF) will be excluded from any analysis population.

The following analysis populations will be defined for statistical analyses:

- **Randomized set:** All randomized patients.
- **Safety set:** All randomized patients that apply treatment at least once.
- **Intention to treat (ITT) set:** all randomized patients that apply treatment at least once in one eye and have a baseline evaluation of the primary efficacy endpoint. The experimental units that interrupt treatment will be considered as “failures” for qualitative variables and their missing quantitative data will be replaced according to the LOCF method (Last Observation Carried Forward).
- **Per protocol:** all randomized patients that completed the study and were not affected by significant protocol violations concerning inclusion/exclusion criteria or that could condition efficacy evaluations.

The efficacy analysis will be performed on the ITT set whereas safety will be evaluated on the safety set.

13.2.2 Statistical Analysis

All data collected in the study will be listed and summarized as appropriate as described below. Continuous data will be summarized by means of common descriptive statistics: mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

Patients will be included in each analysis based on available assessments. Unless stated otherwise, two-sided p-values <0.05 will be considered statistically significant.

All statistical tables, listings, figures and analyses will be generated using SAS® release 9.4 or later (SAS Institute Inc., Cary NC, USA).

Further details about data analysis will be provided in the Statistical Analysis Plan document.

All data about patient demographics and baseline characteristics will be summarized on the ITT set, overall, by means of summary descriptive statistics.

The number and percentages of subjects meeting all eligibility criteria at screening will be provided. The analysis populations will be described and the reasons for excluding a patient from any particular population will be provided with the number of protocol deviators per each criterion.

A complete description of patients' disposition will be provided specifying the number of randomized patients, the number of patients at each visit, the number of completed and discontinued patients and the reason for the discontinuation.

Medical history data will be presented by Medical Dictionary for Regulatory Activities MedDRA dictionary system organ class (SOC) and preferred term (PT).

Concomitant medications and significant non-drug therapies will be presented by WHO Drug Dictionary ATC class and preferred term.

- **Primary efficacy analysis**

The closed sequential design will be applied as described in [Section 7.1](#). No analysis is required (the sequential design automatically leads to a conclusion).

- **Secondary efficacy analysis**

- Summary statistics of raw data and percent change from baseline to Visit 3 for the total score of Grading Scales for Meibomian Gland Dysfunction will be presented by treatment group.
- Summary statistics of raw data and change from baseline to Visit 3 for the OSDI will be presented by treatment group. Between-group differences will also be analyzed.
- Patient preference for one of the two treatments at Visit 3 will be presented in terms of number and percentage of patients preferring the standard or the study treatment.
- Overall study treatment compliance will be summarized by means of descriptive statistics.

- **Safety**

Results of the physical examination at each assessment will be presented overall.

The incidence of ocular and systemic Adverse Events (AEs) and Serious Adverse Events (SAEs) reported throughout the study will be presented by MedDRA system organ class (SOC) and preferred term (PT).

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments, applicable provisions of ICH guidelines for good clinical practice (ICH-GCP), and all applicable laws and regulations.

14.2 INFORMED CONSENT

The Investigator, or a person designated by the Investigator, shall inform the patient of all the aspects of the clinical trial to the fullest extent possible, and in language and terms they are able to understand, including the written information giving approval/favorable opinion by the Ethics Committee (EC).

Prior to a patient's participation in the clinical trial, the written informed consent form shall be signed and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be given to the patient.

The informed consent form must be reviewed and approved by the Sponsor prior to submission to the EC for approval/favorable opinion.

14.3 INDEPENDENT ETHICS COMMITTEE (EC)

The Investigator or the Sponsor must submit this clinical trial protocol to the appropriate EC as per local regulations, and is required to forward to the other party a copy of the dated approval/favorable opinion signed by the Chairman with EC composition.

The clinical trial (study number, protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form etc.) and the date of the review should be clearly stated on the written EC approval/favorable opinion.

During the study, any amendment or modification to the protocol must be submitted to the EC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the EC should be informed as soon as possible. The EC should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial. All safety updates will be sent to the EC.

A progress report shall be sent to the EC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol. The Investigator agrees to provide reliable data and all information requested by the protocol and to ensure Sponsor representatives direct access to source documents.

The confidentiality of the patient's data shall be protected at all times.

The Investigator may appoint other individuals as Sub-investigators to assist in the conduct of the clinical trial. All Sub-investigators shall be listed and shall work under the responsibility of the Investigator. All Sub-investigators shall be provided with a copy of the protocol and trained.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, protocol compliance, and integrity and validity of data. The site will be contacted at regular intervals by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent issues. Monitoring contacts will include a review of patient informed consent, patient recruitment and follow-up, AE documentation, product allocation, product accountability and data quality.

15.3 SOURCE DOCUMENT REQUIREMENTS

In accordance with ICH-GCP, the monitoring team shall check CRF entries against source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee and the regulatory authorities to have direct access to original medical records that support CRF data. These personnel shall maintain the confidentiality of all personal identity and personal medical information (according to confidentiality and personal data protection norms).

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of the Investigator and Sub-investigator shall be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES

The Investigator shall maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator shall retain the study documents at least 15 years after the completion or discontinuation of the clinical trial, or longer should this be required by regulatory requirements.

Should archiving no longer be ensured by the Investigator, he or she shall inform the Sponsor and the relevant records will be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data relating to the patients, CRFs and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to not disclose any information to any third party without the Sponsor's written prior approval.

16.4 PROPERTY RIGHTS

All information, documents and product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

All the results, data, documents and inventions that arise directly or indirectly from the clinical trial in any form shall be the immediate and exclusive property of the Sponsor.

16.5 DATA PROTECTION

The patient's personal data shall be processed in compliance with all applicable laws and regulations.

The Sponsor shall take all appropriate measures to safeguard and prevent access to personal data pertaining to the Investigator and/or to the patients by any unauthorized third party.

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the EC or regulatory authorities.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

The Investigator shall permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to study records for review, being understood that these are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to assist with the audits and inspections by providing access to all facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he or she shall inform the Sponsor and authorize the Sponsor to participate in this inspection. Any result and information arising from the inspections by the regulatory authorities shall be immediately communicated to the Sponsor.

The Investigator shall provide appropriate corrective actions for all issues detected during the audit or inspections.

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

The Sponsor has the right to terminate the study at any time, for any reason.

The Investigator may terminate participation upon thirty (30) days prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study, for any reason whatsoever, the EC and regulatory authorities must be informed according to applicable regulatory requirements.

16.9 PUBLICATIONS AND COMMUNICATIONS

The results of this study may be published or presented at scientific meetings. Should this be foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

Any change or addition to the protocol can be made only through a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the EC. Only amendments that are required for patient safety may be implemented prior to EC approval. Despite the need for approval of formal protocol amendments, the investigator is expected to take

any immediate action required for the safety of any patient even if this represents a deviation from the protocol.

18 BIBLIOGRAPHIC REFERENCES

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