



Evaluation of the efficacy and safety of DM05 versus Optive™ on the treatment of moderate to severe ocular dryness

Clinical Investigational Plan for Medical Device according to ISO standard 14155:2011 and its updates

Clinical Investigational plan #:	15E1122
ANSM registration number:	2016-A01843-48
Investigational medical device :	1. DM05
Comparative medical device	2. Optive™
Form :	1. Sterile emulsion (multidose) 2. Sterile solution (multidose)
Application(s) :	Ocular route
CRO :	DERMSCAN - PharmaScan 114 Boulevard du 11 Novembre 1918 69100 VILLEURBANNE FRANCE
Coordinating Investigator:	Pr Christophe BAUDOUIN Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts 28 Rue de Charenton 75012 Paris FRANCE
Sponsor :	HORUS PHARMA 148 Avenue G.Guynemer Cap Var 06 700 SAINT LAURENT DU VAR FRANCE
Clinical Investigation Plan date and version #:	Final Version 4.0 of 04/09/2017

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ABREVIATION LIST:

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
ANSM	Agence Française de Sécurité Sanitaire des Produits de Santé
CA	Competent Authority
CIP	Clinical Investigational Plan
CNIL	Commission Nationale Informatique et Libertés
CPP	French Ethics Committee - Comité de Protection des Personnes
CRA	Clinical Research Assistant
CRF	Case Report Form
CRO	Clinical Research Organization
CSP	Code de la Santé Publique
D	Day
DMC	Data Monitoring Committee
EC	Ethics Committee
ICH	International Conference on Harmonisation
ITT	Intent To Treat
MD	Medical Device
OSDI	Ocular Surface Disease Index
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TBUT	Tera film Break-Up Time

1- GENERAL INFORMATION

1.1 INTRODUCTION

Dry eye syndrome is 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 affects millions of people worldwide. Symptoms of dry eye vary between patients and can include itching, gritty feeling, burning, foreign body sensation, dryness, photosensitivity, pain, blurred vision, and contact lens intolerance. Dry eye can have an adverse effect on patient quality of life, affecting, in particular, reading, computer use, watching television, and driving. The first mainstay for treatment of stage 1 dry eye is the use of artificial tears, which are predominantly aqueous-based and do not contain a lipid component and probably only provide momentary relief from symptoms and therefore, low patient satisfaction. Given the lipid layer is compromised in certain forms of dry eye, it's often beneficial to add lipids to compensate.

DM05 is a medical device of class IIb. It consists in non-preserved single dose eye drops, containing sodium hyaluronate and lipids which, due to its physical properties (non-irritant water soluble polymer and lipid to avoid evaporation), is used for the moistening and lubrication of the ocular surface. In medical practice, DM05 is intended to improve signs and symptoms related to dry eye.

The objective of this study is to compare DM05 with another medical device already commercialized, Optive™, in terms of improvement of ocular signs and symptoms, on patients with moderate to severe ocular dryness and already treated by artificial tears for at least 3 months. Ninety subjects are planned to be included (45 subjects using each product), with moderate to severe ocular dryness. The efficacy and safety of each product, used between 4 and 6 times per day, will be assessed after 35 and 84 days of treatment.

1.2 IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN (CIP)

TITLE OF THE CIP: Evaluation of the efficacy and safety of DM05 versus Optive™ on the treatment of moderate to severe ocular dryness

CIP #: 15E1122

VERSION AND DATE OF THE CIP: FINAL VERSION 3.0 OF 24/03/2017

SUMMARY OF THE REVISION HISTORY IN THE CASE OF AMENDMENTS:

VERSION 4.0 OF 04/09/2017: MODIFICATION OF SAMPLE SIZE CALCULATION AND SUBJECT NUMBER, ADDITION OF ONE CENTER IN POLAND AND 2 CENTERS IN SPAIN.

VERSION 3.0 OF 24/03/2017: SUPPRESSION OF ONE CENTER IN TUNISIA, ADDITION OF ONE CENTER IN SPAIN, ADDITION OF ONE CENTER IN FRANCE.

VERSION 2.0 OF 05/01/2017: ADDITION OF ONE CENTER IN SPAIN AND E-CRF.

VERSION 1.0 OF 17/11/2016: INITIAL PROTOCOL

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DATA MANAGEMENT AND STATISTICS

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1.5 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

ANSM registration #:	<u>2016-A01843-48</u>
Clinical investigation #:	15E1122
Title of the Clinical Investigation:	Evaluation of the efficacy and safety of DM05 versus Optive™ on the treatment of moderate to severe ocular dryness
Sponsor:	HORUS PHARMA 148 Avenue G.Guynemer Cap Var 06 700 SAINT LAURENT DU VAR FRANCE
Objectives:	<p>Main objective: To demonstrate the non-inferiority of DM05 in comparison with Optive™, in terms of cornea and conjunctiva staining (Oxford score) on patients with moderate to severe ocular dryness, after 35 days of treatment.</p> <p>Secondary objectives</p> <ul style="list-style-type: none"> • To evaluate the efficacy of DM05 in comparison with Optive™ on other signs and symptoms associated to moderate to severe ocular dryness, after 35 and 84 days of treatment • To evaluate the safety of DM05 over 84 days of treatment.
Design:	Multicentric, comparative, randomized, investigator-blinded, in parallel groups study.
Planned Sample Size:	80 subjects included
Number of centers:	7 centers in France, 2 in Poland and 4 in Spain

Inclusion criteria:	<ul style="list-style-type: none"> • Sex: male or female. • Age: more than 18 years. • Subject with a dry eye syndrome needing artificial tears in the 3 months preceding the inclusion. • Subject having used only artificial tears without preservative (NaCl 0.9%, Hydrabak®) during 1 or 2 weeks before inclusion (at 3 drops per day). • Diagnosis of moderate to severe ocular dryness defined by a score OSDI (Ocular Surface Disease Index) ≥ 18. • Subject with at least one eye with: <ul style="list-style-type: none"> - Global ocular staining (cornea and conjunctiva) ≥ 4 and ≤ 9 (Oxford scale from 0 to 15) • AND one the following criteria: <ul style="list-style-type: none"> - Schirmer test $\geq 3\text{mm}/5\text{ min}$ and $\leq 9\text{mm}/5\text{ min}$ • OR - Sum of 3 measurements of Tear film Break-Up Time (TBUT) $\leq 30\text{s}$. • Subject, having given freely and expressly his/her informed consent. • Subject who is able to comply with the study requirements, as defined in the present protocol, at the Investigator's appreciation. • In France: subject being affiliated to a health social security system. • Female subjects of childbearing potential should use a medically accepted contraceptive regimen since at least 12 weeks before the beginning of the study, during all the study and at least 1 month after the study end.
Exclusion criteria:	<ul style="list-style-type: none"> • Pregnant or nursing woman or planning a pregnancy during the study. • Subject deprived of freedom by administrative or legal decision. • Subject in a social or sanitary establishment. • Major subject who is under guardianship or who is not able to express his consent. • Subject being in an exclusion period for a previous study. • Subject suspected to be non-compliant according to the Investigator's judgment. • Subject wearing contact lenses during the study. • Far best corrected visual acuity $< 1/10$ • Subject with severe ocular dryness with one of these conditions: <ul style="list-style-type: none"> - Eyelid or blinking malfunction - Corneal disorders not related to dry eye syndrome - Ocular metaplasia - Filamentous keratitis - Corneal neovascularization • Subject with severe meibomian gland dysfunction (MGD) • Within the last 3 months prior to the inclusion, history of ocular trauma, infection or inflammation not related to dry eye syndrome. • Within the last 12 months, history of ocular allergy or ocular herpes.

Exclusion criteria:	<ul style="list-style-type: none"> Refractive or cataract surgery within the last 6 months. Any laser other than refractive surgery within the last 3 months. Any troubles of the ocular surface not related to dry eye syndrome. Ocular hypertension or glaucoma needing an hypotonic treatment Subject having used artificial tears in the 6 hours preceding the inclusion visit. Use during the month preceding the inclusion or during the study of: isotretinoid, cyclosporine, tacrolimus, sirolimus, pimecrolimus, punctual plugs. Any not stabilized systemic treatment, which can have an effect on performance or safety criteria, at the investigator appreciation.
Investigational device: Name / code:	DM05
Galenic form:	Sterile emulsion (multidose)
Comparator device: Name / code:	Optive™
Galenic form:	Sterile lotion (multidose)
Dosage:	1 to 2 drops in each eye between 4 and 6 times per day
Duration:	84 days
Administration route:	Ocular route
Efficacy Parameters:	<p><u>Main criterion:</u> Evaluation of the non-inferiority of DM05 in comparison with Optive™, in terms of cornea and conjunctiva staining (Oxford score), on worse eye, between D0 and D35.</p> <p><u>Secondary criteria:</u></p> <ul style="list-style-type: none"> Comparison of D35 versus D0 and D84 versus D0 for each product and comparison between products for the following parameters: <ul style="list-style-type: none"> Evolution of cornea and conjunctiva staining (Oxford score) on worse eye. Evolution of OSDI score (Ocular Surface Disease Index). Evolution of Van Bijsterveld score (Lissamine green staining) in worse eye. Evolution of Schirmer test result in worse eye. Evolution of Tear film Break-Up Time (TBUT) in worse eye. Evolution of ocular dryness severity by evaluation of each main symptom by the patient and total score of all symptoms Evaluation of treatment performance by the investigator and the patient. Evaluation of the average frequency of use during 84 days for DM05 and Optive™.
Safety Parameters:	Collection of adverse events and adverse device effects.
Study Procedures:	<p>Selection visit: D-14 to D-7</p> <p>Wash-out period: 1 to 2 weeks with preservative-free 0.9% NaCl at 3 drops per day (Hydrabak®):</p> <p>D0 : inclusion visit</p> <p>Follow-up visits: D35, D84</p>

Statistics:	<p>Three population will be defined:</p> <ul style="list-style-type: none"> - Intention to treat (ITT) population corresponding to all patients randomized - Safety population corresponding to all patients randomized and having received at least one dose of treatment. - Per protocol (PP) population corresponding to patients of the safety population who will not present major protocol deviation (decided by the Data Review Committee during a blind review process days). <p><u>Analysis of the main criterion</u></p> <p><i>Main analysis:</i></p> <p>The main analysis of the main criterion will be conducted on the PP population. The hypothesis of non-inferiority of DM05 compared to Optive® will be tested by calculating the bilateral 95% CI of the difference between groups (DM05 – Optive®) of the change from baseline of global ocular staining in the worse eye on Day 35. A two-way analysis of covariance (ANCOVA) model will be constructed using main effects of treatment and baseline score as covariate. Adjusted means (least square mean and error standard of the mean) by treatment will be presented as well as an estimate of the difference between adjusted means.</p> <p>A 95% two-sided confidence interval, based on the ANCOVA model, will be computed for the difference of DM05 minus Optive®.</p> <p>If the upper bound is no higher than 2 points for the PP population, it will be concluded that the null hypothesis can be rejected and that DM05 is non-inferior to Optive®.</p> <p>The p value of non-inferiority will be expressed taking on board the predefined margin of non inferiority.</p> <p>This analysis will be based on observed cases</p> <p><i>Sensitivity analysis of the main criterion:</i></p> <p>Same analysis will be performed on ITT population with imputation of values in case of missing data with LOCF technique (baseline value or value in case of withdrawal) and without imputation (observed cases).</p> <p>In case of conclusion of non inferiority of DM05 compared to Optive®, the superiority of DM05 compared to Optive® will be tested. The superiority analysis carried out on the ITTT population will be considered as the main analysis. Results will be also provided on the PP population.</p>
Study Duration:	<p>Clinical investigation beginning : February 2017</p> <p>Clinical investigation end: February 2018</p> <p>Clinical investigation global duration: 12 months</p> <p>Duration by subject: 84 days of treatment + 7 to 14 days of wash-out</p>

2- IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 SUMMARY DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND ITS INTENDED PURPOSE

Identification of the device: DM05.

Device classification: Class IIb according to Rule 5 of Annex IX Directive 93/42/EEC amended by Directive 2007/47/EC.

Indication: DM05 is recommended in cases of moderate to severe sensations of dry eyes.

Composition: sodium hyaluronate (0.18%), triglycerides and phospholipids, Sodium carboxymethylcellulose, sodium citrate, citric acid, sodium chlorure and water.

Properties:

DM05 is an emulsion which stabilizes the tear film by acting on the three layers: lipid layer, aqueous layer and mucus layer. It restores the lipid layer thanks to its lipids (triglycerides and phospholipids) to improve lubrication and decrease tear film evaporation. It also contains sodium hyaluronate, component naturally present in the eye, which contributes to protect and moisturize the ocular surface. Thanks to the physical properties of sodium hyaluronate, DM05 has high water retention and viscoelastic properties, which allows the creation of a lubricant, homogeneous and protective film on the ocular surface. In this way, it has an effect on the aqueous layer to moisturize and protect the ocular surface. DM05 is hypo-osmolar to compensate the harmful inflammation induced by the tears hyper-osmolarity in case of ocular dryness. Sodium hyaluronate also has mucus-like properties, which allow to stimulate tear film integration. It is preservative and surfactant free to optimize local tolerance.

Contra-indications:

DM05 is contraindicated in case of hypersensitivity to any component.

Adverse effects:

In some very rare cases, some transitory troubles can appear such as conjunctiva mild irritation, foreign body sensation, ocular redness or burning or temporary blurred vision.

2.2 DETAILS CONCERNING THE MANUFACTURER OF THE INVESTIGATIONAL DEVICE

Legal manufacturer: Horus Pharma - 148 Avenue Georges Guynemer, 06700 Saint-Laurent-du-Var.

2.3 NAME OR NUMBER OF THE MODEL/TYPE

DM05.

2.4 TRACEABILITY OF THE INVESTIGATIONAL DEVICE

Each product will be assigned a batch number to insure its traceability from its production to destruction. During the study, each product will be labelled with a specific label:

The labelling of the products will be realized by DERMSCAN.

Here is presented an example of the labels which will be pasted on each product, in French language:

Primary packaging if applicable:

- Study number:
- Treatment number:
- Product name and batch number:
- Administration route:

Secondary packaging:

- Study site (name and address) :
- Principal investigator: Dr. xxxxx
- Emergency phone number :
- Study number :
- Treatment number :
- Study period :
- Administration route:
- Storage conditions :
- Expiry date :
- Product name and batch number:
- Mention: For clinical use only. External use. Keep out of reach of children

2.5 INTENDED PURPOSE OF THE INVESTIGATIONAL DEVICE IN THE PROPOSED CLINICAL INVESTIGATION

The intended purpose of the investigational device in this clinical investigation is to improve ocular signs and symptoms related to moderate to severe dryness.

2.6 POPULATIONS AND INDICATIONS FOR WHICH THE INVESTIGATIONAL DEVICE IS INTENDED

This medical device is intended for symptomatic treatment of moderate to severe sensations of dry eye. The population that will be included in this clinical investigation will be patients previously treated by artificial tears for at least 3 months and with signs and symptoms of moderate to severe ocular dryness at the inclusion: Ocular Surface Disease Index (OSDI) ≥ 18 and tear deficiency as assessed by Schirmer test and/or TBUT (Tear film Break-up Time).

2.7 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Reference	DM05																		
Formula	<table border="1"> <thead> <tr> <th>Components</th><th>Quantity (%)</th></tr> </thead> <tbody> <tr> <td>Sodium hyaluronate</td><td>0.18 %</td></tr> <tr> <td>Medium chain triglycerid - Miglyol 812</td><td>0,10%</td></tr> <tr> <td>Soy lecithin – Epikuron 170</td><td>0,10%</td></tr> <tr> <td>Sodium carboxymethylcellulose</td><td>0,10%</td></tr> <tr> <td>Citrate 3Na 2H₂O</td><td>0.0412 %</td></tr> <tr> <td>Citric acid</td><td>0.021 %</td></tr> <tr> <td>NaOH (1 N)</td><td>QS pH 6.7</td></tr> <tr> <td>Water for injection</td><td>qsp 100 ml</td></tr> </tbody> </table>	Components	Quantity (%)	Sodium hyaluronate	0.18 %	Medium chain triglycerid - Miglyol 812	0,10%	Soy lecithin – Epikuron 170	0,10%	Sodium carboxymethylcellulose	0,10%	Citrate 3Na 2H ₂ O	0.0412 %	Citric acid	0.021 %	NaOH (1 N)	QS pH 6.7	Water for injection	qsp 100 ml
Components	Quantity (%)																		
Sodium hyaluronate	0.18 %																		
Medium chain triglycerid - Miglyol 812	0,10%																		
Soy lecithin – Epikuron 170	0,10%																		
Sodium carboxymethylcellulose	0,10%																		
Citrate 3Na 2H ₂ O	0.0412 %																		
Citric acid	0.021 %																		
NaOH (1 N)	QS pH 6.7																		
Water for injection	qsp 100 ml																		
Galenic form	Hypo-osmolar sterile emulsion																		
Route/ mode of administration	Ocular route. Instillation in the eyes. Always shake the single-dose unit before instillation.																		
Packaging	Multidose 10 ml vials																		
Confidentiality procedure	Commercial packaging																		
Storage	At room temperature (below 25°C)																		

2.8 SUMMARY OF THE TRAINING AND EXPERIENCE NEEDED TO USE THE INVESTIGATIONAL DEVICE

The use of the investigational device is very simple and doesn't need a special training or experience, as it's intended to be used by the subjects themselves. The instructions for use are described in paragraph 6.2.1.2.

2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE INVESTIGATIONAL DEVICE

Not applicable.

3- JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 SUMMARY OF THE RESULTS OF THE RELEVANT PRE-CLINICAL TESTING/ASSESSMENT CARRIED OUT TO JUSTIFY THE USE OF THE INVESTIGATIONAL DEVICE IN HUMAN SUBJECTS

3.1.1 Cytotoxicity test

The cytotoxicity direct contact test was performed on “DM05” according to ISO 10993-5:2009 in 2014. For the cytotoxicity test by direct contact a confluent BalbC 3T3 cell culture in exponential phase of growth was used.

A qualitative evaluation was performed observing cell culture by an inverted microscope, while a quantitative evaluation was performed using the Neutral Red Uptake method (NRU). The NRU is a method that allows to measure cell vitality using their capacity to incorporate and to bind a cellular vitality “DM05” was applied to the monolayer of BalbC 3T3 and was incubated at 37°C +/- 1°C in CO₂ atmosphere for 24 hours.

After 24 hours of incubation the cells were observed to microscope (qualitative evaluation) to evaluate the biological reaction.

After 24 hours of contact, in the cell treated with test item no detectable zone around or under specimen was observed (reactivity grade 0).

After the qualitative evaluation cells were treated for 3 hours with the Medium containing the cell vitality dye and then with a Desorb Solution that allows to obtain a cell lysate. The optic density was then calculated after a 540 nm spectrophotometric reading.

Cells treated with test sample have shown a cell vitality reduction of 52%.

On the basis of the results, interpreted according to ISO- 10993-5:2009, the test item “DM05” must be considered cytotoxic on this model. This result could be due to the osmolarity of the solution (around 150 µosml-1 instead of 300 and lipid in the solution).

A comparison of the corneal healing process under OPTIVE®, OPTIVE Fusion TM, VISMED® Multi and “DM05” against 0.01 % BAC as positive control in the Ex Vivo Eye Irritation Test (EVEIT) – long-term was performed.

“DM05” showed a rapid corneal healing on day 2 that was superior to any of the other tested products. A minor signs of toxicity was observed at 6 days but are not well understood. Of all listed ingredients in the given concentrations only Miglyol® 812 has been shown to cause minor irritation to the conjunctiva in an animal model, the Draize test. However, one drop per hour is used during 6 days (night and day). This model is not representative of the usual posology (one to two drops 6 times a day as a maximum) In contrast, the safety sheet of the product indicates no ocular toxicity.

3.1.2 Sensitization test

A guinea pig maximization test according to ISO 10993-10:2010 was performed in 2014 on ““DM05”.

A preliminary test was effected on three guinea pig in order to select the adequate concentration.

“DM05” was intradermally injected (induction I) and topically applied (induction II) to ten test guinea pig in attempt to induce delayed sensitization. A negative control solution of 0,9% NaCl was similarly injected and topically applied to five control guinea pigs. Following a recovery period, all the test and control animals received a challenge patch.

All sites were scored at 24 (± 2) and 48 (± 2) hours after patch removal.

No clinical sign was observed throughout the study. No evidence of sensitization by topical route was observed with “DM05” (sensitization grade 0).

Under the condition of this study, the topical application of “DM05” evaluated at a concentration of 100%, according to the ISO 10993-10 standard, did not induce delayed sensitization in the guinea pig (grade

0). Based on this results, “DM05” was not considered a sensitizer in the guinea pig maximization model.

3.1.3 Irritation test

An ocular irritation test according to ISO 10993-10:2010 was performed in 2014 on “DM05”. Each day during 5 consecutive days, 6 instillations of 0,1 mL of MD19 were instilled into the lower conjunctival sac of the left eye of 3 rabbits and 0,1 mL of 0,9 % NaCl solution was instilled into the lower conjunctival sac of the right eye (negative control). Ocular reaction were evaluated by slit-lamp evaluation daily (before and 1 hour \pm 0,1 h after each instillation) and 24 (\pm 2), 48 (\pm 2) and 72 (\pm 2) hours after the last instillation and graded according to the system for grading ocular lesion. The observation of both eye before and after each instillation and 24 (\pm 2), 48 (\pm 2) and 72 (\pm 2) hours after the last instillation did not reveal any ocular irritation. **Under the conditions of this study, “DM05” met the requirement of the eye irritation test according to the procedure described in the ISO 10993-10 standard.**

3.1.4 Conclusion on biological safety evaluation

According to the results of the three above tests, and according to the well-established use of sodium hyaluronate and lipids in medicinal product for many years, “DM05” biological safety could be considered as acceptable.

3.2 SUMMARY OF CLINICAL DATA RELEVANT TO THE PROPOSED CLINICAL INVESTIGATION

The tolerance and efficacy of the tested medical device (DM05) was evaluated in a clinical study realized in Mauritius in 2015.

22 subjects were included in the study.

Product DM05 was well tolerated 30 minutes after its first use and after 14 days of use. Some subjects reported slight functional signs after product use and 4 subjects had a slight corneal staining after instillation on D14. These signs were considered as not relevant by the investigator because they are usual after an instillation of a product in the eyes.

At least 85% of the subjects who presented uncomfortable sign on D0 observed an improvement of their signs from the first product application and the improvement was even better after 14 days of product use.

The product “DM05” was efficient in reducing ocular dryness after 14 days of use.

Product “DM05” was very well appreciated by the subjects for its efficacy on eye dryness, after 14 days of use.

4- RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFITS

Improvement of the signs and symptoms associated to ocular dryness.

4.2 ANTICIPATED ADVERSE DEVICE EFFECTS

In some very rare cases, some transitory troubles can appear such as conjunctiva mild irritation, foreign body sensation, ocular redness or burning or temporary blurred vision.

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4.3 RESIDUAL RISKS ASSOCIATED WITH THE INVESTIGATIONAL DEVICE AS IDENTIFIED IN THE RISK ANALYSIS REPORT

DM05 is contraindicated in case of hypersensitivity to any component.

4.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

There will not be additional risks for the patients, associated with their participation in the clinical investigation.

4.5 POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Maintain a minimum interval of 15 minutes between instillation of another eye drops.

4.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

In case of adverse reaction to the studied MD, the subjects will be asked to call the investigator who will decide if the subject must stop the product use or not. The Investigator can prescribe a rescue treatment if needed.

4.7 RISK-TO-BENEFIT RATIONALE

The benefits for the patients will be a possible improvement of their ocular symptoms and signs associated to ocular dryness.

On the other hand, no specific risk has been identified with the use of this medical device, except the following events that can also be observed with similar devices: stinging or eye glued sensation related to the instillation of the product in the eye.

The balance benefit-risk is then more in favor of the benefits.

5- OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 MAIN OBJECTIVE

To demonstrate the non-inferiority of DM05 in comparison with OptiveTM, in terms of cornea and conjunctiva staining (Oxford score) on patients with moderate to severe ocular dryness, after 35 days of treatment.

5.2 SECONDARY OBJECTIVE(S)

- To evaluate the efficacy of DM05 in comparison with OptiveTM on other signs and symptoms associated to moderate to severe ocular dryness, after 35 and 84 days of treatment.
- To evaluate the safety of DM05 over 84 days of treatment.

5.3 PRIMARY AND SECONDARY HYPOTHESES TO BE ACCEPTED OR REJECTED BY STATISTICAL DATA FROM THE CLINICAL INVESTIGATION

Non-inferiority of DM05 in comparison with OptiveTM, in terms of cornea and conjunctiva staining (Oxford score) after 35 days of treatment on worse eye, with a limit of non-inferiority equal to 2.

5.4 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS THAT ARE TO BE ASSESSED

Non applicable.

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6- DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL INFORMATION

6.1.1 Description of the type of clinical investigation

The clinical investigation will be:

- ◆ single blind (investigator-blinded)
- ◆ randomized
- ◆ in parallel groups,
- ◆ versus comparator,
- ◆ multicentric in France, Poland and Spain,
- ◆ on ambulatory patients.

6.1.2 Description of the measures to be taken to minimize or avoid bias

Because the comparator will be in commercial packaging, the blinding of the subject is not possible.

However, the study will be blinded for the investigator: evaluations will be done by an independent investigator, different than the person who will distribute the product. Subjects will be identified by a patient number. Each patient number will be associated to a treatment number, according to a randomization list provided before the beginning of the clinical investigation, and randomized either in one of both treatment groups (DM05 or Optive®).

6.1.3 Primary and secondary endpoints with rationale for their selection and measurement

6.1.3.1 Primary endpoint

Evaluation of the non-inferiority of DM05 in comparison with Optive™, in terms of cornea and conjunctiva staining (Oxford score), on worse eye, between D0 and D35.

6.1.3.2 Secondary endpoints

- Comparison of D35 versus D0 and D84 versus D0 for each product and comparison between products for the following parameters:
 - Evolution of cornea and conjunctiva staining (Oxford score on a scale) on worse eye.
 - Evolution of OSDI score (Ocular Surface Disease Index).
 - Evolution of Van Bijsterveld score (Lissamine green staining) in worse eye.
 - Evolution of Schirmer test result in worse eye.
 - Evolution of Tear film Break-Up Time (TBUT) in worse eye.
 - Evolution of ocular dryness severity by evaluation of each main symptom by the patient and total score of all symptoms
 - Evaluation of treatment performance by the investigator and the patient.
 - Collection of adverse events and adverse device effects.
- Evaluation of the average frequency of use during 84 days for DM05 and Optive™.

6.1.4 Methods and timing for assessing, recording and analysing variables

At selection and inclusion visits (D-14 to D-7 and D0), evaluations will be done on both eyes.

On D0, the worse eye will be defined as follows:

- If only one eye is eligible (i.e., fulfills all ophthalmological inclusion criteria with no ophthalmological exclusion criteria), the study eye is the eligible eye.

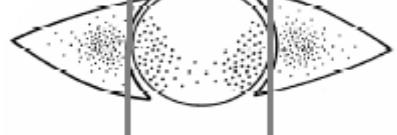
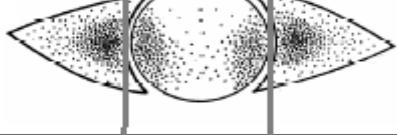
- If both eyes are eligible, the worse eye will be the eye with the highest Oxford score. If both eyes have the same Oxford score, the worse eye will be the eye with the highest Van Bijsterveld Score. If both eyes have the same Van Bijsterveld Score, the worse eye will be the eye with lowest Schirmer test result or lowest TBUT, if both eyes have the same scores, the worse eye will be the right eye.

On D35 and D84, all evaluations except symptoms evaluations (evaluation on average on both eyes) will be done only on the worse eye.

6.1.4.1 Performance criteria

6.1.4.1.1 Cornea and conjunctiva staining (Oxford score)

Cornea and conjunctiva staining will be assessed with a slit lamp after instillation of unpreserved fluorescein in the examined eye. In order to optimize the fluorescein staining signal without any masking by the fluorescence quenching effect, 1 drop of fluorescein will be instilled in the examined eye. Cornea and conjunctiva staining is represented by punctate dots on a serie of panels (A-E). Staining ranges from 0-5 for each zone and from 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on the log scale (Oxford scale) below:

PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than E
<input type="text"/> FROM 0-5	<input type="text"/> FROM 0-5	<input type="text"/> FROM 0-5
	TOTAL SCORE:	<input type="text"/> FROM 0-15

6.1.4.1.2 Ocular Surface Disease Index (OSDI)

The OSDI is assessed on a scale from 0 to 100, with higher scores representing greater disability. The patients will be asked the following 12 questions:

Have you experienced any of the following during the last week?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light.	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answers 1 to 5					A

Have problems with your eyes limited you in performing any of the following <u>during the last week</u> ?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	NA
6. Reading?	4	3	2	1	0	NA
7. Driving at night?	4	3	2	1	0	NA
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	NA
9. Watching TV?	4	3	2	1	0	NA
Subtotal score for answers 6 to 9					B	

Have your eyes felt uncomfortable in any of the following situations <u>during the last week</u> ?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	NA
10. Windy condition?	4	3	2	1	0	NA
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	NA
12. Areas that are air conditioned	4	3	2	1	0	NA
Subtotal score for answers 10 to 12					C	

Add subtotals A, B and C to obtain D (D=sum of scores for all questions answered)	D
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Total number of questions answered (do not include questions answered NA)	E
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OSDI is calculated according to the following formula: $OSDI = D \times 25 / E$

6.1.4.1.3 Van Bijsterveld score

The ophthalmologist will realize a colorimetric test with Lissamine green dye. Lissamine green stains dead and degenerate cells, and does not stain healthy epithelial cells. The evaluation will be done from 1 to 4 minutes after the staining.

The ophthalmologist will determine the dry eye severity with the following scales (Van Bijsterveld Score from 0 to 9¹⁾):

Nasal bulbar conjunctiva

0	1	2	3
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No staining	Confluent staining		

Temporal bulbar conjunctiva

0	1	2	3
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No staining	Confluent staining		

Cornea

0	1	2	3
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No staining	Confluent staining		

Total score: / 9

6.1.4.1.4 Schirmer test

The Schirmer test is a method used to evaluate aqueous tear production.

It consists in inserting a strip (measuring 35 by 5 mm), without anaesthesia, over the lower lid margin of the eye during 5 minutes and then measuring the length of paper wetting in millimeters. The results is expressed in mm/5min.

6.1.4.1.5 Tear Break Up Time (TBUT)

The Tear Break Up Time (TBUT) is the measurement of the break-up time of lacrymal film. This is the time needed by the lacrymal film to cover in an homogeneous and coherent way all the ocular surface. TBUT is assessed with slit lamp examination and expressed in seconds.

To measure TBUT, fluorescein is instilled into the patient's tear film and the patient is asked not to blink while the tear film is observed with slit lamp. The TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film.

The TBUT will be assessed three times and the sum of these three measurements will be calculated.

6.1.4.1.6 Ocular dryness symptoms

The subjects will score their ocular symptoms (**one global score for both eyes**) on structured scales from 0 to 10. These scales are presented below.

1. Discomfort

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

2. Burning / stinging

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

3. Eye dryness sensation

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

4. Itching

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

5. Sandy feeling / Foreign body sensation

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

6. Photophobia

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

7. Blurred vision

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>										
None						Very important				

In case of other symptom(s) declared by the patient, it will be also recorded in the CRF (free text).

The sum of all symptom scores will be calculated to obtain a score from 0 to 70.

6.1.4.1.7 Global treatment performance score

Performance of the treatment will be assessed by the investigator and the patient using the following rating scale:

1. Very satisfactory
2. Satisfactory
3. Not very satisfactory
4. Unsatisfactory

6.1.4.2 Safety criteria

All systemic and ocular adverse events (AE) and adverse device effects (ADE) will be collected and reported by the investigator (see paragraph 14) throughout the study. A daily-log will be given to the subject at each visit in order to write eventual concomitant treatments or adverse events.

6.1.5 Timing for assessing and recording the variables

Procedure	Visit 1 Selection visit (D-14 to D-7)	Visit 2 Day 0	Visit 3 Day 35 ± 3 days	Visit 4 Day 84 ± 7 days
	Wash-out period			
	Treatment period			
Written informed consent	●			
Checking of the inclusion and exclusion criteria	●	●		
Medical history, previous and concomitant treatments, demographic data	●			
Urinary pregnancy test for female subjects with childbearing potential		●		●
Distribution of Hydrabak® (NaCl 0.9%)	●			
Inclusion and random assignment		●		
OSDI score	●	●	●	●
Global ocular staining (Oxford score)	●	●	●	●
Schirmer test	●	●	●	●
TBUT	●	●	●	●
Van Bijsterveld score		●	●	●
Symptoms evaluation by the patient		●	●	●
Treatment performance evaluation by the patient and the investigator			●	●
Distribution of treatments by a third person		●	●	
Distribution of a daily-log	●	●	●	
Adverse events recording		●	●	●
Concomitant medication		●	●	●

6.1.6 Equipment to be used for assessing, recording and analysing variables and arrangements for monitoring maintenance and calibration

Each investigator will use his own slit lamp. Dyes (Fluoresceine Faure 0.5% SDU, Lissamine green) and Schirmer strips will be given by the Sponsor.

6.1.7 Any procedures for the replacement of subjects

No replacement condition is foreseen.

Drop-outs will not be replaced as it is foreseen to randomize 80 subjects for having at least 68 subjects to be analysed.

6.2 INVESTIGATIONAL DEVICE(S) AND COMPARATOR(S)

6.2.1 Description of the exposure to the investigational device(s) or comparator(s), if used

6.2.1.1 Dosage

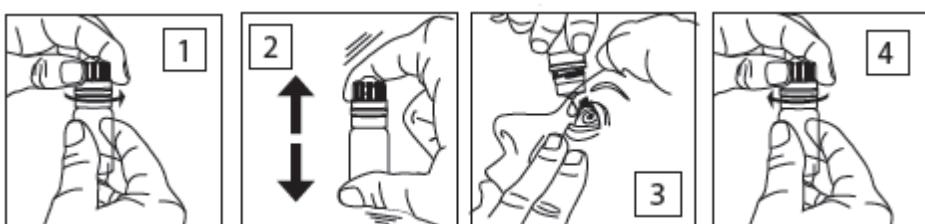
For both investigational medical device (DM05) and comparator (Optive®), one to two drops will be instilled in each eye from 4 to 6 times per day.

6.2.1.2 Instructions for use

DM05:

Wash hands carefully before application.

1. For the first application, verify that the cap seal is not broken and unscrew the cap. You will hear the tamper-proof ring when it breaks for the first time.
2. Always shake the vial before application.
3. Apply 1 to 2 drops from 4 to 6 times per day. With your index finger, draw the lower eyelid gently downwards, while looking up, and then squeeze the vial to apply the eye drops. Do not touch the eyes or eyelids with the tip of the vial. After application, spontaneous blinking will evenly distribute the emulsion over the surface of the eye, creating a transparent and durable film.
4. Seal the vial with the protective cap after every use.



Optive®

Instil one to two drops in each eye from 4 to 6 times per day.

6.2.1.3 Precautions for use

DM05:

- For external use only.
- Do not swallow.
- Store at room temperature (below 25°C).
- Wash hands carefully prior to instillation.
- Always shake the vial before application.
- Do not touch the tip of the vial with hands, eyes or eyelids (risk of microbial contamination).
- Replace the protective cap on the tip of the vial after every use (risk of microbial contamination).

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- Do not use if the vial is damaged (risk of microbial contamination).
- Maintain a minimum interval of 15 minutes between administration of two ophthalmic products.
- Do not use after the expiry date stated on the vial and the package (risk of microbial contamination).
- Keep out of reach and sight of young children.

Optive®

- Do not use if you are allergic to one of the constituent.
- Do not swallow.
- To avoid any contamination, ensure that the dropper does not touch any surface and avoid any direct contact with the eye.
- Carefully close the bottle after use.
- Do not use after the expiry date stated on the bottle
- Keep out of reach of children.
- Keep at room temperature.
- Do not use the bottle if the inviolability cap on the bottle neck is damaged before the first use of the product.
- Respect at least 5 minutes between administration of two ophthalmic products.

6.2.2 Justification of the choice of comparator(s)

Optive®, number two on the French market of medical devices indicated for moderate to severe ocular dryness with 28% of market share (source : GERS- May 2016) and part of the European leaders in ocular dryness is the chosen comparator.

6.2.3 List of any other medical device or medication to be used during the clinical investigation

All patients will be given preservative free artificial tears during the wash-out period.

- **Name of the auxiliary product:** HYDRABAK® (NaCl 0.9%)
- **Composition:**

Name of the ingredients	Centesimal formula (g): 10 mL vial
Active ingredient	
Sodium chloride	0.090 g
Other ingredients	
Sodium dihydrogen phosphate dihydrate	0.0067 g
Disodium phosphate dodecahydrate	0.0317 g
Water for injections	ad 10 mL

- **Form:** Hydrabak® is unpreserved NaCl 0.9 % eye drops, coming from commercially purchased batches. Hydrabak® is to be used within 8 weeks after opening and stored at temperatures below 25°C.
- **Instructions for use**
1 instillation in both eyes 3 times per day.
Instillation of preservative-free artificial tears should not be performed within the 6 hours prior to the D0 visit.

6.2.4 Number of investigational devices to be used, together with a justification

DM05: Each subject will receive 2 vials of 10 ml.
Optive: each subject will receive 2 vials of 10 ml

6.3 STUDIED POPULATION

6.3.1 Inclusion criteria for subject selection

- Sex: male or female.
- Age: more than 18 years.
- Subject with a dry eye syndrome needing artificial tears in the 3 months preceding the inclusion.
- Subject having used only artificial tears without preservative (NaCl 0.9%, Hydrabak®) during 1 to 2 weeks before inclusion (at 3 drops per day).
- Diagnosis of moderate to severe ocular dryness defined by a score OSDI (Ocular Surface Disease Index) ≥ 18 .
- Subject with at least one eye with
 - Global ocular staining (cornea and conjunctiva) ≥ 4 and ≤ 9 (Oxford scale from 0 to 15)
- **AND** one the following criteria:
 - Schirmer test ≥ 3 mm/5 min and ≤ 9 mm/ 5 min
 - **OR**
 - Sum of 3 measurements of Tear film Break-Up Time (TBUT) ≤ 30 s.
- Subject, having given freely and expressly his/her informed consent.
- Subject who is able to comply with the study requirements, as defined in the present protocol, at the Investigator's appreciation.
- In France: subject being affiliated to a health social security system.
- Female subjects of childbearing potential should use a medically accepted contraceptive regimen since at least 12 weeks before the beginning of the study, during all the study and at least 1 month after the study end.

6.3.2 Exclusion criteria for subject selection

- Pregnant or nursing woman or planning a pregnancy during the study.
- Subject who had been deprived of their freedom by administrative or legal decision.
- Subject in a social or sanitary establishment.
- Major subject who is under guardianship or who is not able to express his consent.
- Subject being in an exclusion period for a previous study.
- Subject suspected to be non-compliant according to the Investigator's judgment.
- Subject wearing contact lenses during the study.
- Far best corrected visual acuity $< 1/10$.
- Subject with severe ocular dryness with one of these conditions:
 - Eyelid or blinking malfunction
 - Corneal disorders not related to dry eye syndrome
 - Ocular metaplasia
 - Filamentous keratitis
 - Corneal neovascularization
- Subject with severe meibomian gland dysfunction (MGD).
- Within the last 3 months prior to the inclusion, history of ocular trauma, infection or inflammation not related to dry eye syndrome.
- Within the last 12 months, history of ocular allergy or ocular herpes.
- History of inflammatory corneal ulcer, recurrent corneal erosion, uveitis.
- Refractive or cataract surgery within the last 6 months.
- Any laser other than refractive surgery within the last 3 months.
- Any troubles of the ocular surface not related to dry eye syndrome.
- Ocular hypertension or glaucoma needing an hypotonic treatment
- Subject having used artificial tears in the 6 hours preceding the inclusion visit.
- Use during the month preceding the inclusion or during the study of: isotretinoid, cyclosporine, tacrolimus, sirolimus, pimecrolimus. punctual plugs.
- Any not stabilized systemic treatment, which can have an effect on performance or safety criteria, at the investigator appreciation.

6.3.3 Point of enrolment

Estimated date of clinical investigation beginning: February 2017.
Estimated date of clinical investigation end: February 2018.

6.3.4 Total expected duration of the clinical investigation

13 months.

6.3.5 Expected duration of each subject's participation

84 days of treatment + 7 to 14 days of wash-out.

6.3.6 Number of subjects required to be included in the clinical investigation

80 patients are expected to be randomized in the clinical investigation: 40 patients in each group of treatment.

6.3.7 Estimated time needed to select this number in the clinical investigation (enrolment period)

9 months.

6.4 PROCEDURES

6.4.1 Description of all the clinical-investigation-related procedures that patients undergo during the clinical investigation

Selection visit (D-14 to D -7)

- The ophthalmologist will propose to his/her patient to participate to the clinical investigation.
- Information of the patient on study aims and schedule.
- Signature of information sheet and consent form in two copies by the patient and the investigator.
- Collection of previous medical and ophthalmological history, previous and actual treatments, demographic data.
- The ophthalmologist will evaluate the Ocular Surface Disease Index, the global ocular staining (Oxford score) and will realize the Schirmer test and TBUT.
- Checking of inclusion and exclusion criteria.
- If the patient is eligible, distribution of Hydrabak® to be used three times per day in both eyes until the inclusion visit, as well as a daily log to write eventual concomitant treatments and adverse events.

Inclusion visit (D0)

- The patient will bring back the Hydrabak® and the daily-log completed.
- Collection of adverse events and concomitant treatments.
- The ophthalmologist will evaluate the Ocular Surface Disease Index, the global ocular staining (Oxford score) and will realize Schirmer test and TBUT.
- Checking of inclusion and exclusion criteria.
- If the patient is eligible, inclusion of the patient and attribution of a randomization number.
- The ophthalmologist will evaluate the Van Bijsterveld score.
- The patient will evaluate his/her ocular symptoms.
- A third person will distribute the treatment according to the randomization list and explain the mode of use of the treatment, as well as a daily log to write eventual concomitant treatments and adverse events

D35

- The patient will bring back the treatments (used and non-used) and the daily-log completed.

- Collection of adverse events and concomitant treatments.
- The ophthalmologist will evaluate the Ocular Surface Disease Index, the global ocular staining (Oxford score), the Van Bijsterveld score and will realize Schirmer test and TBUT.
- The patient will evaluate his/her ocular symptoms.
- The patient and the investigator will evaluate the treatment performance on a 4-point scale.
- A third person will distribute the treatment according to the randomization list and remain the patient about the mode of use, as well as a daily log to write eventual concomitant treatments and adverse events.

D84

- The patient will bring back the treatments (used and non-used) and the daily-log completed.
- Collection of adverse events and concomitant treatments.
- The ophthalmologist will evaluate the Ocular Surface Disease Index, the global ocular staining (Oxford score), the Van Bijsterveld score and will realize Schirmer test and TBUT.
- The patient will evaluate his/her ocular symptoms.
- The patient and the investigator will evaluate the treatment performance on a 4-point scale.

6.4.2 Description of activities performed by Sponsor representatives (excluding monitoring)

The Sponsor has delegated the following activities to the CRO (Dermscan):

- Submission of the study files to the EC and competent authority
- Monitoring of the study
- Data management
- Statistical analysis and clinical investigation report writing.

6.4.3 Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results

Not applicable.

6.5 MONITORING

The monitoring of the study will be done by Dermscan. The monitor has the responsibility to familiarise the Investigator(s) and the centre staff involved in the study with all study procedures if necessary. The monitor has the responsibility of reviewing the ongoing study with the Investigator(s) to verify adherence to the CIP and to deal with data queries as well as any problems that arise during the conduct of the study.

6.5.1 Monitoring visits

6.5.1.1 Selection visit

Before any involvement of a clinical research centre/private practice into the study, the CRA and/or the study monitor should perform a selection visit in order to verify:

- adequate human and technical resources,
- adequate recruitment capabilities,
- availability regarding planning constraints.

6.5.1.2 Initiation visit

Before any subject's enrolment, the CRA and/or the study monitor will conduct an initiation visit in order to familiarize the centre's staff with the study CIP and schedule.

This visit will also be the occasion to review with the center:

- the Investigator file which should contain:
 - the study CIP,

- the curriculum vitae of the Investigator,
- the Authorization as a clinical centre, if applicable,
- the insurance certificate,
- the favourable opinion of the ethic committee,
- the approval of CA,
- the Investigator brochure,
- the financial agreement between all parts,
- all necessary documents for study follow-up, etc.
- the CRF and the way to complete it,
- the information sheet and consent forms and the way to obtain consent,
- the investigational products,
- the study material (pregnancy test, etc.),
- and all other necessary aspects and materials detailed in the study CIP.

6.5.1.3 Monitoring visits

For the duration of the study, monitoring visits may be performed by the CRA in order to check the study performance in accordance with the study CIP.

The Clinical Research Associate ensures the coherence and the veracity of the data reported in the Case Report Form compared to the source data. He/she verifies that the study is performed according to the CIP and that all documentation necessary to ensure a good follow-up of the study is present and well completed.

These visits will also serve to ensure product accountability.

During these visits, the CRA reserves the right to ask for queries resolution, directly in the document(s) concerned or with specific data clarification forms. He/she ensures the completion of the Investigator file and retrieves all documents necessary for updating the trial master file.

When applicable, the CRA may retrieve duplicate of the CRF to be sent to the data management department.

6.5.1.4 Close-out visit

A close out visit will take place after the study has come to a conclusion. The CRA will retrieve all study products, materials, CRFs, consent forms (if applicable) and to confirm the completion of the Investigator file, including all study related documents. When necessary, the Sponsor may also ask for the resolution of any delayed queries in the CRFs.

6.5.2 Access to source data

In accordance with good clinical practices and the standards of the data protection law, data obtained in the course of a biomedical research has to be treated confidentially to guarantee the subjects' privacy.

The Investigator agrees that, subject to local regulations and ethical considerations, the Sponsor representatives designee and/or and any regulatory agency have direct access to all study records, CRFs, corresponding subject medical records, study drug dispensing records and study drug storage area, and any other documents considered source documentation. The Investigator also agrees to assist the representative, if required.

7- STATISTICAL CONSIDERATIONS

7.1 STATISTICAL DESIGN, METHOD AND ANALYTICAL PROCEDURES

A Statistical Analysis Plan (SAP) specifying analyses in detail will be written before blind review and locking the database.

The statistical analysis will be performed after the data has been cleaned and after the database is locked.

No interim analysis is planned.

7.1.1 Analysed population

Three populations will be defined:

- Intention to treat (ITT) population corresponding to all patients randomized
- Safety population corresponding to all patients randomized and having received at least one dose of treatment
- Per protocol (PP) population corresponding to patients of the safety population who will not present major protocol deviation (decided by the Data Review Committee during a blind review process)

7.1.2 Primary endpoint

7.1.2.1 Main analysis

The main analysis of the main criterion will be conducted on the PP population. The hypothesis of non-inferiority of DM05 compared to Optive® will be tested by calculating the bilateral 95% CI of the difference between groups (DM05 – Optive®) of the change from baseline of global ocular staining in the worse eye on Day 35. A two-way analysis of covariance (ANCOVA) model will be constructed using main effects of treatment and baseline score as covariate. Adjusted means (least square mean and error standard of the mean) by treatment will be presented as well as an estimate of the difference between adjusted means.

A 95% two-sided confidence interval, based on the ANCOVA model, will be computed for the difference of DM05 minus Optive®.

If the upper bound is no higher than 2 points for the PP population, it will be concluded that the null hypothesis can be rejected and that DM05 is non-inferior to Optive®.

The p value of non-inferiority will be expressed taking on board the predefined margin of non-inferiority.

This analysis will be based on observed cases.

7.1.2.2 Sensitivity analysis

Same analysis will be performed on ITT population with imputation of values in case of missing data with LOCF technique (baseline value or value in case of withdrawal) and without imputation (observed cases).

In case of conclusion of non-inferiority of DM05 compared to Optive®, the superiority of DM05 compared to Optive® will be tested. The superiority analysis carried out on the ITTT population will be considered as the main analysis. Results will be also provided on the PP population.

7.1.3 Secondary endpoint(s)

Quantitative data:

Quantitative variables will be summarized by number of patients, mean, median, standard deviation, minimum, and maximum for each time point. Changes from baseline will also be calculated and tabulated for each time-point (D35-D0 and D84-D0).

A mixed ANOVA model (PROC MIXED) for repeated measures will be fitted to raw data, including the factor treatment as fixed (2 levels), time as fixed (3 levels), and product by time interaction, as well as the patient effect as random.

From this model, the contrasts of interest will be built on the adjusted means:

- * to test whether each change from baseline (D35-D0 and D84-D0) differ significantly from 0 by product.
- * to test whether the products differ significantly for each change from baseline (D35-D0 and

D84-D0).

The underlying assumptions (normality and homoscedasticity) will be checked using Shapiro-Wilk test and graphical representations of the residuals. In case of strong deviation, a non-parametric approach will be performed.

Qualitative data:

Categorical variables will be summarized with frequency and percentages for each time point.

For the global performance, treatments groups will be compared with a Chi2 test.

For other qualitative variables, the changes from baseline for each product will be assessed with a Wilcoxon signed-rank test. The comparison between the treatments will be assessed with a Mann-Whitney test for each change from baseline (D35-D0 and D84-D0).

Safety data:

The safety data will be summarised using descriptive statistics by treatment group in the Safety population.

Summary safety assessments include AEs, best-corrected visual acuity, ocular symptoms and the global tolerance assessment by the investigator.

The adverse events will be coded using the MedDRA dictionary. The evaluation of the adverse events only considers the treatment-emergent AEs (TEAEs) with onset date on or after the day of the first study drug instillation.

The ocular TEAEs and the non-ocular TEAEs will be analysed separately.

The number and percentage of patients experiencing at least one AE will be provided by treatment group, by primary SOC and PT, for the following categories of events:

- All AEs
- All TEAEs
- Maximum severity for all events by PT (regardless of causality)
- Treatment-related AEs
- Serious AEs
- AEs that lead to study withdrawal.

The difference between treatments groups on the incidence rate will be analyzed for each PT using Fisher's exact test.

The statistical significance level of 5% will be applied for the safety analyses.

- The best-corrected visual acuity will be described in the worse eye and in the contralateral eye, at each visit and change from baseline.
- The usual severity and the usual duration of each ocular symptom upon instillation will be described at each D35 and D84 visits.
- The global tolerance assessment by the investigator will be described at each D35 and D84 visits.

7.2 SAMPLE SIZE AND ITS STATISTICAL JUSTIFICATION

The primary objective of this study is to confirm the non-inferiority of DM05 in comparison with Optive™ reference for global ocular staining assessed with a 0-15 score (Oxford score). The clinical non-inferiority margin was set at 2 points on the Oxford score. Assessing a standard-deviation equal to 2.5, a total of 68 patients (34 patients in each group) is required to reach a power of 90% to set-up the non-inferiority based on a bilateral confidence interval at 95%.

Assuming a drop-out rate of 15%, 80 patients will be randomized in the study to keep sufficient power for main analysis of the primary end point (analysis on PP population).

7.3 LEVEL OF SIGNIFICANCE AND POWER OF THE CLINICAL INVESTIGATION

All statistical tests will be assessed at $\alpha = 5\%$ level of significance in a bilateral approach.

7.4 STATISTICAL PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE CLINICAL INVESTIGATION

Non-inferiority of DM05 versus Optive with a non-inferiority margin set at 2 points on the Oxford score.

7.5 PROVISION FOR AN INTERIM ANALYSIS, WHERE APPLICABLE

No interim analysis is foreseen.

7.6 CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

As no intermediary statistical analysis has been planned, no statistical criteria for the termination of the clinical investigation has been defined.

7.7 PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any modification to the statistical analysis plan due to a substantial modification of the CIP will be documented as an amendment and will be described in the final study report if applicable.

7.8 SPECIFICATION OF SUBGROUPS FOR ANALYSIS

Not applicable.

7.9 PROCEDURES THAT TAKE INTO ACCOUNT ALL THE DATA

Three populations will be defined:

- Intention to treat (ITT) population corresponding to all patients randomized
- Safety population corresponding to all patients randomized and having received at least one dose of treatment
- Per protocol (PP) population corresponding to patients of the safety population who will not present major protocol deviation (decided by the Data Review Committee during a blind review process).

7.10 TREATMENT OF MISSING, UNSUED OR SPURIOUS DATA, INCLUDING DROP-OUTS AND WITHDRAWALS

In the case of missing values, the last observation carried forward (LOCF) method will be applied using at each visit the last observation available for analysis on FAS and PP.

7.11 EXCLUSION METHOD OF PARTICULAR INFORMATION FROM THE TESTING OF THE HYPOTHESIS, IF RELEVANT

Not applicable.

7.12 IN MULTICENTRE INVESTIGATIONS, MINIMUM AND MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED BY EACH CENTRE

The recruitment will be competitive between the different centers. No minimum and maximum number of patients will be set for each center.

8- DATA MANAGEMENT

8.1 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING AND ISSUING/RESOLVING DATA QUERIES

8.1.1 Identification of source data

All clinical data in the CIP and collected by the Investigator will be notified in the source document. OSDI questionnaire and daily log completed by the subjects will be considered as source documents.

8.1.2 Case report Form completion

e-CRFs will be used for this study. The investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. An investigator who has signed the protocol signature page or his/her authorized designee is to personally sign the eCRFs (as indicated on the eCRF) to

validate that the observations and findings are recorded on the eCRFs correctly and completely. The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed, and explained, if necessary, and shall not obscure the original entry (ie, an audit trail shall be maintained); this applies to both written and electronic changes or corrections.

8.1.3 Data management and review

8.1.3.1 Data management

Data management will consist in the different following steps:

- Redaction of a data management plan and a data validation plan.
- Redaction of e-CRF specifications and completion guidelines for the investigators
- Redaction of annotated CRF
- Programming and validation of consistency controls
- Data Clarifications Forms (DCFs) emission and database correction
- Data listings emission
- MedDRA coding of AE/ADE and WhoDrug for concomitant medications and validation of the coding by an expert
- Data Management report

8.1.3.2 Data Review

A blind data review will be organised at DERMSCAN – PharmaScan, 114 Boulevard du 11 Novembre 1918, 69100 VILLEURBANNE – FRANCE or by phone.

Will be present a minima the sponsor, DermScan project manager, the statistician and the study monitor. Study coordinating investigator may be present by phone.

The study review will aim at determining the analysis population by:

- reviewing the conditions of study's realisation,
- determining the populations for the statistical analyses,
- specifying all the protocol's deviations as major or minor,
- reviewing the statistical analysis plan.

Following the study review, the statistical analysis populations will be defined and a report will be written and validated by DERMSCAN and the Sponsor. The data base will thus be corrected and locked.

8.1.4 Preparation and lock of the Database

The database will be locked upon resolution of all queries. A copy of the locked database will be sent to the Sponsor. A signed database lock form will be provided.

After the database will be locked, any change to the database can only be done from database correction forms approved by the Project Manager and the Sponsor. If the database will need to be corrected, lock/unlock of the database must be clearly documented by the Project Manager in the study file.

8.1.5 Data unblinding at study end

Unblinding of the assigned treatments will occur after the completion of the following steps:

1. All CRF data are entered into the computer;
2. All data clarifications, if any, are resolved;
3. Major deviations or intercurrent events, if any, are defined and identified;
4. All information necessary to analyze the data is integrated into the data base;
5. The database is formally locked.

8.2 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS, IF APPLICABLE

Not applicable.

8.3 PROCEDURES FOR DATA RETENTION AND SPECIFIED RETENTION PERIOD

The Sponsor must archive the CIP, documentation, approvals and all other essential documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out, for 15 years DermScan - PharmaScan will archive all documents concerning the study as detailed below:

- All documents must be archived in a secure place and treated as confidential material.
- Paper documents relating to this study are stored maximum during one year on site before to be transmitted for archiving to an approved service provider.
- Data will be archived securely as digital and paper version for 15 years from the date of dispatch of the final report's acceptance.

At the end of this period of 15 years, the study archives will be destroyed unless otherwise stipulated in writing by the Sponsor.

8.4 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE, AS APPROPRIATE

In order to ensure the conformity of the studies entrusted to Good Clinical Practices and regulatory requirements, DERMSCAN has implemented a quality management system which has been certified ISO 9001:2008. This system consists of procedures and quality controls.

9- AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Any modification to the CIP will be treated as a substantial or non-substantial modification, according to its nature, and will be submitted for opinion/approval to the Ethics Committee and/or Competent Authority.

10- DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

10.1 STATEMENT SPECIFYING THAT THE INVESTIGATOR IS NOT ALLOWED TO DEVIATE FROM THE CIP

The Investigators are not allowed to deviate from the CIP, excepted under emergency circumstances, to protect the rights, safety and well-being of the subjects. In this case, such deviations shall be documented and reported to the Sponsor and the EC as soon as possible.

10.2 PROCEDURES FOR RECORDING, REPORTING AND ANALYSING CIP DEVIATIONS

All CIP deviations will be managed according to DermScan SOP.

A priori, subjects having at least a major deviation and subjects with insufficient treatment duration or without any evaluation of main criterion will be excluded from PP analysis.

Nevertheless, all observations will be discussed during the « data review » which occurs before data analysis.

10.3 NOTIFICATION REQUIREMENTS AND TIME FRAMES

All deviations observed by the CRA during monitoring visits will be reported to the Sponsor in the monitoring report, within maximum 10 days after the visit.

In case of serious GCP and protocol deviations the CRA should report to the Sponsor by a phone call or writing an email within 24 hours.

At the study end, all deviations will be summarized and analyzed in the data review report, sent to the Sponsor.

10.4 CORRECTIVE AND PREVENTIVE ACTIONS AND PRINCIPAL INVESTIGATOR DISQUALIFICATION CRITERIA

If major deviations from an investigator are observed during monitoring, the CRA will warn the investigator of the importance to respect the CIP. An investigator who continuously violates the CIP despite CRA warnings could be excluded from the investigation after agreement of the Sponsor.

11- DEVICE ACCOUNTABILITY

The IMD should only be dispensed only under the supervision of a physician approved for the study. The Investigator (or delegate) is responsible for dispensing the study products to the patients who are randomised in the study. The study devices must not be administered to patients who are not randomised in the study.

A preprinted accountability form provided by the CRO must be kept current and must identify the subject number/the number of the IMD dispensed, and the amount of IMD dispensed to and returned by each subject at each visit, with the corresponding dates.

All IMD supplies (empty containers, as well as partly used and unused IMD) must be available for inspection at every monitoring visit. The CRA or Sponsor delegate should verify the investigational site's

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products accountability records against record of administrated doses in the CRF. All used and non-used products will be destructed after signature of the clinical report.

12- STATEMENTS OF COMPLIANCE

12.1 DECLARATION OF HELSINKI

The investigation will be performed on patients, in accordance with the ethical principles that have their origin in the declaration of Helsinki.

The current revision of the Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the CIP. Independent assurance that subjects are protected can only be provided by an ethics committee/institutional review board and freely obtained informed consent. It is the responsibility of the Investigator(s) to ensure that the study is conducted in full conformance with the principles of the current Revised Version of the Declaration of Helsinki.

12.2 ISO 14155 STANDARD AND LOCAL REGULATIONS

The investigation will be performed according to standard ISO 14155:2011 and its updates, and any regional or national regulations.

12.3 EC AND/OR REGULATORY AUTHORITIES

It is the responsibility of the Sponsor or its legal representative to submit a copy of the CIP and detailed patient information sheet and consent form to an ethics committee/institutional review board in order to obtain independent approval to conduct the study. Ethics committee/institutional review board approval must be obtained before the study is started. The approval of the ethics committee/institutional review board must be sent in writing, to the Sponsor or its legal representative. The Ethics Committee approval letter must mention the Ethics Committee members and their function.

In parallel or after the Ethics Committee submission, the Sponsor or its legal representative must address an authorization request to the national competent authority, if applicable.

Any clinical trial cannot be performed without having obtained the agreement of the Ethics Committee and the inherent authorization of the national competent authority (if applicable).

12.4 INSURANCE

The Sponsor has subscribed an insurance contract to cover the liability of the Investigators, the Sponsor himself and anyone involved in the study.

The copy of the insurance certificate is presented separately in the EC and CA submission file.

13- INFORMED CONSENT PROCESS

13.1 GENERAL PROCESS FOR OBTAINING INFORMED CONSENT

It is the responsibility of the Investigator(s) to obtain informed consent from each subject participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study.

It should be completely and unambiguously clear to each subject that she/he is free to refuse to participate in the study, or that she/he can withdraw her/his consent at any time and for any reason, without incurring any penalty or withholding of treatment on the part of the Investigator.

The consent obtaining should be done under such conditions that permit to the subject to consider in the best way the ratio benefits/ risks associated to his/her participation in the study.

The Investigator insures that the content of the information and consent form is appropriate to the study and that the process for obtaining the consent is in conformity with the applicable regulation.

In the frame of this study, the consent will be obtained before any study-specific procedures were performed, and thus in accordance with the Helsinki declaration.

No subject could be included and/or randomized before having signed the consent form, written in an understandable language.

Each subject will receive oral and written information concerning the studied product(s), its nature, the duration and the conditions of the study. The consent will be personally signed and dated by the subject in two copies and by the person in charge of the consent obtaining.

Each subject will receive an original of the information sheet and consent form, dated and signed. The second original of the signed and dated consent form will be archived in the Investigator file. The Investigator will complete and keep a list of subjects having given their consent. No copy of this list will be given to the Sponsor.

13.2 INFORMED CONSENT PROCESS IF THE SUBJECT IS UNABLE TO GIVE IT

Non applicable.

14- ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 DEFINITIONS

Table 1 below presents categorization of adverse events

Table 1- Adverse event categorization

ADVERSE EVENTS	Non-device-related	Device- or procedure-related	
Non-serious	Adverse Event (AE) ^a	Adverse Device Effect (ADE)	
Serious	Serious Adverse Event (SAE) ^b	Serious Adverse Device Effect (SADE)	
		Anticipated	Unanticipated
Anticipated Serious Adverse Device Effect (ASADE)		Unanticipated Serious Adverse Device Effect (USADE)	

^a Includes all categories
^b Includes all categories that are serious

The definitions of the different terms are presented below.

14.1.1 Adverse event (AE)

"Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device".

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This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational medical devices.

14.1.2 Adverse device effect (ADE)

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

This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

14.1.3 Device deficiency

“Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.”

Device deficiencies include malfunctions, use errors, and inadequate labeling.

14.1.4 Serious adverse event (SAE)

A serious adverse event is defined as an adverse event that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 - 1. a life-threatening illness or injury, or
 - 2. a permanent impairment of a body structure or a body function, or
 - 3. in-patient or prolonged hospitalization, or
 - 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death, or a congenital abnormality or birth defect

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

14.1.5 Serious adverse device effect (SADE)

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

14.1.6 Unanticipated Serious Adverse Device Effect (USADE)

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

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

14.1.7 New fact definition (Article L. 1123-10 du CSP)

Fact concerning the sequence of the research and likely to endanger the subjects security. In general it concerns all new information which might lead to a negative re-evaluation of the benefit/risk ratio of the research or which might be sufficient for modifications to be envisaged in the administration of the experimental product, the line of research, or documents related to the research.

14.1.8 Severity

Severity is a clinical determination of the intensity of an adverse event. The severity assessment for a clinical adverse event is to be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

14.1.9 Relationship to the investigational medical device

The Investigator must determine the relationship (if any) between an adverse event and the device or treatment procedure. An adverse event could be considered treatment-related when, in the judgment of the Investigator, it is reasonable to believe that the event may have been caused by the device or is associated with the procedure, such as an event that can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

14.2 TIMELINES FOR REPORTING

The Investigator must report the different types of adverse events according to the following table:

Table 2- Timelines for reporting

Adverse Event Type	Reporting by the Investigator to the Sponsor	Reporting by the Sponsor to the EC and competent authorities
AES, ADEs	Record on CRF adverse event form upon awareness for review by the clinical monitor	<i>Not reported</i>
SAEs, SADEs	Record on Serious Adverse Event Form and fax or email to the Sponsor within 24 hours of awareness	<p>- SAE associated with an impending risk of death, or for an injury or serious disease and requiring a quick medical treatment for others patients / subjects, users or other person or for any new information: immediately upon awareness, at the latest within 7 days in France, Tunisia, Poland and Spain. For Tunisia, when the death concerns a subject included in Tunisia, this delay is shortened to 48 hours.</p> <p>-in other SAE or any related news: immediately upon awareness, at the latest within 15 days in France, Tunisia and Spain and within 7 days in Poland.</p>

14.3 GENERAL PROCESS FOR REPORTING ADVERSE EVENTS AND DEVICE DEFICIENCIES

14.3.1 Documentation

All adverse events shall be documented in a timely manner throughout the clinical investigation in the source file and the CRF and shall be reported as specified below.

All adverse events shall be reported in an interim or final report of the clinical investigation.

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the Sponsor.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

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

shall be reported as specified below.

14.3.2 Reporting by the Investigator

The principal Investigator shall:

- a) record every adverse event and observed device deficiency, together with an assessment,
- b) report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports,
- c) report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or by the EC,

- d) report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations,
- e) supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

14.3.3 Reporting by the Sponsor

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

- a) review the Investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the Sponsor and the principal Investigator(s), the Sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,
- b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the Sponsor and the principal Investigator(s), the Sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,
- c) report or ensure the reporting to the EC by the principal Investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the EC,
- d) report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP,
- e) report all relevant safety information to the DMC, if established, according to written procedures,
- f) in the case of a multicentre clinical investigation, inform all principal Investigators in writing of all the serious adverse events at all investigation sites that have been reported to the Sponsor, and ensure that they are reported to their EC, if required by national regulations or by the EC, whichever is more stringent; this information shall be sent to all the principal Investigators within a time frame established based on the perceived risk as defined in the risk analysis report,
- g) ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation,
- h) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

14.4 PROCESS FOR REPORTING SERIOUS ADVERSE EVENTS AND CONTACT DETAILS

14.4.1 Documentation and declaration of Serious Adverse Event (SAEs, SADEs) by the Investigator to the Sponsor

The declaration of Serious Adverse Event (Events, Reactions, or suspicion of Serious Adverse Reactions), Adverse Reactions requiring a medical treatment or which seem to have a character of seriousness is a legal requirement.

The Investigator must report all these adverse events in the source file, the "adverse event documentation" form in the CRF, and in the SAE notification form.

The Investigator must immediately notify by telephone, fax, or e-mail the Sponsor and DERMSCAN at the latest, **within 24 hours of the Investigator becoming aware of the event**, all SAE except for those recorded in the CIP or the Investigator's brochure as not requiring an immediate notification.

Materiovigilance Department
 Horus Pharma
 Address 148 avenue G Guynemer Cap Var 06700
 Saint Laurent du Var France
 TEL: +33 (0)4 93 19 54 03
 FAX: +33 (0)4 93 19 54 09
vigilance@horus-pharma.fr

This first notification is confirmed by sending the form by fax (fax n° indicated in the CIP) or by e-mail with an acknowledgement of receipt, to the Sponsor and DERMSCAN **within 48 hours of knowledge by the Investigator**. Without acknowledgement of receipt of fax or e-mail, a letter with acknowledgement of receipt is also sent to the Sponsor accompanied by the form.
 As a part of monitoring of serious adverse events, if necessary, this 1st notification will be followed by additional detailed written reports.

The Investigator must notify the Sponsor of adverse events and of the results of abnormal analyses defined in the CIP as determining factors for the evaluation of the safety of individuals participating in biomedical research, in conformance with the notification requirements specified in the CIP and within the time constraints also specified in the CIP.

In notifications, individuals participating in research are identified by a code number.

14.4.2 Declaration of the serious adverse events (SAEs, SADEs) by the Sponsor in France

In conformance with the French Public Health law 2004-806 of 9 August 2004, its decree of application and orders, the Sponsor reports all serious adverse events occurred during the research by electronic mail to the Competent Authority and to the Ethics Committee by electronic mail, fax or post mail (all with acknowledgement of receipt).

In case of clinical investigation conducted with a blind, the Sponsor lifts the blind prior to reporting a Suspected Unanticipated Serious Adverse Device Effect (SUSADE) to the CA and the EC concerned.

The notification deadline to the CA and the EC are:

- in the event of SAE associated with an impending risk of death, or for an injury or serious disease and requiring a quick medical treatment for others patients / subjects, users or other person or for any new information: immediately, at the latest within 7 days.
- in other SAE or any related news: immediately, at the latest within 15 calendar days of the Sponsor becoming aware of the event.

14.4.3 Declaration of the serious adverse events (SAEs, SADEs) by the Sponsor in Tunisia, Poland and Spain.

The serious adverse events, including the ones related to the study device, shall be reported by the Sponsor to the regulatory authorities and EC as required by national regulations applicable for medical products. This declaration will be delegated by the Sponsor to DermScan.

14.4.3.1 Sponsor's annual report to the Competent Authority and to the Ethics Committee

Once per year for the duration of the research or on request the sponsor transmits a safety report with all the available safety information to the CA and the EC. This report includes notably, the list of all the suspected serious adverse reactions and an analysis of the information regarding the safety of individuals participating in the research.

14.5 PROCESS FOR REPORTING A PREGNANCY

The occurrence of a pregnancy (reported or diagnosed) after screening but before inclusion (first use of the investigational product) in the study is not reported to the Sponsor unless severity criteria (like SAE related to CIP procedures). If the pregnancy is confirmed, the studied product must not be administrated and the subject immediately withdrawn from the study.

If the pregnancy is suspected during products administration phase, the product must be stop immediately and until result of the pregnancy test.

If the pregnancy is confirmed, the product is definitively stopped and the subject withdrawn from the study.

The Investigator must immediately notify the Sponsor of the pregnancy using specific form and reports it in the "adverse event documentation" of the CRF.

Women who become pregnant during the study will be followed until the outcome of the pregnancy is known, and reported to the Sponsor (baby health).

14.6 LIST OF FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

In some very rare cases, some transitory troubles can appear such as conjunctiva mild irritation, foreign body sensation, ocular redness or burning or temporary blurred vision.

14.7 INFORMATION REGARDING THE DATA MONITORING COMMITTEE (DMC), IF ESTABLISHED

Not applicable.

15- VULNERABLE POPULATION

Not applicable. The population studied during the clinical investigation is not considered as a vulnerable population

16- SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 CRITERIA AND MODALITIES OF PREMATURE END OF TREATMENT OR SUBJECT EXCLUSION FROM THE CLINICAL INVESTIGATION

Subjects will be free to withdraw from the study at any time if they wish so and for any reason, without having to provide any justification to the Investigator.

The Investigator has the right to withdraw a subject for any reason, for subject's best interests, including illness or adverse events.

The Sponsor may decide to withdraw subjects for major deviation to the CIP, for administrative reasons or for any other valuable reason ethically justified.

Subjects may discontinue the study for the following reasons:

1. *Subject consent withdrawal*: subjects have the right to exit from the study at any time and for any motive, without their right to treatment being affected.
2. *Medical reasons or adverse events*: the Investigator has the right to withdraw a subject in case of intercurrent illness or adverse events or if in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
3. *Appearance of an exclusion criterion*.

4. *Failure to follow-up:* if a subject does not come to the scheduled visits, several attempts have to be done to try to contact him/her; to obtain the reasons for non-attendance.
5. *Violations and deviations from the CIP.*
6. *Administrative reasons.*

16.2 CRITERIA FOR ACCESS AND TO BREAKING THE BLINDING/MASKING CODE DURING THE CLINICAL INVESTIGATION

The Investigator will receive a sealed code envelope for each patient entered in the study, for use in emergency. Each envelope will contain the identity of patient's treatment. A set of code envelopes will also be retained by the CRO and the Sponsor.

The code envelopes may only be opened in the case of an emergency, such as a Serious Adverse Event, that requires knowledge of the identity of the investigational product in order to manage the patient's condition.

If opened, the time, date and reason for opening the code envelope must be written on the envelopes and signed by the Investigator; the Sponsor must be immediately notified in this instance.

At the end of the study all envelopes (opened and unopened) must be returned to the Sponsor, along with the completed case report forms. The envelopes will be checked at each monitoring visit by the study monitor/CRA to ensure that the seals are either unbroken, or that any opening is adequately accounted for.

16.3 REQUIREMENTS FOR SUBJECT FOLLOW-UP

16.3.1 Modalities and calendar of recording data

Withdrawal due to intercurrent disease or adverse event must be fully documented in the case report form and should include any available and/or appropriate complementary information.

In all cases, the reason for withdrawal must be recorded in the case report form. The subject must be followed up to state the reason for withdrawal and to establish whether the reason is an adverse event. Since the moment the Investigator knows the early termination or exclusion, the withdrawal of the subject must be formalized by a visit. If possible, all examinations scheduled for the final study day must be performed on all subjects who received the investigational product but do not complete the study according to CIP.

The Investigator must make every effort to contact subjects who dropped-out of the study early. In the case where no visit is possible, this withdrawing must be recorded by the Investigator in the case report form and the source data documentation, and, if necessary, the registered letter with acknowledgement of receipt, to the subject. All the documentation concerning that subject must be as complete as possible.

16.3.2 Modalities for replacing these subjects if any

No replacement condition is foreseen (see paragraph 6.1.7).

16.3.3 Modalities for the follow-up of these subjects

When the premature exit is due to an adverse device effect, the subject will be followed until the resolution or the stabilization of the symptoms.

17- PUBLICATION POLICY

The Sponsor reserves the right to review all the manuscript(s) and abstract(s) before their submission for publication or presentation. Publication of data will be at the discretion of the Sponsor

This is not intended to restrict or hinder publication or presentation, but to allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator(s).

18- BIBLIOGRAPHY

18.1 CONCERNING STUDY RATIONALE

1. Van Bijsterveld O.. Diagnostic test s in the sicca syndrome . Arch Ophthalmol 1969;82:10—4.
2. Anthony J. Bron, FCOPhtth, FMedSci *et al*, Grading of Corneal and Conjunctival Staining in the Context of Other Dry Eye Tests. CORNEA. Volume 22, Number 7, October 2003.
3. J.L. Gayton. Etiology, prevalence, and treatment of dry eye disease. Clinical Ophthalmology 2009;3 405–412.
4. M. Amrane, C. Creuzot-Garcher. Ocular tolerability and efficacy of a cationic emulsion in patients with mild to moderate dry eye disease – A randomized comparative study. Journal français d'ophtalmologie (2014) 37. 589-598.
5. T. Kaercher, U. Thelen, G. Brief, R.J. Morgan-Warren, R. Leaback. A prospective, multicenter, noninterventional study of Optive Plus in the treatment of patients with dry eye: the prolipid study. Clinical Ophthalmology 2014;8 1147–115.
6. V. Baeyens, A. Bron, C. Baudouin. Efficacy of 0.18% hypotonic sodium hyaluronate ophthalmic solution in the treatment of signs and symptoms of dry eye disease. Journal français d'ophtalmologie (2012) 35, 412—419.

18.2 ETHICAL ASPECT

1. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI/ Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates
2. ICH TOPIC E6/ Note for guidance on Good Clinical Practice- CPMP / ICH / 135 / 95, January 1997
3. LOI HURIET SERUSCLAT/ CSP Titre II – Recherches Biomédicales- n°88-138 du 20 décembre 1988 modifié par la loi française 2004-806 du 9 août 2004, concernant la santé publique
4. LOI "INFORMATIQUE ET LIBERTES"/ Loi n°78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés mise à jour par la loi n°2004-801 du 6 août 2004 concernant la protection des personnes pour la déclaration à la CNIL

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19- CIP SIGNATURES

We agree to conduct the study in accordance with the study CIP described in this document and in compliance with GCP and applicable regulatory requirements.

FOR THE SPONSOR:

Chantal COUDERC

Date

Signature

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FOR THE CRO/SMO:

Audrey NATALIZIO
Project Manager

Date

Signature

Cédric JUNG
Biostatistician

Date

Signature

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FOR THE COORDINATING INVESTIGATOR:

Pr. Christophe BAUDOUIN

Date

Signature

APPENDIX 1 : AE AND SAE forms

SAE form

I. INFORMATION ABOUT THE INVESTIGATOR / INFORMATION SUR L'INVESTIGATEUR

1. Investigator name: <i>nom de l'investigateur</i>	Tel:	2. Report 2.a Date of this report <i>Rapport</i> <input type="checkbox"/> initial /initial <input type="checkbox"/> follow-up / <i>complémentaire</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <i>Date de ce rapport :</i>
Profession (speciality): <i>Profession (spécialité)</i>	Fax:	2.b. Notification date <i>date de notification</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Street address: <i>adresse</i>	City/ ville: Zip Code/Postal Code/Zone: <i>code postal</i>	Reception date <i>date de réception</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
State/Province: <i>état/région</i>	Country/ pays:	Identification # / N° d'identification <input type="checkbox"/> (1)

II. ADVERSE EVENT INFORMATION / INFORMATION SUR L'EVENEMENT

3. Birth date / date de naissance du sujet Day / jour <input type="checkbox"/> Month / mois <input type="checkbox"/> Year / année <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	3.a. Age / âge <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Years-Months ⁽¹⁾ / ans-mois ⁽¹⁾	4. Sex / sexe <input type="checkbox"/> 1 ♂ <input type="checkbox"/> 2 ♀	5. Weight/poids <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> kg / kg	6. Height/ taille <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> cm / cm	
7. Serious Event (check the appropriate boxes) <i>Événement grave (cocher les cases appropriées)</i> :	8. Event description (also exams and/or laboratory results) <i>description de l'événement (y compris les éventuels examens et/ou résultats de laboratoire)</i>				
<input type="checkbox"/> 1 death / décès date / date : <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	8.a Place of the serious event / Lieu de survenue de l'événement grave :				
<input type="checkbox"/> 2 life threatening / <i>mise en jeu du pronostic vital</i> <input type="checkbox"/> 3 lasting or significant incapacity / <i>incapacité ou handicap important ou durable</i> <input type="checkbox"/> 4 hospitalization or prolongation of existing hospitalization / <i>hospitalisation ou prolongation d'hospitalisation</i> duration of hospitalization / <i>durée de l'hospitalisation</i> <input type="checkbox"/> <input type="checkbox"/> years, months, days ⁽¹⁾ <i>années, mois, jours</i> ⁽¹⁾ <input type="checkbox"/> ongoing / <i>en cours</i> <input type="checkbox"/> 5 congenital anomaly/ birth defect <i>anomalie ou malformation congénitale</i> <input type="checkbox"/> 6 other, define / autre, préciser :	9. Severity / <i>sévérité</i> <input type="checkbox"/> 1 light / <i>Légère</i> <input type="checkbox"/> 2 moderate / <i>Modérée</i> <input type="checkbox"/> 3 severe / <i>sévère</i>	10. Outcome of the subject (complete for a follow-up report or SAE end) / issue pour le sujet <i>(compléter pour un rapport complémentaire ou à la clôture de l'EIG)</i> <input type="checkbox"/> 1 completely recovered / <i>guérison complète</i> <input type="checkbox"/> 2 condition still present and unchanged / <i>affection toujours présente et inchangée</i> <input type="checkbox"/> 3 recovered with sequelae / <i>guérison avec séquelles</i> <input type="checkbox"/> 4 condition deteriorating / <i>aggravation de l'affection</i> <input type="checkbox"/> 5 condition improving / <i>amélioration de l'affection</i> <input type="checkbox"/> 6 death / <i>décès</i> ➔ autopsy / <i>autopsie</i> <input type="checkbox"/> 1 yes/oui <input type="checkbox"/> 2 no/non <input type="checkbox"/> 7 unknown (lost to follow-up) / <i>évolution inconnue</i>			
11. Event onset date (2) <i>date de début de l'événement</i>			12. Event termination date <i>date de fin de l'événement</i>		
Day / jour	Month/ mois	Year/ année	Day/jour	Month/mois	Year/année

(1) delete as appropriate /
(1) barrer les mentions inutiles

ongoing / en cours

III. STUDIED PRODUCT(S) INFORMATION / INFORMATION SUR LE(S) PRODUIT(S) A L'ESSAI

13. Tested product(s) produit(s) testé(s)		13.a. batch # / N° de lot
14. Dosage / posologie	15. Administration route voie d'administration	<input type="checkbox"/> ₁ oral / orale <input type="checkbox"/> ₂ parenteral / parentérale <input type="checkbox"/> ₃ transmucous / transmuqueuse <input type="checkbox"/> ₄ cutaneous / cutanée <input type="checkbox"/> ₅ other / autre (to specify / préciser :)
16. Kind of product : <input type="checkbox"/> ₁ cosmetic / cosmétique, <input type="checkbox"/> ₂ drug / médicament, <input type="checkbox"/> ₃ medical device / dispositif médical, Type de produit <input type="checkbox"/> ₄ other / autre (to specify / préciser) :)		
17. Dates of tested product administration Dates d'administration du produit à l'étude		18. Treatment duration durée du traitement years, months, days ⁽¹⁾ années, mois, jours <input type="checkbox"/> not applicable / sans objet <input type="checkbox"/> ongoing / en cours
from /du <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> to /au <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> ongoing / en cours <input type="checkbox"/> not applicable / sans objet		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
19. Definitive termination of studied product arrêt définitif du produit à l'étude		19.a. Temporary suspension of the studied product arrêt temporaire du produit à l'étude <input type="checkbox"/> ₁ yes / oui → if yes, number of days of stopping <input type="checkbox"/> ₀ no / non si oui, nombre de jours d'arrêt
20. Event resolved with termination of treatment? Disparition de l'événement après arrêt du traitement ?		21. Event reappeared with reintroduction of treatment? réapparition de l'événement après réintroduction du traitement ? <input type="checkbox"/> ₀ no / non <input type="checkbox"/> ₁ yes / oui <input type="checkbox"/> ₂ not applicable / sans objet
22. Product administered: was the code blinded out? / produit administré : le code a-t-il été levé ? <input type="checkbox"/> ₀ no / non <input type="checkbox"/> ₁ yes / oui <input type="checkbox"/> ₂ not applicable / sans objet		

IV. ASSOCIATED DRUG(S) AND MEDICAL HISTORY / MEDICAMENT(S) ASSOCIE(S) ET ANTECEDENTS

23. ASSOCIATED DRUGS (excluding therapy to treat SAE)/MEDICAMENTS ASSOCIES (excepté les traitements ayant servi à résoudre l'EIG)

Drug médicament	Indication indication	Dosage posologie	Administration route voie d'administration	Beginning date date de début	End date date de fin	Event related lié à l'EIG
a.			<input type="checkbox"/> ₁ oral / orale <input type="checkbox"/> ₂ parenteral / parentérale <input type="checkbox"/> ₃ transmucous / transmuqueuse <input type="checkbox"/> ₄ cutaneous / cutanée <input type="checkbox"/> ₅ other/autre :	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> ongoing / en cours	<input type="checkbox"/> ₁ yes / oui <input type="checkbox"/> ₀ no / non
b.			<input type="checkbox"/> ₁ oral / orale <input type="checkbox"/> ₂ parenteral / parentérale <input type="checkbox"/> ₃ transmucous / transmuqueuse <input type="checkbox"/> ₄ cutaneous / cutanée <input type="checkbox"/> ₅ other/autre :	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> ongoing / en cours	<input type="checkbox"/> ₁ yes / oui <input type="checkbox"/> ₀ no / non
c.			<input type="checkbox"/> ₁ oral / orale <input type="checkbox"/> ₂ parenteral / parentérale <input type="checkbox"/> ₃ transmucous / transmuqueuse <input type="checkbox"/> ₄ cutaneous / cutanée <input type="checkbox"/> ₅ other/autre :	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> ongoing / en cours	<input type="checkbox"/> ₁ yes / oui <input type="checkbox"/> ₀ no / non

24. RELEVANT MEDICAL HISTORY / ANTECEDENTS MEDICAUX PERTINENTS

V. ACTION TAKEN / ACTION ENTREPRISE**25. Action taken / action entreprise**

(1) no action taken / aucune action entreprise
 (2) Concomitant medication taken to treat the event (complete Field 26) / traitement concomitant pris pour traiter l'événement (compléter le champ 26)
 (3) no drug therapy given (if checked, note therapeutic measures in Field VII) / pas de traitements correcteurs prescrits (si cette case est cochée, donner les mesures thérapeutiques prises au champ VII)

26. DRUG THERAPY GIVEN / MEDICAMENTS AYANT SERVI À TRAITER L'EIG

Drug médicament	Indication indication	Dosage posologie	Administration route voie d'administration	Beginning date date de début	End date date de fin
			<input type="checkbox"/> 1 oral / orale <input type="checkbox"/> 2 parenteral / parentérale <input type="checkbox"/> 3 transmucous / transmuqueuse <input type="checkbox"/> 4 cutaneous / cutanée <input type="checkbox"/> 5 other/autre :		
			<input type="checkbox"/> 1 oral / orale <input type="checkbox"/> 2 parenteral / parentérale <input type="checkbox"/> 3 transmucous / transmuqueuse <input type="checkbox"/> 4 cutaneous / cutanée <input type="checkbox"/> 5 other/autre :		
			<input type="checkbox"/> 1 oral / orale <input type="checkbox"/> 2 parenteral / parentérale <input type="checkbox"/> 3 transmucous / transmuqueuse <input type="checkbox"/> 4 cutaneous / cutanée <input type="checkbox"/> 5 other/autre :		

**27. LABORATORY FINDINGS (enter only those findings significant or necessary for SAE diagnosis) /
RESULTATS D'EXAMENS (noter uniquement les résultats nécessaires au diagnostic de l'EIG ou significatifs)**

Test / lab name test / nom de l'examen	Unit unité	Value valeur	Date date	Test / lab name test / nom de l'examen	Unit unité	Value valeur	Date date

27.a. COMMENTS ON LABORATORY FINDINGS in Field VII / REMARQUES SUR LES RESULTATS D'EXAMENS en VII**VI. CONCLUSION**

According to the investigator, the SAE is linked: selon l'investigateur, L'EIG semble plutôt lié :	29. According to the sponsor, the SAE is linked: selon le promoteur, l'EIG semble plutôt lié :
28a. to the studied product/ au produit à l'essai <input type="checkbox"/> 0 Excluded / exclue <input type="checkbox"/> 1 Unlikely/ douteux <input type="checkbox"/> 2 Not clearly attributable/ possible <input type="checkbox"/> 3 Likely/ vraisemblable <input type="checkbox"/> 4 Very likely / très vraisemblable	28b.to the study procedures / aux procédures de l'essai <input type="checkbox"/> 0 Excluded / exclue <input type="checkbox"/> 1 Unlikely/ douteux <input type="checkbox"/> 2 Not clearly attributable/ possible <input type="checkbox"/> 3 Likely/ vraisemblable <input type="checkbox"/> 4 Very likely / très vraisemblable
	<input type="checkbox"/> 1 to the studied product / au produit à l'essai <input type="checkbox"/> 2 to the study procedures / aux procédures de l'essai <input type="checkbox"/> 3 other, define / autre, préciser : <input type="checkbox"/> 0 no relationship / sans relation
30. If, according to the sponsor, the SAE appears to be related to the studied product, the event is: si selon le promoteur, l'EIG paraît plutôt lié au produit à l'essai, l'événement indésirable est :	<input type="checkbox"/> 1 expected / attendu <input type="checkbox"/> 0 unexpected / inattendu
31. Sponsor comments / commentaires du promoteur	

VII. ADDITIONAL INFORMATION / INFORMATIONS COMPLEMENTAIRES

FOR ADDITIONAL INFORMATION / POUR COMPLEMENT D'INFORMATION:

Date of report / Date du rapport :	Signature / Signature :
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AE form

PARTIE I : 1ère documentation de l'événement <small>First documentation of the adverse event</small>	N°/ #	<p>1. Description de l'événement / Event description En cas de réaction cutanée, préciser sa localisation et si elle correspond à la zone d'application du produit testé / In case of cutaneous reaction, specify its localisation and if it corresponds to the product application area</p>		
	2. Date de début de l'événement <small>Event onset date</small>		3. Sévérité / severity	4. Photo des signes cliniques / Pictures of clinical signs
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		<input type="checkbox"/> ₁ légère / <i>mild</i> <input type="checkbox"/> ₂ modérée / <i>moderate</i> <input type="checkbox"/> ₃ sévère / <i>severe</i>	<input type="checkbox"/> ₀ NON / NO <input type="checkbox"/> ₁ OUI / YES <input type="checkbox"/> ₃ NA*
	5. Actions entreprises vis-à-vis du produit étudié <small>Actions taken with the studied product</small>		6. Actions entreprises vis-à-vis de l'événement <small>Actions taken due to the event</small>	7. Événement Indésirable Grave (EIG) <small>Serious Adverse Event (SAE)</small>
	<input type="checkbox"/> ₀ aucune / <i>none</i> <input type="checkbox"/> ₁ arrêt définitif / <i>definitive interruption</i> <input type="checkbox"/> ₂ arrêt transitoire / <i>temporary interruption</i> → Durée / Duration <input type="checkbox"/> ₃ diminution de la dose / <i>dose decrease</i>		<input type="checkbox"/> ₀ aucune / <i>none</i> <input type="checkbox"/> ₁ traitement correcteur / <i>corrective treatment</i> Compléter le tableau des traitements concomitants / <i>Complete concomitant treatment form</i> <input type="checkbox"/> ₂ autre, à spécifier / <i>other, define</i> : 	<input type="checkbox"/> ₀ NON / NO <input type="checkbox"/> ₁ OUI / YES Si "OUI", remplir un formulaire de déclaration d'EIG. <i>If "YES", complete a SAE declaration Form.</i>
	8. Délai entre l'événement et la dernière prise/application du produit étudié ? <small>Timeframe from the last product taken/application</small>		9. Relation de causalité avec le(s) produit(s) étudié(s) <small>Event relationship with the study product(s)</small>	10. Relation avec les procédures de l'étude <small>Event relationship with the study methods</small>
	<input type="text"/> minutes/heures/jours <small>minutes /hours /days</small>		<input type="checkbox"/> ₀ oui / <i>yes</i> <input type="checkbox"/> ₁ non / <i>no</i> <input type="checkbox"/> ₂ possible / <i>possible</i>	<input type="checkbox"/> ₀ oui / <i>yes</i> <input type="checkbox"/> ₁ non / <i>no</i> <input type="checkbox"/> ₂ possible / <i>possible</i>
	11. Evolution / Outcome		12. Commentaires / Comments <small>(Intensité, antécédents... / Intensity, medical history...)</small>	
	<input type="checkbox"/> Non connue / <i>Unknown</i> <input type="checkbox"/> En cours* / <i>ongoing</i> * commentaire obligatoire / <i>Compulsory comment</i> → Remplir la partie II et/ou la partie III à la prochaine cinéétique <input type="checkbox"/> Guéri <small>Resolved</small>		Si EI en cours, évolution à ce jour / If AE ongoing, evolution this day: <input type="checkbox"/> ₁ amélioration / <i>improved</i> <input type="checkbox"/> ₂ pas de changement / <i>unchanged</i> <input type="checkbox"/> ₃ aggravation / <i>worsened</i> <input type="checkbox"/> ₄ perdu de vue / <i>lost to follow-up</i>	
	Date de guérison <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
	Durée Duration <input type="text"/> (secondes/minutes/heures/jours) <small>Seconds /minutes /hours /days</small>			
	Date du rapport/ Report Date :		Nom et signature / Name and signature :	

STOP : REMPLIR LES PARTIES CI-DESSOUS LORS DES PROCHAINES CINETIQUES UNIQUEMENT POUR LES EI EN COURS

PARTIE II : suivi <small>Follow up</small>	Evolution de l'EI à chaque cinéétique (amélioration ou aggravation) / Evolution of the adverse event <u>Dater et parapher chaque commentaire</u> / date and initial each comment.		

PARTIE III : Guérison ou fin d'étude / Event or study termination	REMPILER LA PARTIE III A LA GUERISON DE L'EI PRECEDEMMENT EN COURS OU A LA FIN DE L'ETUDE		
	Date de guérison <small>Event stop date</small> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/> EI toujours en cours à la fin de l'étude / AE ongoing at the study end Date de fin de l'étude : <small>Study stop date</small> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
	Sujet perdu de vue <input type="checkbox"/> <small>Untraceable subject</small>	L'EI nécessite-t-il un suivi ? NON / NO <input type="checkbox"/> ₁ <small>Does this AE need a follow up?</small> OUI **/YES <input type="checkbox"/> ₂ si oui, date prévue pour le suivi ** : <small>The predictive date for the follow up</small> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
Date du rapport / Report Date :	Nom et signature / Name and signature :		

*NA = Non applicable/ *Not applicable*Rappel des définitions en fin de CRF/ *Definitions at the CRF end*