Groupe Axonal-Biostatem
Parc d'activités Via Domitia
205, avenue des Gardians
34160 CASTRIES - FRANCE
☎: 33 (0) 4 67 04 87 54
🖷: 33 (0) 4 67 04 87 71
e-mail : contact@biostatem.com

Sponsor

HORUS PHARMA
148 Avenue G.Guynemer
Cap Var
06 700 SAINT LAURENT DU VAR
FRANCE

STATISTICAL ANALYSIS PLAN

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

15E1122

Type of study:	Clinical study on medical device
Statistician:	Muriel Tounsi / Hugo Lacour
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2	All	21MAR2018	M	Sponsor's feedback
3	All	28MAR2018	M	Sponsor's feedback

(*) C: Creation, M: Modification, A: Addition, D: Delete

SIGNATURE FORM

Author of the Statistical Analysis Plan: Hugo LACOUR, Statistician

Date: 28MAR2018

Signature:

Proofreading and validation Axonal-Biostatem:

Position	Name	Date / signature
Head of statistics	Muriel TOUNSI	

Proofreading and validation Sponsor:

Position	Name	Date / signature
Methodologist	Dr Marc Marty	
Head of Clinical Affairs	Chantal Couderc	
Project Manager Dermscan	Audrey Natalizio	

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LIST OF ABBREVIATIONS

AE	Adverse Events
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
D	Day
ICH	International Conference on Harmonisation
ITT	Intent to Treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
OSDI	Ocular Surface Disease Index
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TBUT	Tear film Break Up Time
TEAE	Treatment Emergent Adverse Event
TMC	Trial Management Committee

1 INTRODUCTION

The present document aims at detailing the statistical analyses that will be performed for the study 15E1122 on the basis of the study protocol (Version 4.0, dated on September 4, 2017). This document has been written by the statistician and reviewed and agreed by the Sponsor of the trial before the database lock, in accordance with ICH Guidelines.

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. Eighty subjects are planned to be included (40 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.

2 STUDY OBJECTIVES

2.1 Primary 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.

2.2 Secondary objectives

- 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.

2.3 Exploratory objectives

Not Applicable

3 STUDY DESIGN

3.1 Overview

This is a randomized, multicentric, comparative, investigator blinded, in parallel group non-inferiority study.

3.2 Study population

3.2.1 Inclusion criteria

- 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:
  - Global ocular staining (cornea and conjunctiva) ≥4 and ≤9 (Oxford scale from 0 to 15)

  AND one the following criteria:
  - Schirmer test ≥ 3mm/5 min and ≤9mm/ 5 min

  OR
  - Sum of 3 measurements of Tear film Break-Up Time (TBUT) ≤ 30s.
- 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.

3.2.2 Exclusion criteria

- 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:
  - 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.
- 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 a 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: isotretinoïd, 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.

3.3 Randomisation

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®).

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.

3.4 Study Product

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.

3.5 Study schedule

The table below displays data collected at each time of the study

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	X			
Checking of the inclusion and exclusion criteria	X	X		
Medical history, previous and concomitant treatments, demographic data	X			
Urinary pregnancy test for female subjects with childbearing potential		X		X
Distribution of Hydrabak® (NaCl 0.9%)	X			
Inclusion and random assignment		X		
OSDI score	X	X	X	X
Global ocular staining (Oxford score)	X	X	X	X
Schirmer test	X	X	X	X
TBUT	X	X	X	X
Van Bijsterveld score		X	X	X
Symptoms evaluation by the patient		X	X	X
Treatment performance evaluation by the patient and the investigator			X	X
Distribution of treatments by a third person		X	X	
Adverse events recording		X	X	X
Concomitant medication		X	X	X

4 STUDY OUTCOME VARIABLES

4.1 Efficacy assessments

4.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the difference of the change from baseline to day 35 of the Oxford total score (cornea and conjunctiva staining) in the worse eye between the two patient groups (DM05- Optive®).

The change of the Oxford total score from baseline to day 35 will be derived as below:
Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 35 – Total Oxford score of the corresponding eye (worse eye) at day 0.

The difference of this change will then be tested between groups in the PP population (DM05 minus Optive®) with a bilateral 95% CI. If the upper bound is no higher than 2 points, then the null hypothesis (DM05 is inferior to Optive®) will be rejected.

In case of conclusion of non-inferiority, the same analysis will be performed on ITT population, with and without imputation (see section 7.6.1, paragraph 'Sensitivity analysis').

4.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are described below.

- For the parameters hereafter: Oxford total score on worse eye, OSDI total score, Van Bijsterveld total score, Schirmer test result on worse eye, TBUT total score on worse eye, all ocular dryness symptoms score separately and then globally (total score):

- For each product, description of the parameter at D0, D35 and D84
- For each product, description of the change of the parameter for each time-point (D35-D0 and D84-D0)
- For each product, comparison of the change of the parameter at D35 versus D84
- Comparison of the change of the parameter between products at D35 and then at D84.

- For the parameters hereafter: OSDI in class, evaluation of performance by the patient, evaluation of performance for the investigator and frequency of use of the product:

- The parameter will be described at D0, D35 and D84 (with frequency and percentage)
- A comparison of the parameter between products at D0, D35 and D84 will be performed.

4.2 Safety assessments

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 (Version 19.1). 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.

4.3 Derived variables

Source data	Derivation rule	Label	Format
Date of last use of study product, date of D0 visit	TRT_DUR_D=Date of last use of study product – date of D0 visit +1	Treatment duration in days	Numeric
Date of end of study, date of selection visit	STUDY_DUR_D=Date of end of study – date of selection visit +1	Study duration in days	Numeric
OSDI total score	IF 0<=OSDI total score < 13 THEN OSDI_CL_D=1 IF 13<= OSDI total score < 23 THEN OSDI_CL_D=2 IF 23<= OSDI total score < 33 THEN OSDI_CL_D=3 IF 33<= OSDI total score < 100 THEN OSDI_CL_D=4	OSDI score in class	1 = ”OSDI none” 2 = ”OSDI Mild” 3 = ”OSDI moderate 4 = ”OSDI severe”
Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 0, Total Oxford score of the corresponding eye at day 35 (i.e. day 84)	EVOL_OX_D0D35 (i.e. D84) = Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 35 (i.e. day 84) - Total Oxford score of the corresponding eye at day 0	Change of the Oxford total score from baseline to day 35 (i.e. day 84)	Numeric
Same derivation rule as above for changes on OSDI total score, Van Bijsterveld total score, Schirmer test result, TBUT total score, all ocular dryness symptoms score from D0 to D35 and from D0 to D84.			

Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 0, Total Oxford score of the corresponding eye at day 35 (i.e. day 84)	EVOL_OXREL_D0D35 (i.e. D84) = (Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 35 (i.e. day 84) - Total Oxford score of the corresponding eye at day 0) / Total Oxford score of the corresponding eye at day 0	Relative change of the Oxford total score from baseline to day 35 (i.e. day 84) in percentage	Numeric
Same derivation rule as above for changes (relative variation) on OSDI total score, Van Bijsterveld total score, Schirmer test result, TBUT total score, all ocular dryness symptoms score from D0 to D35 and from D0 to D84.			
Adverse Event	IF at least one adverse event is reported for the patient, ALO_AE=1 ELSE, ALO_AE=0	At least one AE	0 = ”No” 1 = ”Yes”
Same derivation rule as above for at least one TEAE, at least one severe AE, at least one AE related to the treatment, at least one SAE, at least one AE that lead to study withdrawal			

5 SEQUENCE OF PLANNED ANALYSES

5.1 Interim analyses

No interim analysis is planned.

5.2 Final analyses and reporting

All final planned analyses identified in the protocol and in this SAP, will be performed only after the last patient has completed assessments scheduled for the study period and the database has been cleaned and locked. A blinded data review will be conducted by members of the Trial Management Committee (TMC) prior to locking and archiving the trial database. Treatment allocations will not be un-blinded and no un-blinded analyses will begin until this SAP has been reviewed by the TMC.

5.3 Changes to statistical information in the clinical trial protocol

Not applicable.

6 STATISTICAL METHODOLOGY

6.1 Detailed power and sample size

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) was 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 endpoint (analysis on PP population).

6.2 Generalities for statistical analyses

Continuous variables will be summarized by number of non-missing observations, mean, standard deviation, minimum, median, maximum.
Categorical data will be summarized by frequency and percentage of patients in each category. Percentages will be based on non-missing observations.
All statistical tests will be 2-tailed with a Type I error of 0.05 unless otherwise stated.

6.3 Multiple Imputations for Handling of Dropouts or Missing data

In the case of missing values on the primary endpoint, a sensitivity analysis with the last observation carried forward (LOCF) method will be applied using at each visit the last observation available for analysis on ITT and PP population.

6.4 Adjustments for Covariates

Subject characteristics collected at the selection visit will be described globally and by treatment group on the PP and the ITT population:

- Sex
- Age
- Total Oxford score of worse eye at D0

If some differences on Age and/or Sex between treatment groups on PP population at inclusion were to be significant, a sensitivity analysis of the primary endpoint will be added. The model considered will be the same as the primary analysis model, including Age and/or Sex as covariate.

If the number of patients included in the ITT population but excluded from the PP population is sufficient, the variables above will also be compared between patients included in the PP population and those excluded from the PP population (among ITT population), to confirm the homogeneity of both sub-populations regarding these outcomes.

6.5 Multiple Comparisons/Multiplicity

Not applicable

7 STATISTICAL ANALYSES

After the database lock and the randomisation code release, the statistical analysis will be performed by the statistician of Axonal-Biostatem, using SAS® software, according to the Statistical Analysis Plan (SAP) approved by the Validation Committee.

7.1 Study Populations

7.1.1 Protocol Deviations

Definition of minor and major deviations will be provided. Number of subjects with at least one major/minor deviations will be computed.
A listing of all the protocol deviations observed during the Data Review will be provided, and protocol deviations will be summarized in tables, for the whole population.

7.1.2 Analysis Populations

Number of patients in each population will be described globally and by treatment group thanks to a flow-chart.

Three population will be defined:

- Intention to treat (ITT) population corresponding to all patients randomized.
- Safety population corresponding to all patient 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.

Protocol deviations will be defined by the Data Review Committee during a blind review process day.

The main analysis of the main criterion will be conducted on the PP population.
The same analysis will be performed on ITT population (with and then without imputation of missing data – see section 7.6.1, paragraph sensitivity analysis).
In case of conclusion of non-inferiority of DM05 compared to Optive®, a superiority analysis will be performed on the ITT population and then on the PP population.

Secondary criteria will be performed on ITT population and PP population.

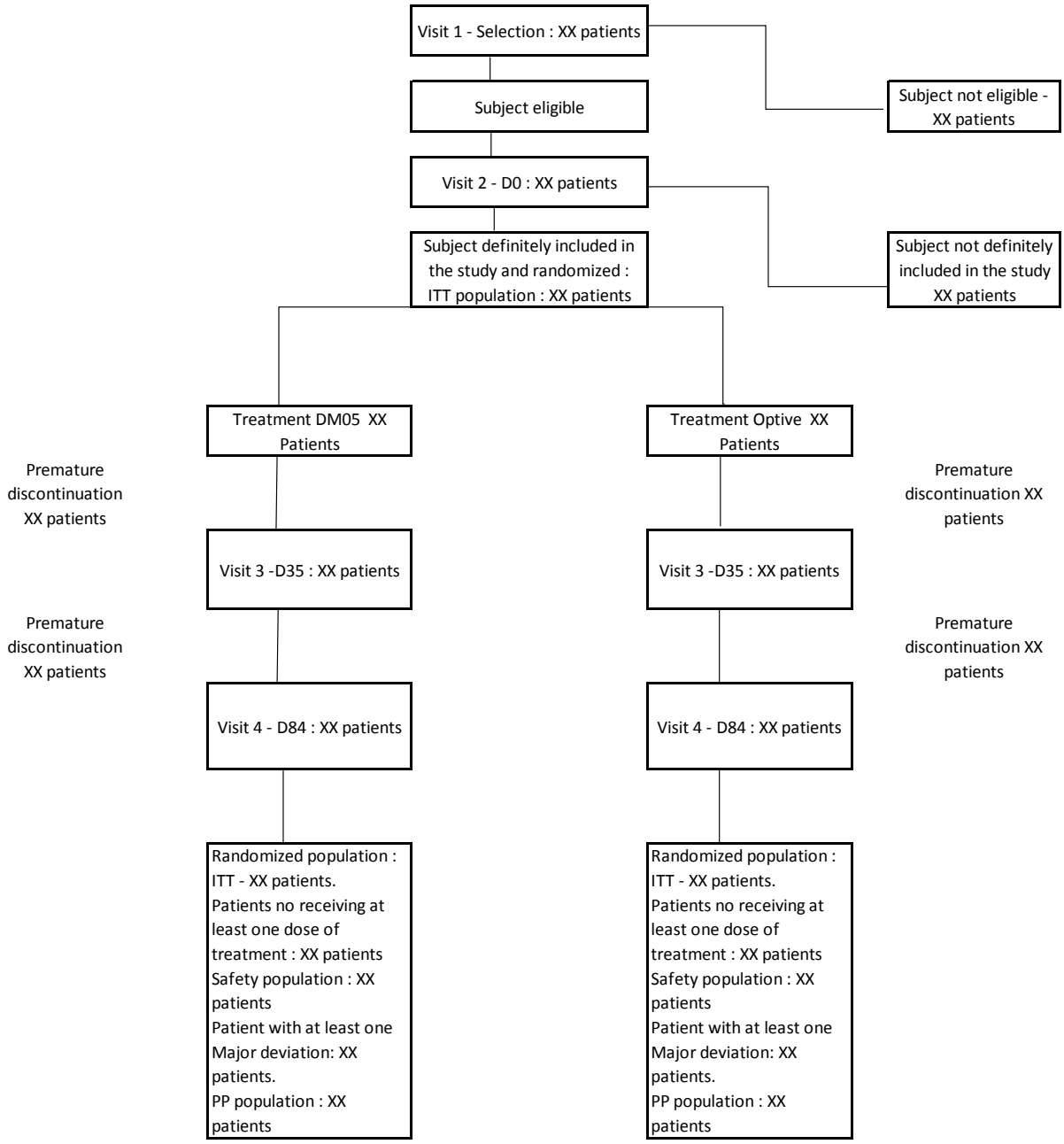
Safety analysis will be performed on the Safety population

7.2 Patient accountability

Will be described:

- Number of included and randomized patients
- Number of randomized patients by treatment groups
- Number of active centre
- Number of included and randomized patients by treatment groups
- Number of included and randomized patients by centre
- Number of patients at each visit.
- Number and percentage of patients having finished the study normally by treatment groups.
- Reason of withdrawal will also be tabulated and a listing of reason of withdrawal will be produced.
- First and last visit date of first patient included as well as first and last visit date of last patient included
- Treatment duration in days will also be described by treatment group. It will be derived according to the formula below:
  Date of last use of study product – date of D0 visit +1
- Study duration in days will also be described by treatment group. It will be derived according to the formula below:
  Date of end of study – date of selection visit +1
- Normal study end (yes/no) and if no, reason

Patients accountability will be described thanks to the flowchart below:



7.3 Demographic and Baseline Characteristics

Parameters below will be described globally and by treatment group on PP population. They will then be compared between patients included in the PP population and those included in ITT population:

- <u>Demographic data</u>
  - Sex
  - Age

- <u>Corneal fluorescent staining (Oxford scale) at D0 visit</u>
  - Total score of worse eye

Parameters below will be described globally and by treatment groups on the ITT population:

- Demographic data
  - Sex
  - Age

- Contraception (for female only)
  - Childbearing potential (yes/no)
  - If no, reason
  - If yes, contraceptive method (yes/no)
  - If yes type of contraceptive method

  A listing of other contraceptive method will be added if applicable

- Medical history at selection visit
  - At least one ophthalmological history among the last 12 months (yes/no)
  - A listing of ophthalmological history will then be produced including event start and end date and event preventing inclusion (yes/no)
  - At least one medical or surgical event among the last 12 months (yes/no) and any allergic history (yes/no)
  - A listing of medical, surgical and allergy history will then be produced

- Product and document dispensation
  - Dispensation of artificial tears without preservative (NaCl 0.9%): Hydrabak®
  - Number of vials dispensed

- Ocular surface disease index (OSDI) at both selection visit and D0 visit
  - Subtotal A, B and C of OSDI score
  - Total OSDI score

- Corneal fluorescent staining (Oxford scale) at both selection visit and D0 visit
  - Subtotal score right, middle and left of right eye
  - Total score of right eye
  - Subtotal score right, middle and left of left eye
  - Total score of left eye

- Tear film Break Up Time (TBUT) at both selection visit and D0 visit
  - Measurement 1, 2 and 3 for both right and left eye
  - Total score for both right and left eye

- Schirmer test at both selection visit and D0 visit
  - Length of paper wetting in mm for both right and left eye
  - Total score for both right and left eye

- Pregnancy test (women with childbearing potential only – D0 visit)

    - Realisation of urinary pregnancy test (yes/no)
    - If no, reason
    - If yes, result of the test

- Definition of the worse eye (D0 visit)
    - Worse eye defined

7.4 Previous and concomitant medication

Will be described, on the ITT population only:

- Did the subject take/stop/modify any medical treatment within the last 6 months at each visit (yes/no)
- An individual data listing of all current or past medication treatment will be produced including centre number / patient id / treatment group / inclusion date (D0) / end of study date / age / sex / drug name / indication / dosage / administration route / specification / treatment start date / treatment end date / duration / treatment relationship / treatment preventing inclusion or leading to exclusion

7.5 Follow-up analyses

Will be described at each follow-up visit, by treatment group, on the ITT population only:

- Product and document dispensation (D35 and D84)

    - Average posology
    - Posology precision
    - Frequency of use
    - Frequency precision

- Pregnancy test (women with childbearing potential only –D84)

    - Realisation of urinary pregnancy test (yes/no)
    - If no, reason
    - If yes, result of the test

7.6 Efficacy analyses

7.6.1 Primary Efficacy Endpoint

Primary endpoint derivation

The primary efficacy endpoint is the difference of the change from baseline to day 35 of the Oxford total score in the worse eye between the two patient groups (DM05- Optive®).

The Oxford scale range to 0 (normal) to 15 (greater cornea and conjunctiva staining). An improving of Oxford scale is expected.

The change of the Oxford total score from baseline to day 35 will be derived as below:

Total Oxford score of the examined eye (i.e. worse eye defined at D0) at day 35 - Total Oxford score of the corresponding eye at day 0.

Descriptive analyses:

- Right, middle and left Oxford sub-scores as well as total score will be described on the worse eye at D0 and D35 by treatment groups on both ITT and PP population.
- Change from D0 to D35 of the Oxford total score on the worse eye will be described by treatment groups on both ITT and PP population.

Non-inferiority analysis (main analysis)

In order to demonstrate the non-inferiority of DM05 compared to Optive®, the difference of this change will then be tested between groups in the PP population (DM05 minus Optive®):

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 of the CI is no higher than 2 points, then the null hypothesis (DM05 is inferior to Optive®) will be rejected.
- Else, if the upper bound is greater than 2, the non-inferiority is not demonstrated.

The result will be presented as follow:

Population	DM05	Optive	Difference DM05 - Optive	95% CI	P non inferiority	P superiority***
Day 0 (baseline) mean (SD)	X1	Y1				
Day 35 mean (SD)	X2	Y2				
Adjusted change between Day 0 and Day 35 - LSM (SEM)	[X2-X1]*	[Y2-Y1]*	[X2-X1] -[Y2-Y1]	[Min - **Max**]**		

* These values were expected as negative, meaning an improvement of the Oxford score.

** The upper bound indicates the maximal difference of change in disfavor of DMO5.

*** In case of demonstration of non- inferiority.

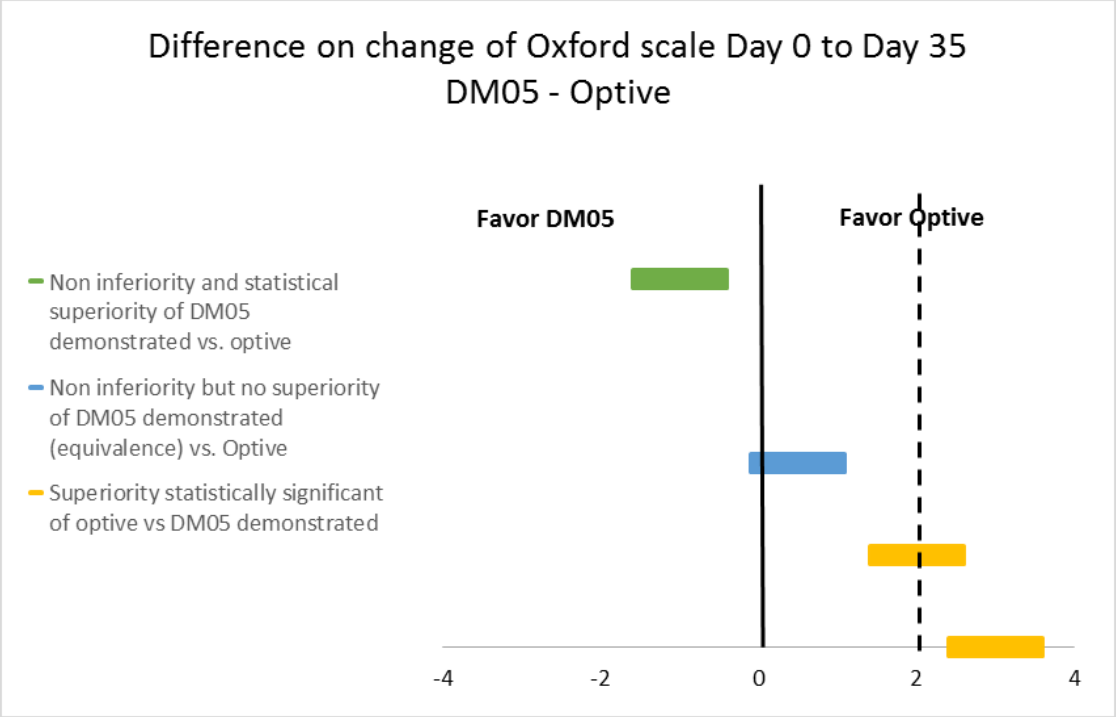


Figure 1: interpretation of results —Estimate of the difference and 95% CI are presented for 4 situations.

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

The MIXED procedure (SAS®) will be used.
SAS code:

```
proc mixed data=XX order=data;
      where PP = 1 ;
      class TT;
      model EVOL = BASELINE TT /* Other covariates can be added here
*/;
      lsmeans TT / diff;
run;
```

In case of conclusion of non-inferiority of DM05 compared to Optive®, the superiority of DM05 compared to Optive® will then be tested on both ITT and PP population in the same way as described above for the non-inferiority:

- If the upper bound of the CI is no higher than 0 points, then the null hypothesis (DM05 is not superior to Optive®) will be rejected. meaning that DM05 is superior to Optive.
- Else, if the upper bound is greater than 0, the superiority is not demonstrated.

Sensitivity analysis

1. If a statistically difference will appear between the 2 groups at baseline on age and/or sex, a sensitivity analysis will be conducted on PP population with the same used for main analysis including this or these factor(s).

The 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).
The result will be presented in the same way as the main analysis.

2. Centre + treatment + interaction treatment*centre will be tested on the primary end point. If p value is lower than 0.10, it is declared that there is an interaction between treatment and centre. In this situation, a sensitivity analysis will be conducted on PP population with the same factors used for main analysis including this factor.

The 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)

7.6.2 Secondary efficacy endpoint

- For the parameters hereafter: Oxford total score on worse eye, OSDI total score, Van Bijsterveld total score, Schirmer test result on worse eye, TBUT total score on worse eye, all ocular dryness symptoms score separately and then globally (total score):

- For each product, description of the parameter at D0, D35 and D84.
- For each product, description of the change of the parameter for each time-point (D35-D0 and D84-D0, relative and absolute variation).
- 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: D0, D35 and D84), 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.

- For OSDI parameter, the different scores will be classified into the following categories:
    - OSDI None: OSDI (0 - <13)
    - OSDI Mild: OSDI (13 - <23)
    - OSDI Moderate: OSDI (23 - <33)
    - OSDI Severe: OSDI (33 - <100)

The parameter will be described at D0, D35 and D84 (with frequency and percentage)
A comparison of the different categories between products at D0, D35 and D84 will be performed, treatments groups will be compared with a Chi2 test.

- For the parameters hereafter: evaluation of performance by the patient, evaluation of performance for the investigator and frequency of use of the product:

- The parameter will be described at D0, D35 and D84 (with frequency and percentage)
- A comparison of the parameter between products at D35 and D84 will be performed: for the evaluation of performance by the patient and by the investigator, and for

frequency of use of the products, treatments groups will be compared with a Chi2 test.

7.7 Safety Analysis

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

7.7.1 Adverse events

The adverse events will be coded using the MedDRA dictionary. All Adverse events will be presented by System Organ Class and Preferred Term.
Treatment-emergent AEs (TEAEs) will be defined as AEs with onset date on or after the first day of the study product instillation. If the AE onset date is not available, AEs will be considered as TEAEs by default.
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 analysed for each PT using Fisher's exact test.
The statistical significance level of 5% will be applied for the safety analyses.

Will be described globally and by treatment groups (the ocular TEAEs and the non-ocular TEAEs will be analysed separately):

Total number of AEs:
- All AEs
- All TEAEs
- All AEs by severity
- AEs by relationship to the treatment
- AEs by seriousness criterion
- AEs that lead to study withdrawal.

Number and percentage of patients who has presented at least one AE:
- At least one AE
- At least one TEAE
- At least one severe AE
- At least one AE related to the treatment
- At least one SAE
- At least one AE that lead to study withdrawal.

The difference between treatments groups on the incidence rate will be analysed for each PT using Fisher's exact test.
The statistical significance level of 5% will be applied for the safety analyses.

An individual data listing of all AEs will be given. With following information: centre number / patient number / treatment group / inclusion date (D0) / age / sex / AE number / AE description / SOC / PT / Time of occurrence* / Duration** (start date / end date) / severity / picture of clinical signs / Actions taken / Seriousness criterion / timeframe from the last product use-application / relationship with the study product / relationship with the study method / outcome / comments.
The same listing will be produced for SAEs.

* Time of occurrence will be derived in days as follow: inclusion date (D0) – AE start date
** duration in days will be derived as follow: end date – start date +1

8 REPORTING CONVENTIONS

8.1 Software used

Statistical analysis will be made using SAS® GUIDE software (version 9.4). Tables results will be computed with SAS® GUIDE software (version 9.4). Figures will be created using Microsoft® Excel or SAS®GUIDE version 9.4.

8.2 General considerations

All p-values will be rounded to 3 decimal places. If a rounded p-value is 0.000 (i.e., the actual p-value is less than 0.0005), then this will be presented as a p-value of "<0.001".
All date fields will be presented in a format of ddmmyyyy (e.g., 01Jan2004) in the listings.

8.3 Statistical summary conventions

For tables, sample sizes for each treatment group will be presented as totals in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values.
Summaries for categorical variables will include only categories that patients had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, mean, and SD. Other summaries (e.g. median, quartiles, 5%, 95% intervals) will be used as appropriate. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

8.4 Examples of tables, listings and figures

8.4.1 Quantitative variables:

Table xx: Description of quantitative variables

		Group A N=xxx	Group B N=xxx	Total N=xxx	p-value
Variable 1	N	x	x	x	
	Missing	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	
	Median	xx.xx	xx.xx	xx.xx	
	Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	
	Min. ; Max.	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	
Variable 2	N	x	x	x	
	Missing	x	x	x	
	Mean ± SD	xx.xx ± xx.xx	xx.xx ± xx.xx	xx.xx ± xx.xx	
	Median	xx.xx	xx.xx	xx.xx	
	Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	
	Min. ; Max.	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx	

95% Confidence Intervals might be presented in the tables.

8.4.2 Qualitative variables:

Table xx: Description of qualitative variables

		Group A N=xxx	Group B N=xxx	Total N=xxx	p-value
Variable 1	N	x	x	x	x
	Missing	x	x	x	x
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Variable 2	N	x	x	x	x
	Missing	x	x	x	x
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

95% Confidence Intervals might be presented in the tables.

8.4.3 Adverse Events:

Table xx: AEs description by SOC and PT

SOC and PT	Total (N=xxx)		
	AE (1)	n (2)	% (3)
TOTAL	xx	xx	xx.x
SOC 1	xx	xx	xx.x
SOC 1 – PT 1	xx	xx	xx.x
SOC 1 – PT 2	xx	xx	xx.x
….	xx	xx	xx.x
SOC 2	xx	xx	xx.x
SOC 2 – PT 1	xx	xx	xx.x
SOC 2 – PT 2	xx	xx	xx.x
….	xx	xx	xx.x

(1) Number of AEs
(2) Number of subjects with at least one AE
(3) % of subjects with at least one AE

Table xx: AE by SOC, PT and by treatment group

SOC and PT	DM05 (N=xxx)			Optive® (N=xxx)			Total (N=xxx)		
	AE (1)	n (2)	% (3)	AE (1)	n (2)	% (3)	AE (1)	n (2)	% (3)
TOTAL	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1 – PT 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 2 – PT 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x

(1) Number of AEs
(2) Number of subjects with at least one AE
(3) % of subjects with at least one AE

9 TABLES, LISTING AND FIGURES

Planned tables, listing and figures are for information purposes, and are subject to change.

9.1 Planned tables

Subjects with at least one major/minor deviations
Protocol deviations
Analysis populations

Number of active centre
Number of included and randomized patients
Number of included and randomized patients by treatment groups
Number of included and randomized patients by centre
Course of the study
Number of patients having finished the study normally by treatment groups.
Reason of withdrawal
Study follow-up
Normal study end

Demographic data by treatment groups – PP population
Demographic data by PP/ITT population
Contraception (for female only) by treatment groups – PP population
Contraception (for female only) by PP/ITT population
Medical history at selection visit by treatment groups – PP population
Medical history at selection visit by PP/ITT population
Product and document dispensation by treatment groups – PP population
Product and document dispensation by PP/ITT population
Ocular surface disease index (OSDI) at selection visit by treatment groups – PP population
Ocular surface disease index (OSDI) at selection visit by PP/ITT population
Ocular surface disease index (OSDI) at D0 visit by treatment groups – PP population
Ocular surface disease index (OSDI) at D0 visit by PP/ITT population
Corneal fluorescent staining (Oxford scale) at selection visit by treatment groups – PP population
Corneal fluorescent staining (Oxford scale) at selection visit by PP/ITT population
Corneal fluorescent staining (Oxford scale) at D0 visit by treatment groups – PP population
Corneal fluorescent staining (Oxford scale) at D0 visit by PP/ITT population
Tear film Break Up Time (TBUT) at selection visit by treatment groups – PP population
Tear film Break Up Time (TBUT) at selection visit by PP/ITT population
Tear film Break Up Time (TBUT) at D0 visit by treatment groups – PP population
Tear film Break Up Time (TBUT) at D0 visit by PP/ITT population
Schirmer test at selection visit by treatment groups – PP population
Schirmer test at selection visit by PP/ITT population
Schirmer test at D0 visit by treatment groups – PP population
Schirmer test at D0 visit by PP/ITT population
Pregnancy test (women with childbearing potential only – D0 visit) by treatment groups – PP population
Pregnancy test (women with childbearing potential only – D0 visit) by PP/ITT population
Definition of the worse eye (D0 visit) by treatment groups – PP population
Definition of the worse eye (D0 visit) by PP/ITT population

Previous and concomitant medication - ITT population

Product and document dispensation at D35 by treatment groups – ITT population
Product and document dispensation at D84 by treatment groups – ITT population
Pregnancy test (women with childbearing potential only – D84) by treatment groups – ITT population

Oxford scores on the worse eye at D0 by treatment groups – ITT population
Oxford scores on the worse eye at D0 by treatment groups – PP population
Oxford scores on the worse eye at D35 by treatment groups – ITT population
Oxford scores on the worse eye at D35 by treatment groups – PP population
Change from D0 to D35 of the Oxford total score on the worse eye by treatment groups – ITT population
Change from D0 to D35 of the Oxford total score on the worse eye by treatment groups – PP population
Results of the non-inferiority analysis (main analysis) – PP population
Results of the superiority analysis (main analysis) – ITT population
Results of the superiority analysis (main analysis) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°1) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°1) – ITT population
Results of the non-inferiority analysis (sensitivity analysis n°2) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°2) – ITT population

For Oxford total score on worse eye, OSDI total score, Van Bijsterveld total score, Schirmer test result on worse eye, TBUT total score on worse eye, all ocular dryness symptoms score separately and then globally (total score):
Description of the parameter at D0, D35 and D84 by treatment groups – PP population
Description of the parameter at D0, D35 and D84 by treatment groups – ITT population
Description of the change of the parameter from D0 to D35 and from D0 to D84 by treatment groups - PP population
Description of the change of the parameter from D0 to D35 and from D0 to D84 - ITT population
Results of the ANOVA model for the parameter – PP population
Results of the ANOVA model for the parameter – ITT population

OSDI in class at D0, D35 and D84 by treatment groups – PP population
OSDI in class at D0, D35 and D84 by treatment groups – ITT population
Evaluation of performance by the patient at D0, D35 and D84 by treatment groups – PP population
Evaluation of performance by the patient at D0, D35 and D84 by treatment groups – ITT population
Evaluation of performance by the investigator at D0, D35 and D84 by treatment groups – PP population
Evaluation of performance by the investigator at D0, D35 and D84 by treatment groups – ITT population
Frequency of use of the product at D0, D35 and D84 by treatment groups – PP population
Frequency of use of the product at D0, D35 and D84 by treatment groups – ITT population

AEs by SOC, PT and by treatment groups – Safety Population
TEAEs by SOC, PT and by treatment groups – Safety Population
Severe AEs by SOC, PT and by treatment groups – Safety Population
Treatment-related AEs by SOC, PT and by treatment groups – Safety Population
Serious AEs by SOC, PT and by treatment groups – Safety Population
AEs that lead to study withdrawal by SOC, PT and by treatment groups – Safety Population

AEs by severity and treatment groups
AEs by relationship to the treatment and treatment groups
AEs by seriousness criterion and treatment groups

9.2 Planned listings

Protocol deviations observed
Reason of withdrawal
Other contraceptive method
Ophthalmological history
Medical, surgical and allergy history
Current or past medication treatment
Individual data listing of all AEs
Individual data listing of all SAEs

9.3 Planned figures

Flowchart of analysis populations
Flowchart of patient accountability
Interpretation of results of the non-inferiority analysis (main analysis) – PP population
Results of the superiority analysis (main analysis) – ITT population
Results of the superiority analysis (main analysis) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°1) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°1) – ITT population
Results of the non-inferiority analysis (sensitivity analysis n°2) – PP population
Results of the non-inferiority analysis (sensitivity analysis n°2) – ITT population

10 REFERENCES

1. Van Bijsterveld O.. Diagnostic test s in the sicca syndrome . Arch Ophthalmol 1969;82:10—4.
2. Anthony J. Bron, FCOphth, 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.
7. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI/ Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates
8. ICH TOPIC E6/ Note for guidance on Good Clinical Practice- CPMP / ICH / 135 / 95, January 1997
9. 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
10. 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

11 APPENDICES

11.1 Appendix 1: Level of validation for analyses programming

This chapter documents the validation of the statistical analysis programs. The level of validation is defined with reference to the procedure "Programming of the statistical analysis".
All the analyses and programs have a default validation level "Basic + NC".
Analysis below have a CR validation level:

Analyses	Validation level	Programs
Primary efficacy endpoint (section 7.6.1)	CR	ANA_PRINC

Key:
Basic = Corresponds to the self-check of the programming by any person who is required to program, as well as the checking of derived variables (see self-check frame)
NC (non-critical) = The tables, listings and figures compiled in a single document shall be verified by one qualified person other than the program developer with the support of the CRF and SAP for the study.
CR (critical) = A double programming and a comparison of the results should be performed by one qualified person other than the program developer.