MEIF/16/MOF-Col/001

A randomized, double-blinded, placebo-controlled, clinical study of the effects of a nutraceutical combination on LDL cholesterol levels in subjects with suboptimal blood cholesterol levels. (Acronym: NATCOL)

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Document status:	Final version 1.0
Release date:	17-DEC-2018

Document History

Status and Version	Release Date	Change Description	Reason/Comment
Draft Version 0.1	07/09/2018	N.A.	N.A.
Draft Version 0.2	04/12/2018	Add explorative analyses	Sponsor's request.
Draft Version 0.3	14/12/2018	Update sections 2.3 and 6.5.4	Sponsor's review
Final Version 1.0	17/12/2018	First Final Release	Sponsor's approval

Authorization

The signatures on this page indicate review and approval of the Statistical Analysis Plan, version 1.0, dated 17/12/2018.

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LIST OF ABBREVIATIONS

AE	Adverse Events
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CPK	Creatinine Phosphokinase
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HDL	High-Density Lipoprotein
HSI	Hepatic Steatosis Index
ICF	Informed Consent Form
ICO	Index of Central Obesity
LAP	Lipid Accumulation Product
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
MDRD	Modification of Diet in Renal Disease
PP	Per Protocol
PV	Pulse Volume
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
TC	Total Cholesterol
TG	Triglycerides

1. INTRODUCTION

1.1. CHANGES FROM THE STUDY PROTOCOL

Not applicable.

1.2. DISCLOSURE OF THE RESULTS

Dissemination of results will not be limited. No independent statisticians nor reviewers are foreseen.

2. STUDY OBJECTIVES

For the rationale of this study, please refer to Chapter 4 of the Study Protocol #4 dated 16 April 2018.

2.1. PRIMARY OBJECTIVE

To evaluate the effect of a combination of phytosterols and DIF1STAT® (fermented red rice titrated in 5 mg monacolin K) on blood LDL-cholesterol levels over an 8-week period in subjects with sub-optimal blood cholesterol levels.

2.2. SECONDARY OBJECTIVES

To evaluate in subjects with sub-optimal blood cholesterol levels the effect of a combination of phytosterols and DIF1STAT® (fermented red rice titrated in 5 mg monacolin K) on the following parameters over an 8-week period:

- Total blood cholesterol (TC)
- Blood High Density Lipoprotein (HDL)-cholesterol
- Blood non-HDL cholesterol
- Blood triglycerides (TG)
- Apolipoprotein B
- TC/HDL and LDL-C/HDL risk ratios
- Pulse Volume (PV) waveform (Endothelial reactivity)
- Glycemia, ALT, AST, gamma-GT, serum creatinine, serum uric acid, Creatinine Phosphokinase (CPK)

2.3. EXPLORATORY OBJECTIVES

Evaluated LDL cholesterol levels and change from baseline focusing on patient subgroups of clinical interest. Evaluated LDL cholesterol decrease between groups of patients

classified according to clinical characteristics at baseline (i.e. LDL levels, eGFR levels, Metabolic syndrome, glucose in fasting conditions altered, proved hypertension).

3. BACKGROUND AND RATIONALE

3.1. STUDY DESIGN

This is an exploratory, monocentric, interventional, non-drug, randomized, placebo-controlled, double-blinded, parallel-group study.
The study duration will be of approximately ten weeks for each subject. Four study visits are planned and will take place in the morning; participants will be asked to fast overnight (12 hours) prior to the visit.

3.2. TREATMENT GROUPS AND RANDOMIZATION

Eligible patients are randomized according to a computer-generated randomization list in a 1:1 ratio to one of the following two treatment arms:

1. Phytosterols 800 mg, + DIF1STAT®, one tablet daily per os.
2. Placebo, one tablet daily per os.

Randomization list has been generated by an independent statistician using a validated computer system program: permuted blocks and no stratification factor have been applied. The randomization and treatment assignment are managed locally at the investigation site that has received all random numbers and all box coded.

At Visit 2, all patients who fulfill all the inclusion/exclusion criteria, after the Investigator's confirmation in a specific section of the paper CRF, receive a randomization number corresponding to a preassigned treatment kit/box code according to the randomization list.

The drug is dispensed to the patients at the end of the randomization visit (V2), which occur 14 days after the screening visit.

3.3. STUDY POPULATION

The study population consists of subjects, aged 30-75 years, with sub-optimal blood LDL-cholesterol levels (LDL-cholesterol = 115 -190 mg/dL and Triglycerides < 400 mg/dL). A total of at least 88 patients meeting the following inclusion and exclusion criteria are to be recruited.

Inclusion criteria

- Age 30-75 years
- LDL-cholesterol = 115-190 mg/dL

- Triglycerides < 400 mg/dL
- Any cardiovascular therapy should be stable for type and dose for at least three months
- Signed, written informed consent

Exclusion criteria

- Intolerance to any ingredient of dietary supplement
- Patients already suffering from cardiovascular diseases or at high risk of developing cardiovascular diseases
- Myopathies
- Uncontrolled diabetes mellitus based on PI judgment
- Chronic renal failure (defined as eGFR<60ml/min/1.73m2) or liver failure (defined as AST and /or ALT>3 Upper Limit of Normal) (ULN)
- Body Mass Index > 32 kg/m2
- Therapy with statins or other drugs or supplements with effects on lipid metabolism
- Patients with acquired immunodeficiency
- Treatment with immunosuppressants
- Pregnant or breastfeeding women
- Women of childbearing potential not willing to use effective birth control methods
- Patients participating in or having participated in another clinical trial within the previous 3 months
- Current or recent history of drug or alcohol addiction based on PI judgment

3.4. STUDY DRUG AND DOSING

The test drug is Phytosterols 800 mg, + DIF1STAT®: 1.300 mg film-coated tablet. Ingredients: phytosterols (61.5%) bulking agent: microcrystalline cellulose, cross-linked sodium carboxymethyl cellulose, fermented red rice titrated at 3% in monacolin K Monascus purpureus went, seed), niacin, anti-caking agents: fatty acid magnesium salts, silicon dioxide; policosanols titrated to 60% octacosanol; coating agents: polyvinyl alcohol, talcum, polyethylene glycol, polysorbate 80; colorants: E120, E172.
Nutritional information: each tablet contains phytosterols (800 mg), Monascus pupureus (167 mg) titrated at 3% in monacolin k (5mg), niacin (27 mg), linear aliphatic alcohols titrated to 60% octacosanol.

A placebo tablet for oral administration identical in appearance, size, shape, weight and taste to the active product. 1,300 mg film-coated tablets. Ingredients: bulking agent: microcrystalline cellulose, cross-linked sodium carboxymethyl cellulose; colorants: red beet, elder extract plv, anti-caking agents: fatty acid magnesium salts, silicon dioxide; coating agents: polyvinyl alcohol, talcum, polyethylene glycol, polysorbate 80; colorants: E120, E172.

Patients take treatment one tablet per os, per day in the evening for 8 weeks.

3.5. PROHIBITED MEDICATIONS

The use of statins or other drugs/products that affect lipid metabolism is prohibited during the study.

3.6. SAMPLE SIZE

Considering the primary endpoint of the study as the reduction from baseline to week 8 in LDL cholesterol level and the data available from literature [Phytomedicine. 2016 Oct 15; 23(11):1113-8], a reduction of LDL level of approximately 10% is expected after the intake of the nutraceutical. Therefore, a mean difference of 15 mg/dL in the reduction of LDL cholesterol level at week 8 between the nutraceutical treatment group and the placebo group is considered clinically significant.
Assuming a baseline LDL level of 145 ±19 mg/dL, a power of 90% and a 5% two-sided alpha level to detect a difference in mean change in LDL from baseline to week 8 equal to 15 mg/dL between the nutraceutical and the placebo group, the total number of patients to be evaluated should be 35 per treatment arm in a 1:1 ratio (NQuery Advisor, 7.0). Allowing for an approximate 20% dropout rate, at least 88 patients should be randomized: 44 patients in each treatment group.

3.7. SCHEDULE OF TIME AND EVENTS

Patients are seen and evaluated according to the flow chart shown in Table 3.7-1:

Table 3.7-1 – Assessment schedule.

	Day -14	Day 0	Day 28 (± 3)	Day 56 (± 3)
	Visit 1^	Visit 2^	Visit 3^	Visit 4^
	Screening	Baseline	Intermediate	End of study
Informed consent	✓			
Inclusion/exclusion criteria	✓	✓		
Medical history	✓			
Weight, height[&], waist circumference, Index of Central Obesity (ICO), Body Mass Index (BMI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP)	✓	✓	✓	✓
Heart rate, blood pressure[#]	✓	✓	✓	✓
Hematology/clinical chemistry*	✓	✓	✓	✓
Urine Pregnancy Test (dipstick)		✓		✓
Endothelial reactivity (Endocheck)		✓		✓
Diet evaluation	✓	✓	✓	✓
Randomization/Dispensation of treatment		✓°		
Compliance with treatment			✓	✓
Concomitant medications	✓	✓	✓	✓
Adverse events (AE)		✓†	✓	✓

^ Visits to take place in the morning. Participants will be asked to fast overnight 12h before the visits.
# Orthostatic and clinostatic, diastolic and systolic blood pressure (average of three measurements).
* Full lipid panel (total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, risk ratio, B apolipoproteins, LDL-C/Apo B), glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula.
§ During Visit 2 – Baseline evaluation – the LDL-C and TG values will be confirmed through a blood test analysis. If the eligibility was confirmed, the patient will be asked to return no later than 3 days after V2 for randomization and treatment dispensation.
† Collection of AEs occurred after signature of informed consent.
& Height only at Visit 1.
+ See Appendix 1 of the protocol for diet guidelines.
° Randomization and dispensation of treatment will take place within 3 days from Visit 2^ - Baseline evaluation and will be considered as "Day 0".

At visit 1 (screening – Day -14), the compliance with inclusion/exclusion criteria and eligibility for the study were evaluated. The subjects undergo the following evaluations:

- Medical history

- Weight, height, waist circumference, Index of Central Obesity (ICO), Body Mass Index (BMI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP)
- Heart rate, blood pressure (average of three measurements)
- Hematology/clinical chemistry in fasting condition (total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, risk ratio, B apolipoproteins, LDL-C/Apo B, glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula)
- Concomitant medication

Standard dietary suggestions to correct unhealthy habits (a Mediterranean-style diet is to be maintained for the entire duration of the study – see Appendix 1 of the protocol for diet guidelines) are given to subjects at the screening visit.

At visit 2 (baseline evaluation – Day 0), LDL-C and TG values has confirmed through a blood test analysis in fasting condition to evaluate compliance with inclusion criteria (LDL-cholesterol = 115-190 mg/dL, Triglycerides < 400 mg/dL). The subjects undergo the following evaluations:

- Weight, waist circumference, Index of Central Obesity (ICO), Body Mass Index (BMI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP)
- Heart rate, blood pressure (average of three measurements)
- Hematology/clinical chemistry in fasting condition (total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, risk ratio, B apolipoproteins, LDL-C/Apo B, glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula)
- Endothelial reactivity test (Endocheck®)
- Urine Pregnancy Test (dipstick)
- Diet evaluation
- Dispensation of treatment
- Concomitant medication
- Adverse events

At visit 3 (intermediate evaluation – Day 28), the following evaluations are performed:

- Weight, waist circumference, Index of Central Obesity (ICO), Body Mass Index (BMI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP)
- Heart rate, blood pressure (average of three measurements)
- Hematology/clinical chemistry in fasting condition (total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, risk ratio, B apolipoproteins, LDL-C/Apo B, glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula)
- Diet evaluation
- Concomitant medication
- Accountability and compliance with treatment
- Treatment tolerability evaluation (adverse events, if any)

At visit 4 (end of study – Day 56), the following evaluations are performed:

- Weight, waist circumference, Index of Central Obesity (ICO), Body Mass Index (BMI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP)
- Heart rate, blood pressure (average of three measurements)
- Hematology/clinical chemistry in fasting condition (total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, risk ratio, B apolipoproteins, LDL-C/Apo B, glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula)
- Endothelial reactivity test (Endocheck®)
- Urine Pregnancy Test (dipstick)
- Diet evaluation
- Concomitant medication
- Accountability and compliance with treatment
- Treatment tolerability evaluation (adverse events, if any)

4. ANALYSIS POPULATIONS

Patients without a valid or adequately obtained Informed Consent Form (ICF) will be excluded from any analysis population.
The following analysis sets are defined for statistical analyses:

- **Full Analysis Set (FAS):** All patients to whom study treatment has been assigned by randomization and who have the assessment for LDL cholesterol at visit 4 (week 8). According to the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to during the randomization procedure. The primary and secondary analysis will be based on the FAS.
- **Per Protocol (PP) Set:** All patients in the FAS who have no major protocol deviations. Results of the analysis of the primary variable conducted in the PP set are considered as supportive.
- **Tolerability Set (TOL):** All patients who received at least one dose of investigational product. Patients are analyzed according to the treatment actually received (if different from treatment assigned through randomization).

The assignment of subjects to analysis populations will be summarized before the database lock in the Patient Validation Document. Final assignment of subjects to analysis populations will be approved by the Sponsor study team.

The list of protocol deviations leading to the exclusion from the analysis populations is reported in the Protocol Deviation Handling Document (PDHD).

Non-protocol deviations (NOPDs) detected through SAS® programming are not protocol violations but they lead to exclusion from analysis populations; they are listed in the following Table 4-1:

Table 4-1: List of non-protocol deviations

Deviation code	Description	Exclusion from analysis population
NOPD001	Subject without the assessment for LDL cholesterol at visit 4 (week 8)	FAS, PP
NOPD002	Subject who did not receive at least one dose of investigation product.	TOL

NOPD = Non-protocol deviations; FAS= Full analysis set; PP = Per Protocol set; TOL = Tolerability set.

5. VARIABLES

5.1. EFFICACY VARIABLES

PRIMARY VARIABLE

The primary variable of the study is the change from baseline to Week 8 in LDL cholesterol levels.

SECONDARY VARIABLES

The secondary variables of the study are defined as change from baseline to Week 8 in:

- Total blood cholesterol
- Blood HDL-cholesterol
- Blood non-HDL cholesterol
- Blood triglycerides
- Apolipoprotein B
- TC/HDL and LDL-C/HDL risk ratios
- Pulse Volume (PV) waveform (endothelial reactivity)
- Glycemia, ALT, AST, gamma-GT, creatinine, uric acid, CPK

5.2. SAFETY VARIABLES

Other variables are as follows:

- Change from baseline at each assessment time point for each laboratory parameter
- Adverse Events
- Vital Signs
- Weight
- Height
- Waist Circumference
- Index of Central Obesity (ICO)
- Body Mass Index (BMI)
- Hepatic Steatosis Index (HSI)
- Lipid Accumulation Product (LAP)

6. DEFINITION AND GENERAL METHODOLOGY

6.1. GENERAL METHODOLOGY

Statistical tables, figures, listings and analyses will be produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA). Continuous data will be summarized by mean, standard deviation (SD), median, 1st and 3rd quartile, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables. Percentages will be computed considering subjects with non-missing information, if not differently specified.

DEFINITION OF BASELINE
The baseline period for the present study is defined as the visit 2 (Day 0 – baseline).

CODING OF THERAPIES AND MEDICAL TERMS
Baseline medical history, pre-existing conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA dictionary, English version 20.0). Prior and concomitant medications will be coded using the WHO Drug Dictionary version B2 Q4 2016.

MISSING OR PARTIAL DATES
For the computation involving dates, the following assumption will be made in case of partially
missing information:

- Day missing => day will be replaced with 15
- Day and month missing => day will be replaced with 1, month will be replaced with 7
- Day, month and year missing => no imputation will be done

HANDLING OF MISSING DATA/IMPUTATION RULES/CENSORING RULES
No missing data imputation will be adopted.

HANDLING OF DROP-OUT PATIENTS
Not applicable.

MULITPLICITY ISSUES
No alpha level adjustment for multiplicity will be adopted.

6.2. STUDY PATIENTS

The number and percentages of screened subjects and reason for screening failure will be summarized overall.

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

The number of protocol and non-protocol deviations and the number of patients per deviation will be summarized.

The numerousness of the analysis populations will be described and the reason excluding the subject from any analysis population will be provided.

PATIENTS DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Patient demographics and baseline characteristics will be summarized on the FAS Population, overall and by planned treatment group, by means of summary descriptive statistics.

Demographic characteristics for patients will include sex, race and age at screening (years). Patients' age at screening will be calculated as the number of completed years since birth at the time of informed consent.

Medical history will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). Ongoing status at informed consent will be also taken into account.

Background characteristics will include the following variables:

- Anthropometric data performed at baseline include weight (Kg), height (m), Body Mass Index (BMI), waist circumference (cm), Index of Central Obesity (ICO), Hepatic steatosis Index (HSI), Lipid Accumulation Product (LAP).
- Vital signs at baseline include heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) calculated as average of three measurements both in orthostatic position and clinostatic position. The three measurements collected in orthostatic position and clinostatic position will be only listed.
- Pregnancy test for women not childbearing potential was assessed at baseline. Result of urine pregnancy test (positive/negative) will be described.
- Endothelial reactivity was performed at baseline and results include baseline brachial pulse volume (PV1), brachial pulse volume after hyperemia (PV2) and pulse volume (PV) waveform (endothelial reactivity) calculated as the root-square of ratio PV2/PV1 will be described.
- Diet Evaluation include data about style diet followed by patients at screening (i.e. Mediterranean-style diet Yes or No), information about diet suggestion to correct

unhealthy habits received or not by patients at screening visit and patient compliant with the diet suggestion at baseline.

- Hematology parameters include total cholesterol, LDL-cholesterol, HDL and non-HDL cholesterol, triglycerides, TC/HDL and LDL-C/HDL risk ratio, B apolipoproteins, LDL-C/Apo B.
- Chemistry parameters include glycemia, ALT, AST, gamma-GT, CPK, uric acid, creatinine, eGFR with MDRD formula.

6.3. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications are collected during the study together with their indication, dosage, unit, route of administration and frequency.

Prior medications are defined as therapies starting prior to the study and ending prior to the start of study treatment (i.e. date of first intake).
Prior medications will be presented by ATC Code Level 2, Preferred Term and ongoing status overall and by planned treatment group on the FAS Population.

Concomitant medications are defined as therapies ending or ongoing after the start of study treatment. Concomitant medications will be presented by ATC Code Level 2, Preferred Term and ongoing status overall and by actual treatment group on the Tolerability population.

A medication with a missing start date will be assumed to be a concomitant medication, unless the stop date is before the first dosing date in which case the medication will be summarized as a prior medication. Medications with start dates before the dosing date and missing end dates or end dates after the first dosing date will be summarized as concomitant medications.

6.4. DRUG EXPOSURE AND TREATMENT COMPLIANCE

Extent of exposure to study treatment is defined as the difference in days between the date of last administration and the date of first treatments administration plus one, regardless of unplanned intermittent discontinuation.
Overall treatment compliance is defined as the actual number of tablets taken compared to the treatment duration (i.e. extent of exposure). Compliance levels are defined as following according to overall treatment compliance:

- < 80%
- <80% and ≤120%
- >120%

A patient that has taken at least 80% and no more than 120% of the required treatment will be considered compliant.

The number and percentage of patients with at least one dose reduction or interruption will be described. The reason for dose reduction or interruption will be only listed.

Extent of exposure and compliance will be summarized by means of descriptive statistics, overall and by actual treatment group on Tolerability population.

6.5. EFFICACY EVALUATION

6.5.1. Primary efficacy analysis

The statistical analysis of the primary variable will be performed on the FAS population.
Summary statistics of LDL cholesterol levels and change from baseline at each assessment time point will be presented overall and by planned treatment group by means of descriptive statistics for continuous data.
An analysis of covariance (ANCOVA) model will be estimated on the changes from baseline to Week 8 in LDL cholesterol levels considering planned treatment group as factor and baseline value of LDL cholesterol as continuous covariate. Results will be reported as Least-Square Means together with associated two-tailed 95% CI; the difference between Least Square Mean of nutraceutical combination group versus placebo will be estimated with two-tailed 95% CI and p-value.
If the assumption of normality of residuals is violated, the ANCOVA model will be fitted on rank transformed data.

6.5.2. Sensitivity analysis on primary endpoint

The same statistical analysis of the primary variable will be performed on the PP population as supportive.

6.5.3. Secondary efficacy analysis

The statistical analyses of the secondary variables will be performed on the FAS population.
Summary statistics for each secondary variable (i.e. total blood cholesterol, blood HDL-cholesterol, blood non-HDL cholesterol, blood triglycerides, apolipoprotein B, TC/HDL and LDL-c/HDL risk ratios, pulse volume(PV) waveform, glycemia, ALT AST, gamma-GT, creatinine, uric acid, CPK) and change from baseline at each assessment time point will be presents overall and overall and by planned treatment group by means of descriptive statistics for continuous data.
For each secondary variable, an analysis of covariance (ANCOVA) model will be estimated on the changes from baseline to Week 8 considering planned treatment group as factor and baseline value of the parameter as continuous covariate. Results will be reported as Least-Square Means together with associated two-tailed 95% CI; the difference between Least

Square Mean of nutraceutical combination group versus placebo will be estimated with two-tailed 95% CI and p-value.

If the assumption of normality of residuals is violated, the ANCOVA model will be fitted on rank transformed data.

6.5.4. Exploratory efficacy analysis

The following exploratory efficacy analysis will be performed on the FAS population:

- Summary statistics of LDL cholesterol levels and change from baseline at each assessment time point will be presented focusing on patient subgroups of clinical interest.
    - Patients with baseline levels of LDL cholesterol
        - Ranging from 115 mg/dl to 159 mg/dl
        - Equal or greater than 160 mg/dl
    - Patients with baseline values of eGFR (computed according to the MDRD formula)
        - Ranging from 60 and 89 ml/min/1.732m2
        - Equal or greater than 90 ml/min/1.732m2
    - Patients with/without Metabolic Syndrome
      According to the 2009 Joint Interim Statement, the Metabolic Syndrome is defined as the presence of an abdominal circumference >102 cm for men or >88 cm for women, and two or more of the following criteria:
        - Glucose in fasting conditions >= 100 mg;
        - SBP >= 135 mmHg or DBP>= 85 mmHg or current treatment with antihypertensive drugs;
        - Triglycerides >150 md/dl;
        - HDL <40 mg/dl for men, <50 mg/dl for women
    - Patients with/without glucose in fasting conditions altered, defined as glucose in fasting conditions out of the following range: from 100 mg/dl and 125 mg/dl.
    - Patients with/without proved hypertension, i.e. patients with SBP >=140 mmHg and/or DBP>=90 mmHg for three consecutive readings performed in orthostatic position.
- Linear regression analysis on LDL change at Week 8 vs. baseline will be performed considering patients age, gender and BMI as predictors.
  In case of violation of the assumption of normality of residuals, the linear regression model will be fitted on appropriate transformed data (i.e. rank transformed data, logarithmic transformed data).
- Linear regression analysis on LDL change at Week 8 vs. baseline will be performed considering patients eGFR and glycemia values at baseline as predictors.

In case of violation of the assumption of normality of residuals, the linear regression model will be fitted on appropriate transformed data (i.e. rank transformed data, logarithmic transformed data).

- Linear regression analysis on endothelial reactivity change at Week 8 vs. baseline will be performed considering patients age, gender and BMI as predictors.
  In case of violation of the assumption of normality of residuals, the linear regression model will be fitted on appropriate transformed data (i.e. rank transformed data, logarithmic transformed data).
- Linear regression analysis on endothelial reactivity change at Week 8 vs. baseline will be performed considering patients eGFR and glicemia values at baseline as predictors.
  In case of violation of the assumption of normality of residuals, the linear regression model will be fitted on appropriate transformed data (i.e. rank transformed data, logarithmic transformed data).

6.6. SAFETY EVALUATION

Safety analyses will be conducted on the Tolerability Population.

6.6.1. Adverse Events

According to the onset date of the event, AEs will be defined as follows:

- treatment-emergent AE, those events with an onset date after treatment initiation
- non-treatment-emergent AE, those events with an onset date between informed consent and treatment initiation

The incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded throughout the study will be presented by actual treatment. Non treatment-emergent AEs will be listed separately.

Tables reporting a general summary of AEs will be produced specifying the number of total events and the absolute and relative frequency of subjects with AEs. As a patient may have more than one AE, the total number of AEs could be greater than the total number of patients. Absolute and relative frequency of patients with drug-related AEs, severe AEs, SAEs, AEs with an outcome of death, AEs leading to temporary or permanent discontinuation of treatment will be also reported. Product-related AEs will be the AEs with causality equal to ‘‘certain”, ‘‘probable’’, ‘‘possible’’ or “unassessable”; if the relationship to study treatment is missing, the treatment-emergent AE will be considered drug related as well. AEs leading to temporary or permanent discontinuation of treatment will be the AEs with action taken with investigational product equal to “Drug interrupted”or “Drug withdrawn.

Treatment-emergent AEs will be summarized by MedDRA dictionary System Organ Class (SOC) and Preferred Term. A summary of treatment-emergent AEs by preferred term and severity will be also provided.

All related treatment-emergent AEs, treatment-emergent AEs with an outcome of death, treatment-emergent AEs leading to discontinuation of treatment will be summarized by MedDRA dictionary System Organ Class (SOC) and Preferred Term (PT) and will also be listed.

Serious treatment-emergent AEs will be summarized similarly.

6.6.2. Laboratory parameters

Laboratory data (hematology and chemistry parameters) and change from baseline at each assessment time point will be summarized overall and by actual treatment group by means of descriptive statistics for continuous data.
Laboratory test results will be classified by the low/normal/high classification based on local laboratory normal ranges, if applicable. The number and percentage of patients will be summarized overall and by actual treatment group.

6.6.3. Vital signs/Physical examination

Vital signs, heart rate and blood pressure, calculated as average of three measurements both in orthostatic position and clinostatic position, will be summarized at each assessment time point overall and by actual treatment group by means of the usual descriptive statistics for continuous variables. Change from baseline on average of measurements at each assessments time point will be also summarized. The three measurements collected in orthostatic position and clinostatic position will be only listed.

Anthropometric data and change from baseline at each assessments time point will be summarized at each assessment time point overall and by actual treatment group by means of the usual descriptive statistics for continuous variables.

6.6.4. Other safety parameters

Pregnancy test results at visit 4 will be listed.

6.7. SUBGROUP ANALYSES

No subgroup analyses are currently planned.

6.8. INTERIM ANALYSIS/DMC

No interim analysis is planned.

7. REFERENCES

Not applicable.

8. APPENDIX

Not applicable.