Protocol No.: ORION-2 (MDCO-PCS-16-02)

NCT02963311

An Open-Label, Single-Arm, Multicenter Pilot Study to Evaluate Safety, Tolerability, and Efficacy of Inclisiran in Subjects with Homozygous Familial Hypercholesterolemia

STATISTICAL ANALYSIS PLAN

14 November 2018

The Orion HoFH Study

Protocol No.: ORION-2 (MDCO-PCS-16-02)

An Open-Label, Single-Arm, Multicenter Pilot Study to Evaluate Safety, Tolerability, and Efficacy of inclisiran in Subjects with Homozygous Familial Hypercholesterolemia

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1. TRIAL DESIGN

1.1. Type/Design of Trial

This study will be a Phase II, open label, single arm, multicenter pilot study in subjects with homozygous familial hypercholesterolemia. Informed consent (and written assent if subject is < 18 years of age) will be obtained from subjects before the initiation of any study-specific procedures.

Subjects who meet study inclusion/exclusion criteria will be instructed to continue to follow a National Cholesterol Education Program (NCEP) Adult Treatment Panel III (or comparable) diet [Appendix C in protocol] and will be required to maintain their current lipid lowering drug therapy for the duration of the study.

In this study, 8-10 subjects will be enrolled and receive open label inclisiran 300mg SC. Dosing interval will be determined by PCSK9 level at Day 60 or 90 or rate of change of PCSK9 levels between Days 60 and 90.

On Day 1, eligible subjects will be enrolled and receive the first SC administration of inclisiran. After first study drug administration, the subject will be observed in the clinic for at least 4 hours post injection before being discharged. Subjects will return at Day 14 and Day 30 and then at monthly intervals. If a second dose of study drug is deemed necessary (if mean serum PCSK9 levels are not suppressed by > 70% at Day 60 or 90, as compared to baseline), subjects will receive this dose at Day 90 or 104 respectively, based on PCSK9 levels from the previous visit.

Study visits will include collection of AE and SAE data, vital signs, ECGs, concomitant medication, and laboratory tests. The study also includes collection of biomarker samples and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetics analyses, unless underlying causal mutations of HoFH are well documented by a validated specialized laboratory.

Efficacy assessments will include measurement of the effects of inclisiran on levels of LDL-C, other lipoproteins including total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], and PCSK9.

Formation of anti-drug antibodies (ADA) will be assessed on Day 1 (prior to and 4 hours after the injection) and on subsequent visits until the end-of-study (EOS).

The EOS visit and the last estimation of lipids will occur at Day 180. Following Day 180 subjects will continue in the study until the observed LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90. Subjects will be encouraged to complete all planned visits.

The decision to initiate a Phase III study will be defined as an observed mean 15% or greater reduction in LDL-C. A number of factors may influence the proportion of subjects achieving this

metric, in particular the specific LDL receptor mutation(s) or other causative mutations of HoFH studied. Given the small sample size for this part of the study, such issues will be taken into careful consideration prior to making the final decision.

The safety/ tolerability and efficacy data from this study will be reviewed by a Safety Committee on an ongoing basis, and the results will be used to guide the decision to initiate a Phase III study in HoFH patients. A recommendation may be taken to stop or amend the study at any of these reviews.

1.2. Objective of Trials

Primary Objective(s):

To characterize the effect of 90 and 180 days of subcutaneous inclisiran on the percentage change from Day 1 in low-density lipoprotein cholesterol (LDL-C) in subjects with homozygous familial hypercholesterolemia

Secondary Objective(s):

- To assess the effect of inclisiran on:
  - Change and percentage change in LDL-C from Day 1 to each subsequent visit until Day 180 or final visit
  - Change and percentage change in PCSK9
  - Change and percentage change in total cholesterol, triglycerides, HDLC, non-HDL-C, VLDL-C, Apo-A1 Apo-B and Lp(a) from Day 1 to each subsequent visit until Day 180 or final visit
- To evaluate the safety and tolerability of inclisiran in subjects with homozygous familial hypercholesterolemia

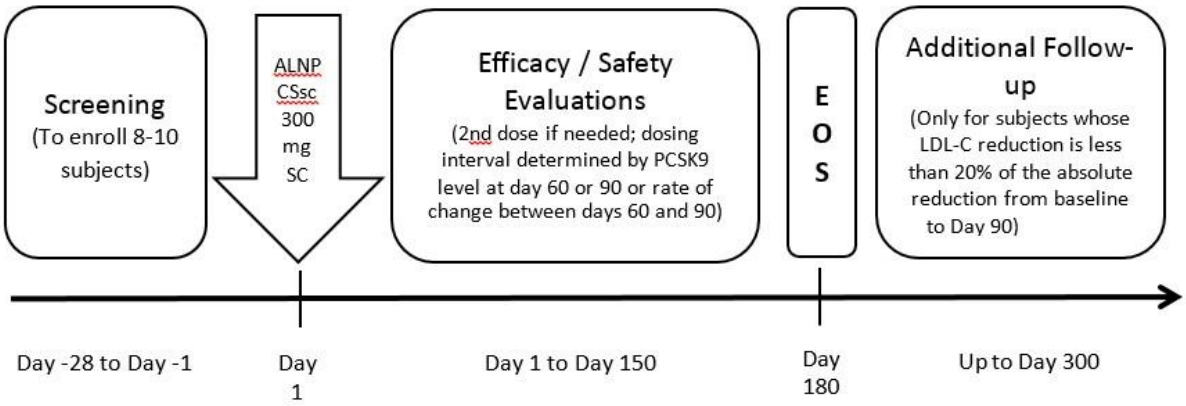
Exploratory:

- To evaluate the formation of Anti-drug antibodies (ADA) to inclisiran
- To assess response of LDL-C by underlying causal mutations of HoFH

1.3. Schematic Diagram of Trial Design

The study design is presented in Figure 1 :

Figure 1: Study Design



1.4. Schedule and Sequence of Procedures

The Schedule of Events/Assessments (Table 1) summarizes the study assessments by time point.

This study consists of four periods: Screening, Treatment, End of Study and Additional Follow-up.

- The Screening period occurs prior to administration of study drug and consists of confirming eligibility.
- The Treatment period occurs from the time of enrolling the subject, collecting Day 1 assessments and study drug administration through Day 90/104.
- The End of Study visit occurs at Day 180.
- The Additional Follow-up period (if necessary) occurs from end of study through Day 300.
- The maximum duration of a subject's participation is from screening/informed consent to end of study (last follow-up) and is expected to be up to 328 days.

Schedule of Assessments

Table 1: Study Design and Schedule of Assessments

	Screening	Treatment Phase								End of Study (EOS)	Additional Follow-Up [p]
Study Day	**-28 to -1**	**Day 1**	**FU1 Day 14 (± 2d)**	**FU2 Day 30 (± 3d)**	**FU3 Day 60 (± 3d)**	**FU4 Day 90 (± 3d) Dose 2? [a]**	**FU4X Day 104 (± 3d) Dose 2? [a]**	**FU5 Day 120 (± 3d)**	**FU6 Day 150 (± 3d)**	**FU7 Day 180 (± 3d)**	**FU8 (Day 210) (± 3) FU9 (Day 240) (± 3) FU10 (Day 270) (± 3) FU11 (Day 300) (± 3)**
Informed consent	X										
Medical History and prior meds	X										
Physical Examination & full neurologic exam	X									X	
Inclusion / Exclusion Criteria	X	X									
Pharmacogenetic sample [o]	X										
Enrollment		X									
Vital Signs [b]	X	X	X	X	X	X	X	X	X	X	
12 Lead ECG [c]		X								X	
Hematology, Coagulation [d, f]	X	X	X	X	X	X	X	X	X	X	X
Biochemistry, Inflammatory markers [d, f]	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X	X				X				X	X [n]
Urinalysis [e,]	X	X [g]								X	X
Pregnancy test [e, h]	X	X [h]	X	X	X	X [h]	X [h]	X	X	X	X [i]

ADA antibodies [j]		X [j, k]		X					X [k]	X [k]	X [k]
Lipids / lipoproteins [m]	X	X	X	X	X	X	X	X	X	X	X
Biomarker (stored samples)[q]	X	X	X	X	X	X	X	X	X	X	X
Study drug admin		X				X [a]	X [a]				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AE reporting		X	X	X	X	X	X	X	X	X	X
SAE reporting		X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies; AE = adverse event; ECG = electrocardiogram; FU=follow-up; EOS = end of study; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

[a] Day 104 visit only for those subjects who receive a second dose of study drug. Dose #2 may be given at Day 90 or 104 depending on PCSK9 levels as compared to baseline

[b] Vital signs: blood pressure and heart rate will be measured prior to injection and at 4 hours after injection. [c] ECG is performed prior to the injection on Day 1.

[d] Hematology, chemistry (including lactate, bicarbonate, glucose, HbA1c, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing. Blood samples for determination of laboratory values will be performed prior to study drug injection where relevant. All laboratory testing will be performed with subjects in a fasted state.

[e] Lab tests performed in participating institution's laboratory. Results must be available before the start of study drug injection on Day 1 to confirm subjects meet eligibility criteria.

[f] Lab tests performed by study's designated Central Lab facility from enrollment to EOS. In addition, subjects in whom LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90 will continue to be followed up on a monthly visit schedule either until this level has been reached or until Day 300.

[g] Urinalysis collection is prior to the injection on Day 1.

[h] Urine pregnancy test performed at each visit for females of childbearing potential. In addition, postmenopausal women who are less than 55 years of age will have a pregnancy test within 24 hours of enrollment and prior to any study drug injection. Results must be available prior to the injection on Day 1 and, if a second dose of study drug is required, on Day 90/104.

[i] Females of childbearing potential will have a pregnancy test at each additional follow-up visit until LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90.

[j] Two ADA samples will be drawn on Day 1: one before the injection and one 4 hours after the injection. [k] Additional aliquots of plasma and serum will be collected at each time point and stored for future analyses.

[l] For subjects in whom LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90, formation of ADA will be assessed at the last visit. [m] Efficacy parameters (Lipids / lipoproteins) will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], and PCSK9.

[n] Day 270 only.

[o] Sample may be taken during screening or anytime during study to be processed and stored, but only after separate consent has been signed. [p] Additional Follow-Up visits only for those subjects in whom LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90.

[q] 3 aliquots of plasma and 3 aliquots of serum will be stored for efficacy and safety biomarker analysis if needed. All samples will be destroyed 1 year following the last subject's last visit in the study.

2. GENERAL CONDUCT OF TRIAL

Written informed consent will be obtained for this study by the principal investigator or sub investigator from all subjects before the performance of any protocol-specific procedure (if the subject is less than 18 years of age, written consent will be obtained from their guardian or legally authorized representative, with verbal assent from the child).

2.1. Screening Period (Days –28 to –1)

The following procedures will be performed within 28 days prior to enrollment:
All screening laboratory tests will be analyzed at the Central Lab, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using the testing materials provided by the Central Lab. The results of all screening laboratory tests should be reviewed prior to enrollment. If these results confirm an exclusion criterion or suggest any contraindication to treatment with inclisiran, and/or other required ancillary medication(s), the subject must not be enrolled.

1. Review of inclusion/exclusion criteria to confirm subject eligibility.
2. Documentation of:
    a. Demography: age, gender and ethnic origin
    b. Medical history
    c. Concomitant medications
3. Full physical examination including height, weight and full neurological examination (asdescribed in Protocol Appendix A).
4. Vital signs (blood pressure and heart rate).
5. Blood samples drawn for screening clinical laboratory tests and results reviewed prior toenrollment. All laboratory testing will be performed with subjects in a fasted state.
    a. Biochemistry
    b. Inflammatory markers
    c. Lipids/lipoproteins
    d. Hematology
    e. Coagulation
    f. HbA1c
    g. Biomarker (stored samples)
    h. Pharmacogenetics (stored samples, only if separate consent has been signed)
6. Urinalysis (local), using standardized supplies from Central Lab.

Urine pregnancy test (local), using standardized supplies from Central Lab, for females of childbearing potential. In addition, postmenopausal women who are less than 55 years of age must have a negative pregnancy test within 24 hours of enrollment.

2.2. Enrollment (Day 1)

Enrollment should only occur once subject eligibility is confirmed.

The following procedures will be performed prior to the injection of study drug:

1. Review of inclusion/exclusion criteria
2. Vital signs (blood pressure and heart rate will be measured prior to injection and at 4 hours after injection)
3. 12-lead ECG
4. Blood samples drawn for clinical laboratory tests (Central Lab):
   a. Biochemistry
   b. Inflammatory markers
   c. Lipids/lipoproteins
   d. Hematology
   e. Coagulation
   f. HbA1c
   g. Anti-inclisiran (ADA) antibodies (prior to and 4 hours after the injection)
   h. Biomarkers (stored samples)
5. Urinalysis (local)
6. Urine pregnancy test (local), for females of childbearing potential. In addition,postmenopausal women less than 55 years of age will have a pregnancy test within 24 hours of enrollment. Results must be available prior to the first injection of study drug
7. Concomitant medications
8. AE reporting
9. SAE reporting
10. Enrollment (only after subject eligibility is confirmed)

If eligible, the subject will receive the first injection (SC) of study drug and will be observed in the clinic for at least 4 hours post-injection before being discharged. The site of injection is the abdomen. The injection site will be marked and mapped for later observation The following procedures will be performed 4 hours after the injection:

11. Vital signs: blood pressure and heart rate
12. Blood samples drawn for Anti-inclisiran (ADA) antibodies
13. Concomitant medications
14. AE reporting
15. SAE reporting

2.3. Follow-up Visits FU 1-6

Subjects will return to the study center after study drug administration for Follow-Up Visits according to the Schedule of Events/Assessments (Table 1) until the end of the study. Procedures will be as follows:

1. Vital signs (blood pressure and heart rate will be measured prior to injection and at 4 hours after injection)
2. Blood samples drawn for clinical laboratory tests:
   a. Biochemistry
   b. Inflammatory markers
   c. Lipids/lipoproteins
   d. Hematology
   e. Coagulation
   f. HbA1c (only at Days 90 and 180 and Day 270 if applicable)
   g. Anti-inclisiran(ADA) antibodies (only at Day 30 and Day 150)
   h. Biomarkers (stored samples)
3. Urine pregnancy test (local) for females of childbearing potential. In addition, on Day 90 or 104 (if a second dose of study drug is required), postmenopausal women less than 55 years of age will have a pregnancy test and results must be available prior to the injection
4. Concomitant medications
5. AE reporting
6. SAE reporting
7. Study drug administration **ONLY** for subjects requiring a second dose of study drug (depending on the degree of suppression of serum PCSK9 as compared to baseline).

If a second dose is deemed necessary, the subject will receive the injection (SC) at **Day 90 or 104**, based on the PCSK9 levels from the previous visit. The site of injection is the abdomen (on the opposite side than the injection on Day 1). The injection site will be marked and mapped for later observation.

2.4. End of Study (EOS) Visit (FU 7)

A subject's participation in the study is complete when all procedures at the last study visit have been completed and all ongoing SAEs have been followed to resolution.

Procedures will be as follows:

1. Vital signs (blood pressure and heart rate)
2. Physical examination (including full neurological examination as described in protocol Appendix A)
3. 12-lead ECG
4. Blood samples drawn for clinical laboratory tests:
   a. Biochemistry
   b. Inflammatory markers
   c. Lipids/lipoproteins
   d. Hematology
   e. Coagulation
   f. Anti-inclisiran (ADA) antibodies

g. Biomarkers (stored samples)

5. Urinalysis (local)
6. Urine pregnancy test (local) for females of childbearing potential
7. Concomitant medications
8. AE reporting
9. SAE reporting

2.5. Additional Follow-Up Visits (FU 8-11, if needed)

These visits are only for those subjects in whom LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90. Procedures will be as follows:

1. Blood samples drawn for clinical laboratory tests:
   a. Biochemistry
   b. Inflammatory markers
   c. Lipids/lipoproteins
   d. Hematology
   e. Coagulation
   f. HbA1c (only at Day 270)
   g. Anti-inclisiran (ADA) antibodies (only at last visit)
   h. Biomarkers (stored samples)
2. Urinalysis (local)
3. Urine pregnancy test (local). Females of childbearing potential will have a pregnancy test at each additional follow-up visit until LDL-C reduction is less than 20% of the absolute reduction from baseline to Day 90
4. Concomitant medications
5. AE reporting
6. SAE reporting

2.6. Assessment of Safety

2.6.1. Adverse Events

Subjects will be carefully monitored for adverse events by the investigator during the designated study period (See Section 3).

2.6.2. Demographics and Medical History

Baseline demographic information will be collected during screening, and will include age, sex and race/ethnicity.

Relevant medical history includes all ongoing medical or surgical issues. Remote medical and surgical history > 5 years from the time of screening should only be included if considered relevant to the study.

2.6.3. Vital Signs

Vital Signs include heart rate and blood pressure

2.6.4. Electrocardiograms

12-Lead ECGs will be collected at Day 1 and at the Day 180 visit only, unless clinically indicated.

2.6.5. Physical Examination

The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, abdominal, extremities, and recording of height, weight.

The physical examination should also include a full neurologic evaluation as described in Appendix A of protocol.

2.6.6. Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 1). Additional aliquots of plasma or serum will be collected at each time point and stored for any clinically indicated efficacy or safety analyses to be conducted at the end of the study.

Subjects will be in a fasted state for all clinical laboratory assessments. Screening lab tests will be performed by the Central Lab, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using testing materials supplied by the Central Lab. Results from these screening tests must be available before the start of study drug injection on Day 1 to confirm subjects meet eligibility criteria.

Laboratory assessments will include:

Biochemistry: AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), uric acid, total bilirubin (TBIL), direct bilirubin, indirect bilirubin, lactate, bicarbonate, sodium, creatine kinase (CK), albumin, total protein urea (BUN), creatinine, potassium, chloride, glucose (fasting), inorganic phosphate, eGFR, calcium, and tryptase (as required).

Inflammatory markers: hsCRP (fasting), IL6, IFN-γ, and TNF-α

Hematology: hemoglobin, hematocrit, erythrocytes, reticulocytes, platelet counts, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), white blood cell count, differential blood count.

Coagulation: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT).

HbA1c: hemoglobin A1c

Urinalysis: Urinalysis will be performed at the time points defined in the Schedule of Assessments and evaluated by dipstick analyses at the investigational site local lab (a standardized dipstick test will be supplied by the Central Lab). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local lab. The following parameters will be assessed: Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells (RBC)/erythrocytes, white blood count (WBC)/leukocytes, pH, urine sediment (microscopic examination will be performed in the event of abnormalities).

Urine pregnancy: Urine pregnancy testing will be conducted locally at the visits specified in the Schedule of Assessments (a standardized pregnancy test will be supplied by the Central lab).

2.6.7. Anti-Inclisiran Antibodies

Additional sample for analysis of the induction of antibodies will be collected at the time points in the Schedule of Assessments (Table 1).

Aliquots of serum samples will be obtained and frozen, to permit future analysis of the effect of inclisiran on the expression of these exploratory biomarkers. Biological samples for biomarker research will be retained on behalf of the Sponsor for one year following the last subject's last visit in the study.

2.7. Assessment of Efficacy

Specimens for assays of lipids/lipoproteins will be obtained at the time points in the Schedule of Assessments (Table 1). Subjects will be in a fasted state for all efficacy laboratory assessments. Parameters to be assessed will include: total cholesterol (TC), triglycerides, LDL-C, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], and PCSK9.

2.7.1. Change in LDL-C

The primary efficacy endpoint is the percentage change in LDL-C at Day 90 and Day 180.

In addition, this study will assess change and percentage change in LDL-C from Day 1 to each subsequent visit until Day 180 or final visit as a secondary efficacy endpoint .

Blood samples for determination of LDL-C (β-quantification) concentrations will be collected at the time points in the Schedule of Assessments.

2.7.2. Change in Lipids/Lipoproteins

Secondary efficacy assessments will include measurement of the effects of inclisiran on levels of lipids and lipoproteins including total cholesterol, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDLC, Apo-A1, Apo-B, Lp(a), and PCSK9.

- Change and percentage change in PCSK9 levels
- Change and percentage change in other lipids, and apolipoproteins
- **Biomarkers** (stored samples): Additional aliquots of plasma and serum will be collected at each time point and stored for additional analyses, including future analysis of biomarkers of CV risk. These samples will be retained for 1 year following the last subject's last visit in the study.

Plasma samples will be analyzed using a validated enzyme linked immunosorbent assay to determine PCSK9 protein concentration. Full details of the analytical methods used will be described in a separate bioanalytical report.

2.8. Assessment of Pharmacogenetics

A blood sample will be collected, preferably during screening, only from subjects who sign a separate consent for pharmacogenetics. Samples will be processed as described in the Laboratory Manual and stored. Genetic assessment will be performed by an accredited laboratory. This assessment will determine if there is a different response for LDL-C lowering based on the type of mutation(s).

3. ADVERSE EVENTS

3.1. Adverse Event

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the study drug was given or the subject was randomized in a clinical study are not to be considered AEs.

Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor/Investigator.

3.2. AE Severity

The severity of an AE will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

Adverse events will be graded on a 3-point scale and reported as indicated on the case report form. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

3.3. Study Drug Causality

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject's clinical condition and medical history

Categorization of causality will be designated by the investigator as stated below:

Reasonable possibility - There are facts (evidence) or arguments to suggest a causal relationship between the event and the IMP.

No reasonable possibility – There are few to no facts (evidence) or arguments to suggest a causal relationship between the event and the IMP

3.4. Serious Adverse Event

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

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, an MI that may be considered minor could also be an SAE if it prolonged hospitalization.

3.5. Medication Errors

Medication error refers to any unintended error in the dosing and administration of the study product as per instructions in the protocol. Medication Errors generally fall into four categories as follows:

1. Wrong study drug
2. Wrong dose (including dosing regimen, strength, form, concentration, amount, including above the maximum or under the minimum recommended dose);
3. Wrong route of administration;
4. Wrong patient (i.e., not administered to the intended subject)

3.6. Adverse Events of Special Interest (AESIS)

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's study drug or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI(s) have been identified for the study drug inclisiran in this protocol. • Injection site reactions (ISR)

Injection site reactions including individual signs or symptoms at the injection site reported following study drug administration will be collected as an AESI.

The grade (severity) of injection site reaction will be determined by the Common Terminology Criteria for Adverse Events (CTCAE) criteria of Injection Site Reaction (General disorders and administration site conditions) (see Table 2).

Table 2: Common Terminology Criteria for Adverse Events (CTCAE) criteria of Injection Site Reaction

Grade I:	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
Grade II:	Pain; lipodystrophy; edema; phlebitis
Grade III	Ulceration or necrosis; severe tissue damage; operative intervention indicated
Grade IV	Life-threatening consequences; urgent intervention indicated
Grade V	Death

Abbreviations: AE = adverse even
Reference source: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Published May 28, 2009

4. MEASURES TO MINIMIZE/AVOID BIAS

This is an unblinded, open label study. The primary endpoint is based on an assessment of LDL-C, which is a measurement that is not likely to be subject to interpretation bias

5. STATISTICAL PLAN

This is an 8-10 subject non-randomized pilot study. Subjects with homozygous familial hypercholesterolemia will be recruited from approximately 5 sites globally. Subjects that qualify for entry into the study will be enrolled to receive inclisiran. The primary objective of this study is to characterize the effect of 90 and 180 days of subcutaneous inclisiran on the percent change from Day 1 in low-density lipoprotein cholesterol (LDL-C) in subjects with homozygous familial hypercholesterolemia.

The primary hypothesis is that inclisiran, when used in combination with maximally tolerated statin therapy with or without ezetimibe, will be well-tolerated, will suppress circulating PCSK9 >70% and will result in reduction of LDL-C, defined as mean percent change from Day 1 following 90 and 180 days of treatment, in subjects with homozygous familial hypercholesterolemia.

5.1. Sample Size

The sample size was chosen based on clinical considerations.

5.2. General Statistical Considerations and Definitions

5.2.1. General Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Categorical variables will be summarized using counts and percentages. Percentages are based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including changes from day 1, will be summarized using descriptive statistics (n, mean, standard deviation [SD], median and interquartile range [first and third quartiles], minimum and maximum). All summaries are presented for all subjects due to the small sample size in this study.

The Statistical Analysis Plan (SAP) will be finalized before database lock.

Statistical analyses will be carried out using SAS statistical analysis software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

5.2.2. Analysis Population

The following populations will be used for data analyses and/or presentation.

5.2.2.1. Modified Intent-to-Treat (mITT) Population

All ITT subjects (who receive at least one dose of study drug), who have baseline and at least one post-baseline measurement for the primary endpoint. This will be the primary population for the efficacy analyses; unless specified otherwise, the mITT will be the default analysis set in this study.

5.2.2.2. Safety Population

All subjects who received at least one dose of study drug. Treatment classification will be based on the actual treatment received. This will be the primary population for the safety analyses.

The primary analysis set is the modified Intent-to-Treat (mITT), which will include all enrolled subjects who have received at least one dose of study drug. Unless specified otherwise, the mITT will be the default analysis set in this study.

5.2.3. Analysis Windows and Baseline

The observational period for the study includes the screening period (Day -28 to Day -1), treatment and follow up period (Day 1 to Day 180), additional follow up period (up to Day 300, subject will continue in the study until the observed LDL-C reduction is less than 20 % of the absolute reduction from baseline to Day 90). Any event occurring beyond the defined observational period, even if collected on the CRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

Unless otherwise specified, for evaluations that are collected at multiple occasions prior to initiation of study drug administration, the latest evaluation will be considered the "Baseline" evaluation for analysis.

5.2.4. Missing data handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

5.3. Statistical Analyses

5.3.1. Demographic and Baseline Characteristics

Subject demographics (age/age group, gender, weight, height, body mass index, race, enthnicity, and country) and confirmation on HoFH (yes, no) at baseline will be summarized using the mITT and safety populations.

5.3.2. Medical History

Medical history(targeted and other medical history) data collected in the eCRFs will be summarized using the mITT and safety populations.

5.3.3. Protocol Deviation

Subjects with protocol deviation(s) will be listed.

5.3.4. Study Drug Exposure

Study drug administration including actual dose injected, time for injection, and missed doses will be listed.

5.3.5. Concomitant Medications

Summary of concomitant (Day 1 or later) medication will be provided. [Medication will be coded with WHO drug dictionary]. Subjects will be counted only once within each period by medication. A listing for all prior (pre Day 1) and concomitant medications will be provided.

5.3.6. Efficacy Analysis

5.3.6.1. Primary Efficacy Endpoints

The primary endpoint is the percent change in LDL-C following 90 and 180 days of treatment.

Summary statistics and 95% CI of this primary endpoint will be provided. Changes of LDL-C from Day 1 by scheduled visits will also be summarized. Response rate of subjects with 15% or greater reduction in LDL-C from Day 1 following 90 and 180 days of treatment will be calculated.

The analysis for the primary endpoint will be descriptive. Means and confidence intervals will be provided. Mean plots with standard error bars will be provided for observed LDL-C value, change in LDL-C value, and percent change in LDL-C value.

5.3.6.2. Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be similar to the primary analysis of the primary endpoint.

The secondary endpoints of this trial are:

- Change and Percentage change in LDL-C from Day 1 to each subsequent visit until Day 180 or final visit
- Change and Percentage change in PCSK9 from Day 1 to each subsequent visit until Day 180 or final visit
- Change and Percentage change in total cholesterol, triglycerides, HDLC, non-HDL-C, VLDL-C, Apo-A1 Apo-B and Lp(a) from Day 1 to each subsequent visit until Day 180 or final visit

5.3.6.3. Exploratory Efficacy Endpoints

The exploratory endpoints of this trial are:

- Formation of Anti-drug antibodies (ADA) to inclisiran
- Response of LDL-C by the causal genetic mutations of HoFH

5.3.7. Safety Analysis

Safety summaries will include the incidence of adverse events, summaries of laboratory parameters (including shift tables), vital signs, ECGs and anti-drug antibodies.

5.3.7.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified as preferred term) occurring during the treatment period will be counted as a treatment emergent AE (TEAE) either if it is not present at day 1 or if it is present at day 1 but increased in severity during the treatment period.

The number (percentage) of subjects reporting TEAEs/Serious TEAEs will be tabulated by system-organ class, and preferred term. If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term.

Subject listing on AEs/SAEs/AEs leading to a discontinuation or death will be presented.

5.3.7.2. Laboratory Tests

Laboratory values will be summarized, including changes and percent changes from baseline at each time point. Analyses will also be performed for pertinent lab parameters (Appendix 1) for incidence rates of potentially clinical significant values for subjects without potentially clinical significant value at baseline.

In addition, subjects with clinically significant laboratory values (Table 3) will be listed.

5.3.7.3. Vital Signs

Change from baseline in vital signs will be summarized descriptively at each scheduled time point.

6. COMPUTER METHODS

Statistical analyses will be performed using SAS (version 9.2 or later version).

7. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

There are no changes to the analyses specified in the protocol.

8. REFERENCES

1. Protocol MDCO-PCS-16-02 Amendment 1.0, 7 Nov 2016
2. Protocol MDCO-PCS-16-02 Amendment 2.0, Netherlands Specific, 18 April, 2017