2. SYNOPSIS

Name of Sponsor/Company: The Medicines Company	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Inclisiran Injection		
Name of Active Ingredient: Inclisiran sodium		

Title of Study:
A Randomized, Double-Blind, Double-Dummy, Placebo- and Positive-Controlled, Crossover Study to Assess the Electrocardiographic Effects of Inclisiran in Healthy Volunteers

Principal Investigator: Carlos Sanabria, MD

Study center:
Spaulding Clinical Research, LLC, 525 South Silverbrook Drive, West Bend, WI 53095

Publications (reference): None

Studied period (years): First subject enrolled (randomized): 24 September 2018 Last subject completed (last contact): 16 April 2019	**Phase of development:** I

Objectives:

Primary Objective:

The primary objective was to assess the effect of a supratherapeutic dose of inclisiran on cardiac repolarization as assessed by the QT interval corrected (QTc) for heart rate (HR) using the Fridericia correction (QTcF).

Secondary Objectives:

The secondary objectives of this study were:

- To assess the effect of inclisiran on other electrocardiogram (ECG) parameters of HR, PR, RR, QRS, ST-, T-, and U-wave morphology, and QTc for HR using the Bazett correction if QTcF failed to adequately correct;
- To assess the effect on QTcF in relation to plasma levels of inclisiran using exploratory concentration-effect modeling;
- To evaluate assay sensitivity using oral moxifloxacin as an active control;
- To evaluate the pharmacokinetic (PK) profile after a single dose of 900 mg inclisiran sodium;
- To evaluate the effect of inclisiran on proprotein convertase subtilisin/kexin type 9 (PCSK9) and low-density lipoprotein cholesterol (LDL-C); and
- To assess safety and tolerability in healthy subjects after a single dose of 900 mg inclisiran sodium.

Study design:

This was a Phase I, randomized, double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover cardiac safety study with a supratherapeutic dose of inclisiran in healthy subjects.

Number of subjects (planned and analyzed):

A total of 48 subjects were planned, enrolled, and completed Day 30; 44 subjects (91.7%) completed the study. All 48 subjects were included in the Safety, PK, ECG, and PK/Pharmacodynamic (PD) Populations.

Diagnosis and main criteria for inclusion:

Subjects were men or women between 18 and 60 years of age, inclusive, with a body mass index between 18 kg/m^2 and 33 kg/m^2, inclusive, and a body weight of 45 kg or greater, who were in good health based on medical history, physical examination findings, clinical laboratory test results, and 12-lead ECG results at Screening. Subjects had not smoked or used nicotine for at least 90 days before Screening. Subjects did not meet exclusion criteria for HR, systolic or diastolic blood pressure, QTcF, or LDL-C.

Test product, dose and mode of administration, batch number:

Inclisiran Injection, supratherapeutic dose of 900 mg (3 subcutaneous [SC] injections of 300 mg in 1.5 mL each), lot number: B170465

Duration of treatment:

Subjects received each of the 3 study treatments administered in a crossover fashion with a minimum 7-day washout period between doses. The total duration of the study was approximately 270 days, including Screening, Check-in, treatment period, primary follow-up, and posttreatment observational period.

Reference therapy, dose and mode of administration, batch number:

- Placebo solution matched to Inclisiran Injection, (0.9% sodium chloride in water; 3 SC injections of 1.5 mL each), lot number: B170498
- Moxifloxacin positive control, 400 mg oral tablet, lot number: 6344628, overencapsulated with 0 mg capsules, lot number: MDCO-PCS-17-09-092118
- Placebo capsule matched to moxifloxacin overencapsulated tablet, 690 mg of cornstarch overencapsulated with 0 mg capsules, lot number: MDCO-PCS-17-09-092118

Criteria for evaluation:

Pharmacodynamics:

Continuous ECG monitoring was performed for all subjects. The following PD endpoints were calculated using the mean of the triplicate continuous 12-lead ECG data:

- dQTcF: baseline-adjusted QTcF
- ddQTcF: time-matched placebo- and baseline-adjusted QTcF

The primary PD endpoint was ddQTcF.

Analogous-derived secondary endpoints were also calculated for HR and PR, RR, and QRS intervals (baseline-adjusted HR [dHR], PR interval [dPR], RR interval [dRR], and QRS interval [dQRS], and time-matched placebo- and baseline-adjusted HR [ddHR], PR interval [ddPR], RR interval [ddRR], and QRS interval [ddQRS]).

Additional PD endpoints were:

- Categorical analysis of absolute QTcF (>450, >480, and >500 msec)
- Categorical analysis of dQTcF (>30 and >60 msec)

- Categorical outliers for HR and PR and QRS intervals
- Changes (or shifts) from Baseline in the appearance or worsening of ST-, T-, and U-wave morphology
- Changes from Baseline in LDL-C and PCSK9

An exploratory endpoint of the relationship between ddQTcF and the plasma concentrations of inclisiran was also investigated.

Pharmacokinetics:

The following plasma PK parameters of inclisiran were calculated using a noncompartmental approach:

- AUC_{0-24}: area under the plasma concentration-time curve (AUC) from time 0 (before dosing) to 24 hours postdose
- AUC_{0-48}: AUC from time 0 to 48 hours postdose
- AUC_{0-t}: AUC from time 0 to the last quantifiable concentration
- AUC_{0-inf}: AUC from time 0 extrapolated to infinity
- AUC_{ext}: percentage of AUC_{0-inf} obtained by extrapolation
- C_{max}: maximum observed plasma concentration
- T_{max}: time to reach C_{max}
- λ_z: apparent terminal elimination rate constant
- $t_{1/2}$: terminal elimination half-life
- CL/F: clearance
- V_d/F: volume of distribution

The PK endpoints included these PK parameters except for AUC_{ext}.

Safety:

Safety parameters included adverse event (AE) assessments, clinical laboratory test results (including antidrug antibodies), vital sign measurements, safety 12-lead ECG results, and physical examination findings.

The safety endpoints included these safety parameters except for physical examination findings.

Statistical methods:

Four study populations were defined:

- The Safety Population included all subjects who received at least 1 dose of any study drug. Subjects in this population were used in the demographic and safety summaries.
- The PK Population included all subjects who received at least 1 dose of inclisiran and provided an adequate number of blood samples for the determination of plasma PK parameters. Subjects in this population were used for all PK summaries.
- The ECG Population included all subjects who received at least 1 dose of study drug and had digital ECG data collected before dosing and at 1 or more time points after dosing. Subjects in this population were used for all digital ECG summaries and analyses.
- The PK/PD Population included all subjects in the ECG Population who had time-matched plasma concentrations of inclisiran. Subjects in this population were used for the PD exploratory analyses.

Pharmacodynamics:

To investigate potential QTc prolongation associated with inclisiran, the primary PD endpoint was the difference between dQTcF for the subjects receiving inclisiran and placebo (ie, ddQTcF). A

mixed-effects model was used to evaluate the primary PD endpoint, and included terms for sequence, treatment (inclisiran, placebo, or moxifloxacin), study period, postdose ECG assessment time points, and study drug-by-postdose ECG time point interaction as fixed effects and subjects nested within sequence as a random effect. Baseline QTcF was included in the model as a covariate. A spatial power law covariance structure (a time-dependent first-order autoregressive covariance designed for unequally spaced time points) was used. The mean and upper 1-sided 95% CI (equal to the upper limit of the 2-sided 90% CI) of the baseline-adjusted difference between QTcF for the inclisiran and placebo groups (ie, ddQTcF) was determined. If the upper 1-sided 95% CI for the mean difference at each postdose time point between the inclisiran and placebo groups excluded 10 msec, then no clinically meaningful QTc interval prolongation was concluded.

Similar analyses were repeated for the secondary endpoints (HR, PR interval, and QRS interval); however, the 2-sided 95% CI rather than the 2-sided 90% CI was presented.

The average of the triplicate values of each time point for all continuous 12-lead ECG data collected was presented in data listings. Data from subjects excluded from the analysis populations were presented in the data listings but were not included in the calculation of summary statistics. For categorical variables, frequencies and percentages were presented. Continuous variables were summarized using descriptive statistics (number of observations, mean, standard deviation [SD], 2-sided confidence bounds [90% for QTcF and 95% for all other ECG parameters], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). The average of the triplicate values at each time point for the continuous 12-lead ECG parameters (QTcF, HR, RR, PR, and QRS) and the corresponding changes from Baseline (denoted as dQTcF, dHR, dRR, dPR, and dQRS) and the arithmetically calculated placebo-adjusted endpoints (denoted as ddQTcF, ddHR, ddRR, ddPR, and ddQRS) were summarized by treatment and time point.

The mean and 2-sided confidence intervals (CIs) (90% for QTcF and 95% for all other ECG parameters) of the baseline-adjusted ECG parameters (dECG) were displayed graphically for QTcF, HR, RR, PR, and QRS parameters.

The parameters of LDL-C and PCSK9 were summarized descriptively by treatment and time point using the absolute and percentage change from Baseline.

Other PD analyses included the following: assay sensitivity, categorical summaries of the absolute postdose QTcF and dQTcF, categorical summaries of outliers for other ECG variables (PR, QRS, and HR), ECG morphology statements, and adequacy of HR correction.

Pharmacokinetics:

Concentrations of plasma inclisiran were summarized using descriptive statistics (number of observations, arithmetic mean, SD, percent coefficient of variation [CV%], median, minimum, maximum, Q1, Q3, geometric mean, and geometric CV%). Individual plasma concentrations were presented in a data listing. Mean and individual plasma concentration-time profiles and spaghetti plots with subject concentration-time profiles were presented.

The PK parameters calculated for plasma inclisiran were summarized for the PK Population using descriptive statistics (number of observations, arithmetic mean, SD, CV%, median, minimum, maximum, Q1, Q3, geometric mean, and geometric CV%). All calculated PK parameters were presented in a data listing.

Pharmacokinetics/Pharmacodynamics:

To evaluate the concentration-QT relationship between change from Baseline in QTcF (ie, dQTcF) versus plasma concentrations of inclisiran for all subjects in the PK/PD Population, both graphical and mixed-effects analyses of dQTcF versus plasma concentrations of inclisiran were performed. The mixed-effects model contained dQTcF as the dependent variable and included the fixed terms for plasma inclisiran concentrations (where placebo concentrations were set to zero), categorical treatment (inclisiran and placebo), categorical time point, and baseline QTcF with random effects on

the intercept and slope. The mixed-effects model was used to estimate, for all subjects, the predicted population mean ddQTcF and its corresponding upper 95% 1-sided (equivalent to the upper 90% 2-sided) CI at the arithmetic mean C_{max} plasma concentration level. A negative result (ie, the model indicated no plasma-concentration effect) was a slope of approximately zero. A plot of the dQTcF values versus the time-matched plasma inclisiran concentrations was provided.

Similar analyses were repeated for HR, PR interval, and QRS interval; however, the 2-sided 95% CI rather than the 2-sided 90% CI was presented.

Safety:

Evaluation of safety was based on summaries of treatment-emergent AEs (TEAEs), clinical laboratory test results including changes from Baseline, vital sign measurements including changes from Baseline and percent changes from Baseline, and safety 12-lead ECG results and changes from Baseline.

All AEs, clinical laboratory test results including clinically significant values, vital sign measurements, safety 12-lead ECG data, and physical examination findings were presented in data listings.

Methodology:

Forty-eight subjects were randomly assigned to receive all 3 of the following treatments, administered in a crossover fashion, with the order randomly selected for each subject and a minimum 7-day washout period between doses:

- Inclisiran sodium supratherapeutic dose (900 mg [3 SC injections of 300 mg in 1.5 mL each]) and 1 placebo matched to moxifloxacin oral overencapsulated tablet
- Placebo solution matched to inclisiran (3 SC injections of 1.5 mL each) and 1 placebo matched to moxifloxacin oral overencapsulated tablet
- Moxifloxacin positive control (400 mg oral overencapsulated tablet) and placebo solution matched to inclisiran (3 SC injections of 1.5 mL each)

Subjects were screened up to 28 days before Day –1. Eligible subjects arrived at the clinical research unit (CRU) on Day –1 and underwent check-in procedures for confinement. Subjects still eligible for enrollment were randomly assigned to receive blinded study drug. Subjects were confined in the CRU from the day of Check-in (Day –1) until after all study procedures were completed on Day 19. Subjects returned to the CRU for the Day 30 end of study (EOS) visit. Subjects were followed during the observation period, with visits on Days 90 and 180, until LDL-C levels had returned to within 50% of the absolute reduction from Baseline or until Day 180, whichever occurred first.

Continuous ECG monitoring was performed for all subjects from at least 60 minutes before dosing through 48 hours (+30 minutes) after dosing on Days 1, 9, and 17. Three 12-lead ECGs were extracted from the continuous recordings (approximately 1 minute apart) and PK blood samples were collected from all subjects at the following time points: 60, 45, and 30 minutes before dosing and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after dosing. The ECG extractions were time matched to the PK samples. The continuous ECGs were read by core laboratory staff blinded to treatment, time, and study day identifiers. Blood samples were also collected to determine PCSK9 and LDL-C levels.

PHARMACODYNAMIC RESULTS:

The primary objective of this study was to assess the effect of a supratherapeutic dose of inclisiran on cardiac repolarization as assessed by QTcF. All ECG-related study objectives were met. The enrollment goal of 48 subjects was achieved with no dropouts through the treatment period. The inclisiran arithmetic mean C_{max} observed in the study (2888 ng/mL) was higher than the mean C_{max} observed in a previous study (ALN-PCSSC-001) at the therapeutic dose of 300 mg SC and about 1.6-fold higher than the mean C_{max} (1760 ng/mL) observed in subjects with severe renal impairment in the renal impairment study (ORION-7) at the same therapeutic dose level. At the maximum

individual inclisiran concentration observed in this study (8430 ng/mL), the model-predicted ddQTcF was 5.7 msec (90% CI 1.14, 10.27 msec). The Fridericia's formula corrected adequately for the HR effect on the QT interval. Adequate assay sensitivity was demonstrated by the moxifloxacin active control.

No clinically significant group changes in QTcF, HR, PR interval, and QRS interval were observed, and there were no categorical values or change values of concern, and no pattern of drug effect (except for the expected effect of moxifloxacin). Inclisiran appears to have no clinically or statistically significant effects on the ECG in humans at a supratherapeutic dose.

A secondary objective of this study was to evaluate the effect of inclisiran on PCSK9 and LDL-C. The mean percent change from Baseline in PCSK9 was approximately –70% to –80% from 8 days after the inclisiran dose through the last sample on Day 180. The mean percent change from Baseline in LDL-C was approximately –30% to –50% from 13 days after the inclisiran dose through the last sample on Day 180. The mean percent changes from Baseline in the PCSK9 and LDL-C values at 29 days after the inclisiran dose (ie, Day 30 for subjects with Sequences ABC and ACB) were –77.5% and –42.0%, respectively.

PHARMACOKINETIC RESULTS:

A secondary objective of this study was to evaluate the PK profile after a single dose of 900 mg inclisiran sodium. All 48 subjects received a dose of inclisiran and provided an adequate number of blood samples for the determination of plasma PK parameters.

Following the inclisiran dose, the geometric mean C_{max} of 2643 ng/mL (geometric CV%: 43.6%) occurred at a median T_{max} of 4.003 hours postdose (range: 0.507 hours to 12.0 hours). The geometric mean $AUC_{0\text{-}inf}$ was 39,110 h*ng/mL (geometric CV% 24.4%). The geometric mean $t_{1/2}$ estimate was 5.834 hours (geometric CV%: 28.8%).

SAFETY RESULTS:

A secondary objective of this study was to assess safety and tolerability in healthy subjects after a single supratherapeutic dose (3 SC injections) of 900 mg inclisiran sodium.

Overall, 15 of 48 subjects (31.3%) reported at least 1 TEAE, with a higher percentage of subjects reporting TEAEs after receiving moxifloxacin (14.6%) compared with inclisiran (10.4%) or placebo (6.3%). No TEAEs were reported by more than 2 subjects (4.2%). Injection site pain was reported by 1 subject (2.1%). One subject (2.1%) reported a TEAE of moderate severity (urticaria; moxifloxacin). All other TEAEs were mild in severity.

A total of 5 subjects (10.4%) reported 10 TEAEs that were considered by the investigator to have a reasonable possibility of being caused by study drug. A higher percentage of subjects reported related TEAEs after receiving moxifloxacin (8.3%, 9 events) compared with inclisiran (2.1%, 1 event) or placebo (0%).

There were no severe TEAEs, deaths, treatment-emergent SAEs, or TEAEs leading to study discontinuation.

There were no clinically meaningful changes in clinical laboratory values (including no samples confirmed positive for antidrug antibodies), vital sign measurements, or safety 12-lead ECG results.

CONCLUSIONS:

- Inclisiran had no clinically significant effect on the QT interval at a dose 3-fold higher than the clinical dose.
- Inclisiran also had no clinically significant effect on the other ECG intervals or diagnostic statements, including those related to ST- and T-wave morphology.
- Following a supratherapeutic dose (900 mg) of inclisiran sodium, PCSK9 and LDL-C levels were decreased; the mean percent changes from Baseline in the PCSK9 and LDL-C values at 29 days after the inclisiran dose (ie, Day 30 for subjects with Sequences ABC and ACB) were

–77.5% and –42.0%, respectively.

- Following a supratherapeutic dose (900 mg) of inclisiran sodium, the geometric mean C_{max} of 2643 ng/mL (geometric CV%: 43.6%) occurred at a median T_{max} of 4.003 hours postdose (range: 0.507 hours to 12.0 hours). The inclisiran arithmetic mean C_{max} was higher than the mean C_{max} of the clinical dose observed in a previous study. The geometric mean $AUC_{0\text{-}inf}$ was 39,110 h*ng/mL (geometric: CV% 24.4%). The geometric mean $t_{1/2}$ estimate was 5.834 hours (geometric CV%: 28.8%).
- A supratherapeutic dose (900 mg) of SC injections of inclisiran sodium was safe and well tolerated by the healthy adult subjects in this study.

Date of the report: 31 July 2019

Sponsor

Novartis

Novartis Study Code

MDCO-PCS-17-09 (orion12)

EudraCT Number

Not applicable

Swiss Authorization Date and Authorization number

Authorization Date: 09 September 2021

Authorization Number: 67836