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 placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C)		
Principal Investigator: Dr. Kausik Ray, MD, Imperial College London, Reynolds Building, St. Dunstan's Road, London, United Kingdom W6 8RP		
Study Center(s): 72 centers in 8 countries: Czech Republic (2 centers), Germany (5 centers), Hungary (4 centers), Netherlands (1 center), Poland (19 centers), South Africa (8 centers), Ukraine (9 centers), and United Kingdom (24 centers).		
Publications (Reference): None		
Studied Period (years): Date first subject enrolled (Randomized): 01 November 2017 Date last subject completed (last subject, last visit): 31 July 2019		**Phase of Development:** III

Objectives:

Primary Objective

To evaluate the effect of inclisiran treatment on:

- Low-density lipoprotein cholesterol (LDL-C) levels at Day 510
- Time adjusted percentage change in LDL-C levels from baseline after Day 90 and up to Day 540 levels

Secondary Objectives

To evaluate the effect of inclisiran on:

- Proprotein convertase subtilisin kexin type 9 (PCSK9), total cholesterol, apolipoprotein B (Apo-B) and non-high-density lipoprotein cholesterol (HDL-C) at Day 510
- LDL-C and PCSK9 levels over time to Day 540
- Mean maximum reduction in LDL-C levels
- LDL-C and PCSK9 levels over time in individual subjects
- Other lipids, lipoproteins, apolipoproteins
- Proportion of subjects achieving prespecified LDL-C targets
- Safety and tolerability profile of inclisiran

Exploratory Objectives

To collect/evaluate the effect of inclisiran on the following:

- Cardiovascular (CV) events such as CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic)

Study Design:

This was an international (non-US), multicenter, Phase III, placebo-controlled, double-blind, randomized study in 1617 subjects. The study was conducted within 72 centers in European countries and South Africa. Subjects with either atherosclerotic cardiovascular disease (ASCVD) (coronary heart disease [CHD], cerebrovascular disease [CVD] or peripheral arterial disease [PAD]) or ASCVD risk equivalents were included in this study. ASCVD risk equivalent is defined as those subjects with type 2 diabetes mellitus, familial hypercholesterolemia [FH], or 10-year risk of 20% or greater of having a CV event assessed by Framingham Risk Score or equivalent (target LDL-C of <100 mg/dL).

Subjects were randomized (1:1) to receive either inclisiran sodium 300 mg or placebo on top of a maximally tolerated dose of a statin (other lipid lowering treatments including ezetimibe were allowed). The study was 18 months in duration with subjects receiving four 300 mg doses of inclisiran sodium (or placebo) on Day 1, Day 90, Day 270, and Day 450.

Number of Subjects (Planned and Analyzed):

Planned: 1500 (at least 1425 evaluable) subjects

Analyzed (ITT Population): 1617 subjects

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

For inclusion into the trial, patients were required to fulfill all of the following criteria:

1. Male or female subjects ≥18 years of age.
2. History of ASCVD (CHD, CVD or PAD) or ASCVD-risk equivalents (type 2 diabetes, familial hypercholesterolemia, and including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <100 mg/dL).
3. Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) for ASCVD subjects or ≥2.6 mmol/L (≥100 mg/dL) for ASCVD-risk equivalent subjects at screening.
4. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
5. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized clinical methodology.
6. Subjects on statins should have been receiving a maximally tolerated dose. Maximum tolerated dose was defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin was documented as historical adverse events (AEs) attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF).
7. Subjects not receiving statin must have had documented evidence of intolerance to all doses of at least two different statins.
8. Subjects on lipid-lower therapies (such as a statin and/or ezetimibe) should have been on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation.
9. Subjects were willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

Exclusion Criteria:

Patients meeting any of the following criteria were excluded from the study:

1. Any uncontrolled or serious disease, or any medical or surgical condition, that could either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate] judgment) if he/she participated in the clinical study.

2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) may have interfered with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%.
4. Cardiac arrhythmia within 3 months prior to randomization that was not controlled by medication or via ablation.
5. Major adverse cardiovascular event within 3 months prior to randomization.
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
7. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.
8. Severe concomitant noncardiovascular disease that carried the risk of reducing life expectancy to less than 2 years.
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
10. Females who were pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of highly effective contraception (failure rate less than 1% per year) (eg combined oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion:
    a. Women >2 years postmenopausal (defined as 1 year or longer since last menstrual period) AND more than 55 years of age.
    b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomization.
    c. Women who were surgically sterilized at least 3 months prior to enrollment.
11. Males who were unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
12. Known history of alcohol and/or drug abuse within the last 5 years.
13. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever was longer.
14. Planned use of other investigational products or devices during the course of the study.
15. Any condition that according to the investigator could have interfered with the conduct of the study, such as but not limited to:
    a. Subjects who were unable to communicate or to cooperate with the investigator.
    b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
    c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
    d. Had any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.

e. Persons directly involved in the conduct of the study.

16. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

Subjects excluded for any of the above reasons could not be re-screened for participation at any time even if the exclusion characteristic had changed.

Test Product, Dose and Mode of Administration, Batch Number:

Inclisiran Injection (SC) filled in 2 mL glass vials with a fill volume of no less than 1.55 mL, to ensure extraction of 1.5 mL. The container closure system consisted of a Type I glass vial, a Teflon-faced 13 mm stopper, and a flip-off aluminum seal. Two lots were used for this study: Lot B170152 (retest date of 30 Sep 2019) and Lot B170356 (retest date of 28 Jan 2020).

Duration of Treatment:

One SC injection on Day 1, Day 90, Day 270, and Day 450.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo was administered as an SC injection of sterile normal saline 0.9%. The placebo vials were filled to the same volume and packaged in the same container closure system as inclisiran. Two lots were used for this study: Lot B170153 (retest date of 25 Sep 2019) and Lot B170498 (retest date of 27 Mar 2020).

Criteria for Evaluation:

***Efficacy*:**

Primary Endpoint(s):

- Percentage change in LDL-C from baseline to Day 510.
- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This was the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

  Note: The time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 analysis reflected LDL-C effect at a steady state. As such, this analysis assessed the effect on LDL-C levels seen with a more chronic dosing regimen. The Day 90 dose was the start of the 6 monthly dosing regimen.

Secondary Endpoint(s):

The key secondary endpoints of this study were:

- Absolute change in LDL-C from baseline to Day 510.
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540.
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C.

The other secondary endpoints of this study were:

- Maximum percentage change in LDL-C. This was calculated by finding the smallest LDL-C value across all post baseline visits for each individual subject. This value was used to compare against each subject's baseline value and calculate the percentage change from baseline to the lowest LDL-C value.
- Absolute change from baseline to Day 510 in PCSK9, total cholesterol, ApoB and non-HDL-C.
- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540.
- Individual responsiveness defined as the number of subjects reaching on treatment LDL C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510.

- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline.
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540.
- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk.

Exploratory Endpoint(s):

- Incidence of CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), and stroke (ischemic and hemorrhagic)
- Proportion of subjects in each group with any LDL-C reduction from baseline at any visit (responders).

***Safety*:**

The safety objectives of this study were to evaluate the safety and tolerability profile of inclisiran as measured by AEs, serious adverse event (SAEs), vital signs, clinical laboratory values, electrocardiogram (ECG) measurements and formation of anti-drug antibodies (ADA) and subsequent characterization of ADA.

Statistical Methods:

Sample Size: The sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C would be no less than 30 mg/dL, with a standard deviation of 20 mg/dL.

Assuming about a 5% drop out rate, the sample size would be approximately 1425 subjects that were evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 1425 evaluable subjects, would provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025. This sample size would also contribute additional sufficient safety data.

Analysis of Primary Efficacy Endpoints: The family-wise type I error rate was controlled at a two-sided significance level of alpha=0.05 by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 was tested first. If the null hypothesis was rejected at a two-sided significance level of alpha=0.05 and superiority of inclisiran over placebo was claimed, then the time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 was tested, also at a two-sided significance level of alpha=0.05.

Percentage change in LDL-C from baseline to Day 510

Missing values were imputed for LDL-C after a reflexive approach using the multiple imputation (100 total imputed datasets) washout model. The primary analysis was conducted on the intent-to-treat (ITT) population and based on an ANCOVA model on the percentage change in LDL-C from baseline to Day 510 on each multiply imputed dataset. The model included fixed effects of treatment group and current use of statins or other lipid-modifying (LMT) therapies at baseline (yes or no) and baseline LDL-C as a covariate.

Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

A control-based pattern-mixture model (PMM) was utilized to explore the possibility of data missing not at random (MNAR) for subjects who discontinued the study. The primary analysis was conducted on the ITT population and based on a mixed-effects model for repeated measurements (MMRM) on the percentage change in LDL-C from baseline over all visits on each multiply imputed dataset (100 total). The model included fixed effects for treatment, visit, baseline value, interaction between treatment and

visit, and current use of statins or other LMT. Linear combinations of the estimated means after Day 90 and up to Day 540 were used to compare treatment effects.

STUDY SUBJECTS:

A total of 2381 subjects were screened and 1617 were randomized and included in the ITT Population. Of the 1617 subjects randomized, 1615 subjects were treated (805 with placebo and 810 with inclisiran) and included in the Safety Population. At Day 510, 1561 (96.5%) were in the study; 96.5% (779/807) of placebo-treated subjects and 96.5% (782/810) of inclisiran-treated subjects. Similarly, most subjects (1542, 95.4%) completed the study (ie, had a Day 540 EOS Visit); 95.4% (770/807) of placebo-treated subjects and 95.3% (772/810) of inclisiran-treated subjects.

Overall, 71.7% (1160/1617) of subjects were male, mean age was 65 years old, and 98.1% (1587/1617) were White. In addition, 71.1% (1150/1617) had renal impairment. Cardiovascular risk factors were balanced between the treatment groups. 87.4% (1414/1617) had ASCVD and 12.6% (203/1617) were ASCVD risk equivalent. Overall, 35.1% (568/1617) of all subjects had diabetes and 80.5% (1301/1617) had hypertension. Of those subjects with ASCVD, 87.5% (1237/1414) had CHD, 16.5% (233/1414) had CVD, and 10.4% (147/1414) had PAD (note: a subject could have been in more than one category). Of those subjects who were ASCVD risk equivalent, 56.2% (114/203) had a risk score of more than 20% for 10 year risk of a cardiovascular event, 5.4% (11/203) were HeFH, and 65.0% (132/203) had diabetes.

At randomization, (Day 1) LMT usage was balanced between the treatment groups. Overall, 96.8% (1565/1617) of subjects received LMT, 94.7% (1532/1617) of subjects received statin therapy and 11.8% (191/1617) received other LMT. A total of 78.0% (1261/1617) of subjects received a high intensity statin, 15.5% (251/1617) of subjects received a moderate intensity, and 0.4% (6/1617) subjects received a low intensity statin at baseline. A total of 7.1% (114/1617) subjects were treated with ezetimibe.

EFFICACY RESULTS:

Primary Endpoint: Percentage Change in LDL-C from Baseline to Day 510

The placebo-adjusted percentage change in LDL-C from baseline to Day 510 using observed values was -53.5% (p<0.0001). The primary analysis used a prespecified washout model to account for missing data. The placebo-adjusted percentage change in LDL-C from baseline to Day 510 was -47.8% (p<0.0001). In addition, using the modified washout model, the placebo-adjusted percentage change in LDL-C from baseline to Day 510 was -49.9% (p<0.0001). We believe this modified washout model is the most appropriate method for imputation of missing data as it provides the best estimate of what the values of missing data points would have been, had they been measured.

Primary Endpoint: Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540

Compared to placebo the time-adjusted percentage change from baseline after Day 90 and up to Day 540 was -49.2% (p<0.0001; Synopsis Table 1).

Synopsis Table 1. Co-Primary Efficacy Endpoint: Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 – ITT Population

	Placebo (N=807)	Inclisiran (N=810)	p-value
Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540*			
LS Mean (95% CI)	3.35 (1.65,5.05)	-45.82 (-47.52,-44.13)	
LS Mean Difference (95% CI) from Placebo		-49.17 (-51.57,-46.77)	<.0001

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

Key Secondary Efficacy Endpoints

Endpoint	Results
Absolute Change in LDL-C from Baseline to Day 510	The placebo-adjusted absolute change in LDL-C levels from baseline to Day 510 was -51.9 mg/dL (p<0.0001).
Time-adjusted Absolute Change in LDL-C from Baseline after Day 90 and up to Day 540	Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -48.9 mg/dL (p<0.0001).
Percentage Change in PCSK9 from Baseline to Day 510	The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -79.3% (p<0.0001).
Percentage Change in Total Cholesterol from Baseline to Day 510	The placebo-adjusted percentage change in total cholesterol from baseline to Day 510 was -29.8% (p<0.0001).
Percentage Change in Apo-B from Baseline to Day 510	The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -38.9% (p<0.0001).
Percentage Change in Non-HDL-C from Baseline to Day 510	The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -43.3% (p<0.0001).

Other Secondary Efficacy Endpoints

Endpoint	Results
Absolute Change and Percentage Change in LDL-C from Baseline to Each Assessment Time up to Day 540	The placebo-adjusted absolute change in LDL-C from baseline up to Day 540 was between -41.8 mg/dL and -54.5 mg/dL up to Day 540 ($p<0.0001$ for all timepoints). The placebo-adjusted percentage change in LDL-C from baseline up to Day 540 was between -42.5% and -54.2% up to Day 540 ($p<0.0001$ for all timepoints).
Absolute Change in PCSK9, Total Cholesterol, Apo-B and Non-HDL-C from Baseline to Day 510	The placebo-adjusted change in PCSK9, Total Cholesterol, Apo-B and Non-HDL-C from baseline to Day 510 were all statistically significant ($p<0.0001$).
Individual Responsiveness Defined as the Number of Subjects Reaching on treatment LDL-C Levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510	At Day 510, 52.7% (425/807) of placebo-treated subjects reached an LDL-C level of <100 mg/dL compared to 81.6% (661/810) of inclisiran-treated subjects. In addition, 12.9% (104/807) of placebo-treated subjects reached an LDL-C level of <70 mg/dL compared to 69.6% (564/810) of inclisiran-treated subjects. Importantly, more than 50% of inclisiran-treated subjects and more than 10% inclisiran-treated subjects reached LDL-C levels of <50 mg/dL and <25 mg/dL, respectively.
Proportion of Subjects in Each Group with Greater or Equal to 50% LDL-C Reduction from Baseline	At any time during the study, 5.9% (47/800) placebo-treated subjects had ≥50% LDL-C reduction from baseline compared to 81.9% (658/803) of inclisiran-treated subjects.
Mean Maximum Percentage Change in LDL-C	The placebo-adjusted mean maximum (based on individual subject's maximum reduction) percentage change in LDL-C from baseline was -68.7% ($p<0.0001$).

Exploratory Efficacy Endpoints

Endpoint	Results
Incidence of CV Death, Resuscitated Cardiac Arrest, Non-Fatal MI, and Stroke (Ischemic and Hemorrhagic)	The incidence of MACE was 10.3% (83/804) in placebo-treated subjects compared to 7.8% (63/811) in inclisiran-treated subjects.
Proportion of subjects in each group with any LDL-C reduction from baseline at any visit (responders)	During the study, 86.4% (691/800) of placebo-treated subjects and 99.4% (797/802) of inclisiran-treated subjects had a reduction in LDL-C at any timepoint.

SAFETY RESULTS:

Adverse Events

Except for adverse events at the injection site, no difference was observed between the inclisiran group and the placebo group for individual AE PTs and AEs were consistent with the subject population and the past medical history of the subjects. A total of 81.5% (655/804) placebo-treated subjects and 82.7% (671/811) inclisiran-treated subjects experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs (at least 5% in either treatment group) were diabetes mellitus, nasopharyngitis, hypertension, upper respiratory tract infection, arthralgia, and osteoarthritis.

Deaths

The incidence of death was 1.9% (15/804) in placebo-treated subjects and 1.7% (14/811) in inclisiran-treated subjects. The most common cause of death was within the cardiac disorders system organ class.

Other Serious Adverse Events

The incidence of TESAEs was 22.5% (181/804) in placebo-treated subjects and 22.3% (181/811) in inclisiran-treated subjects. There was no difference in the frequency or nature of treatment-emergent serious adverse events (TESAEs) between the treatment groups. Treatment-emergent SAEs were predominantly CV events and about one-half of TESAEs in both groups were considered severe. The incidence of TEAEs leading to withdrawal was 2.2% (18/804) in placebo-treated subjects and 2.8% (23/811) in inclisiran-treated subjects. There was no difference in the frequency or nature of TEAEs leading to discontinuation of study drug between the treatment groups. Two inclisiran-treated subjects withdrew from study drug due to AEs at the injection site.

Adverse Events at the Injection Site

Fewer placebo-treated subjects (1.7%; 14/804) reported TEAEs at the injection site than did inclisiran-treated subjects (7.6%; 62/811). The time to first TEAE at the injection site was usually observed more than 12 hours after the time of injection. Overall, the incidence of TEAEs at the injection site was low, resolved without sequelae, and all were mild or moderate in severity.

Anti-drug Antibodies

The anti-inclisiran antibody analysis was performed on 4054 samples collected from 811 inclisiran treated subjects. At Day 1 prior to dosing, 15 samples, collected from 15 subjects, were confirmed positive for antibodies cross-reacting with the drug. The prevalence of pre-existing antibodies to inclisiran was 1.9% (15/808).

Out of the 609 post-dose study samples, from 191 subjects, which screened potentially positive, 87 samples from 39 subjects were confirmed positive. Of these, 20 samples were collected on V2 Day 30, 8 samples on V3 Day 90, 10 samples on V4 Day 150, 10 samples on V5 Day 270, 13 samples on V6 Day 330, 11 samples on V7 Day 450 and 15 samples on V8 Day 510.

Other Special Safety Topics

Other specific safety topics included: hepatic safety, renal safety, diabetes, hypersensitivity, neurologic events and neurocognitive disorders, and ophthalmological events, myopathy, inflammatory markers, hematology and coagulation. No differences from placebo were observed with inclisiran based on assessments of AEs and laboratory evaluations (when applicable) for these other specific safety topics.

OVERALL CONCLUSIONS:

The ORION-11 study is one of three Phase III LDL-C lowering trials supporting the initial marketing application for inclisiran. The results of this study confirm that inclisiran sodium 300 mg SC administered on Day 1, Day 90, and every 6 months is safe, well tolerated and exhibits potent and durable reductions in LDL-C levels over the 18 month study duration in subjects with ASCVD and ASCVD risk equivalents.

The efficacy and safety data of this study support a positive benefit-risk profile for inclisiran for subjects with ASCVD and those who are ASCVD risk equivalent being treated with maximally tolerated statin therapy yet still requiring additional LDL-C reduction.

Date of the Report: 20 November 2019

Sponsor

Novartis

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