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**		
Name of Active Ingredient: **Inclisiran sodium (ALN-PCSSC)**		

Title of Study: A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of Inclisiran ALN-PCSSC given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C

Principal Investigator: Kausik K Ray, MD, Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, United Kingdom

Study Centers: 12 centers in Canada, 6 centers in Germany, 14 centers in the Netherlands, 14 centers in the United Kingdom, and 8 centers in the United States

Publications (Reference): Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 17 March, 2017. DOI: 10.1056/NEJMoa1615758.

Studied Period (years):	**Phase of Development:**
Date first subject enrolled (randomized): 21 January 2016 Date last subject completed Day 210 End of Study Visit: 6 January 2017	II

Objectives:

Primary Objective

To evaluate the effect of inclisiran treatment on LDL-C levels at Day 180.

Secondary Objectives

To evaluate the effect of inclisiran on the following:

- LDL-C levels at Day 90
- LDL-C levels at other time points
- PCSK9 levels over time
- Other lipids, lipoproteins, apolipoproteins
- Proportion of subjects achieving prespecified global lipid guidelines
- Individual responsiveness to different doses
- Duration of lipid-lowering effect of different doses
- Safety and tolerability profile of inclisiran

Exploratory Objectives

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

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

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**		
Name of Active Ingredient: **Inclisiran sodium (ALN-PCSSC)**		

- Evaluation of anti-drug antibodies (ADA) for the investigational product

Study Design:

Placebo-controlled, double-blind, randomized, multi-national, multi-center study in subjects with ASCVD or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of inclisiran injection(s).

Treatment allocation was stratified by country and by concurrent use of statins or other lipid-modifying therapies at randomization.

Single Dose (one or two injections on Day 1): placebo for 200 mg; 200 mg inclisiran; placebo for 300 mg; 300 mg inclisiran; placebo for 500 mg; 500 mg inclisiran [two injections, 200 mg plus 300 mg to achieve 500 mg dose].

Double Dose (one injection on Day 1 and one injection on Day 90): placebo for 100 mg; 100 mg inclisiran; placebo for 200 mg; 200 mg inclisiran; placebo for 300 mg; 300 mg inclisiran.

After first study drug administration, the subject was observed in the clinic for at least 4 hours post injection and was then discharged. Subjects returned on Day 14 and Day 30 and then at monthly intervals for 6 months. Once subjects' LDL-C levels return to baseline levels and they complete the study to Day 210, subjects will be given the opportunity to enroll in a separate long-term extension study in order to collect long-term efficacy and safety data.

An independent Data Monitoring Committee (DMC) reviewed safety data beginning after the first 40 subjects had received the first dose of inclisiran or placebo and completed the Day 14 follow-up visit. Thereafter, the DMC reviewed safety data every 2 months until the end of the trial. A recommendation could be taken to stop the study at any of these reviews.

Any subjects in whom LDL-C levels had not returned to >80% of baseline values by Day 210 continued to be followed on a monthly visit schedule in this study until either this level had been reached or until a maximum of Day 360 at which point they will be given the opportunity to enroll in the long-term extension study. At each visit, LDL-C levels, AEs, SAEs, concomitant medications, and safety laboratory assessments were collected.

The data presented in this clinical study report include the Day 180 primary analysis and all data through the Day 210 End of Study Visit. Data from the additional follow up period (Day 210 through Day 360) for those subjects that require additional follow up will be presented in an addendum to this clinical study report.

Number of Subjects (Planned and Analyzed):

Planned: 480 subjects
60 subjects per each of six inclisiran dose groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six dose groups)

Analyzed: 501 subjects
Single Dose Groups: placebo (single dose placebo groups pooled), 65 subjects; 200 mg inclisiran, 60 subjects; 300 mg inclisiran 62 subjects; 500 mg inclisiran, 66 subjects

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**		
Name of Active Ingredient: **Inclisiran sodium (ALN-PCSSC)**		

Double Dose Groups: placebo (double dose placebo groups pooled), 62 subjects; 100 mg inclisiran, 62 subjects; 200 mg inclisiran 63 subjects; 300 mg inclisiran, 61 subjects

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

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

1. Male or female subjects ≥18 years of age.
2. History of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia, including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent had 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 local clinical methodology.
6. Subjects on statins should have been receiving a maximally tolerated dose (investigator's discretion).
7. Subjects on lipid-lowering therapies (such as 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.
8. Willing and able to give written and informed consent before initiation of any study related procedures and willing to comply with all required study procedures.

Exclusion Criteria

Subjects meeting any of the following criteria immediately prior to randomization 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) could interfere with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class II, III or IV heart failure or last known left ventricular ejection fraction <30%.
4. Cardiac arrhythmia within 3 months prior to randomization that was not controlled by medication or via ablation.
5. Any history of hemorrhagic stroke.
6. Major adverse cardiac event within 6 months prior to randomization.
7. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti hypertensive therapy.

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

8. Poorly controlled Type 2 diabetes, ie, glycated hemoglobin A1c (HbA1c) >10.0% prior to randomization.
9. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained ALT, aspartate aminotransferase (AST), elevation >2x ULN or total bilirubin elevation >1.5x ULN at screening confirmed by a repeat measurement at least 1 week apart.
10. Serious comorbid disease in which the life expectancy of the subject was shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses). This included all cancers with the exception of treated basal-cell carcinoma occurring >5 years before screening.
11. Females who were pregnant or nursing, or who were of childbearing potential and unwilling to use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device or tubal litigation) . Women who were >2 years postmenopausal defined as ≥1 year since last menstrual period AND if <55 years old with a negative pregnancy test within 24 hours of randomization or surgically sterile were exempt from this exclusion.
12. Males who were unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
13. Known history of alcohol and/or drug abuse within the last 5 years.
14. Treatment with other investigational medicinal products or devices within 30 days or five half-lives, whichever was longer.
15. Use of other investigational medicinal products or devices during the course of the study.
16. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    a. Inappropriate for this study, including 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 was 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. Involved with, or a relative of, someone directly involved in the conduct of the study.
    f. Any known cognitive impairment (eg, Alzheimer's disease).
17. Previous or current 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 if

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

the exclusion characteristic had changed.

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

Inclisiran Solution for Injection (subcutaneous [SC] use): 100 mg vial (200 mg/mL)

Lot B140356 (expiry date 18 September 2016)

Single Dose: 200 mg, 300 mg, 500 mg
One or two SC injections on Day 1 (two injections, 200 mg plus 300 mg, to achieve the 500 mg dose)

Double Dose: 100 mg, 200 mg, 300 mg
One SC injection on Day 1 and one SC injection on Day 90

Duration of Treatment:

Single Dose: Day 1

Double Dose: Day 1 and Day 90

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

Placebo: sterile normal saline 0.9% for SC injection

Placebo was administered as an SC injection in an amount matched to the doses within each injection regimen

Criteria for Evaluation:

Efficacy:

Subjects were in a fasted state for all efficacy laboratory assessments. Parameters assessed included: total cholesterol (TC), triglycerides, LDL-C, 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)), high sensitivity C-reactive protein (hsCRP), and PCSK9.

The primary efficacy endpoint was the percentage change in LDL-C from baseline to Day 180.

In addition, this study assessed:

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 104, 120, 150, and 210
- Proportion of subjects in each group with LDL-C greater than 80% of the baseline value at Day 180 and Day 210
- Duration of time on treatment for subjects to return to 80% of baseline or greater LDL-C or PCSK9 protein
- 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 Days 90, 120, and 180
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at Days 90, 120, and 180

Secondary efficacy assessments included the measure of the effects of inclisiran on levels of lipids and lipoproteins including TC, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, Lp(a),

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

hsCRP, and PCSK9.

- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, 180, and 210
- Percentage change in other lipids, and apolipoproteins from baseline at each subsequent visit to Day 210
- Proportion of subjects in each group who attained global lipid modification targets for their level of ASCVD risk

Safety:

The safety objectives of this study were to evaluate the safety and tolerability profile of inclisiran. Safety assessments included adverse events, serious adverse events, adverse events of special interest (AESI), clinical laboratory assessments (hematology, coagulation, biochemistry, urinalysis), vital signs, and electrocardiograms.

In this study, injection site reactions including individual signs or symptoms at the injection site reported following study drug administration were collected as an AESI.

Potential formation of anti-drug antibodies was also evaluated.

Statistical Methods:

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

Assuming about a 15% drop out rate, the sample size was planned to be approximately 100 evaluable subjects total across the placebo groups and approximately 50 subjects in each of six inclisiran groups. This sample size of at least 400 evaluable subjects was expected to provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one inclisiran dose group.

Analysis of Primary Efficacy Endpoint: The primary endpoint of this trial was percentage change in LDL-C from baseline to Day 180. Two sample t tests were performed to test the superiority of any dosing group over placebo. A Dunnet multiple t test procedure was applied to adjust for multiple comparisons with six different dosing regimens.

Interim Analysis: An interim analysis of lipids and PCSK9, unblinded by dose cohort only, was prepared upon completion of Day 90 by the Statistical Reporting Organization. The interim analysis was performed for all subjects completing Day 90 and these data were used to help select the inclisiran dose for subsequent clinical trials.

EFFICACY RESULTS:

Change in LDL-C from Baseline

At baseline, and as per the inclusion criteria for the study, clinically significant elevated baseline levels of LDL-C were reported in all subjects, with a mean LDL-C of greater than 120 mg/dL in all groups. Following administration of inclisiran on Day 1, mean LDL-C was reduced by at least 34 mg/dL (27%) by Day 14 and at least this level of reduction was maintained through Day 210 in all inclisiran dose

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

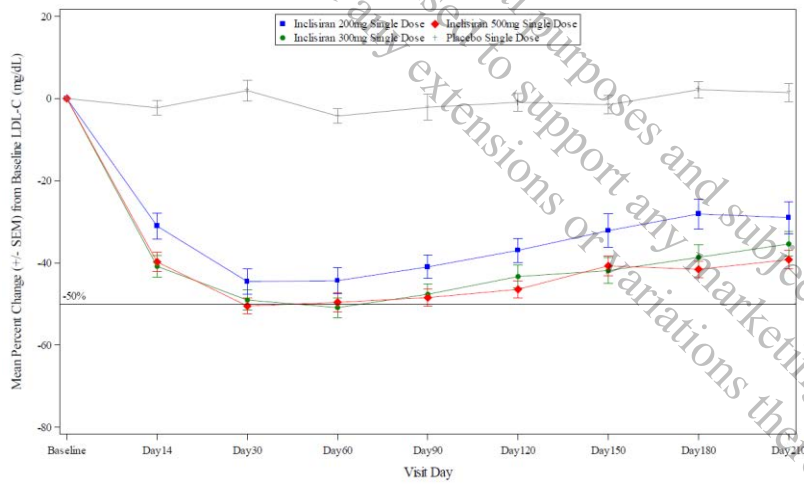
groups. LDL-C levels were unaffected in the placebo group through Day 210.

Single Dose Groups: The response showed dose dependency between single doses of 200 mg and 300 mg, with no additional effect at a single dose of 500 mg. The maximum mean LDL C reduction of 50.9% was observed at Day 60, following administration of a single dose of 300 mg inclisiran on Day 1.

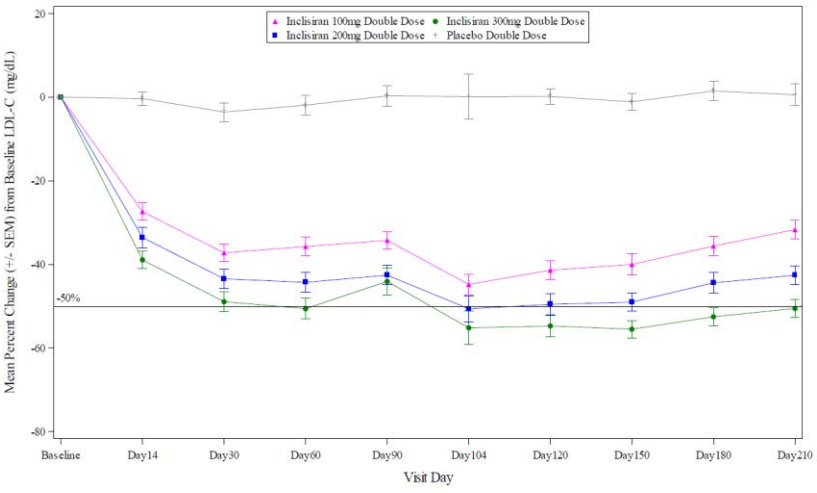
Double Dose Groups: Maximal LDL-C reduction was observed after the second dose at Day 90. The response showed dose dependency across the dose range studied (double doses of 100 mg, 200 mg and 300 mg). The highest dose of 300 mg administered on Day 1 and Day 90 resulted in a maximum mean LDL C reduction of 55.5% at Day 150.

Percent Change from Baseline Beta-Quantification LDL-C by Dose Group over Time – mITT Population

Single Dose Groups



Double Dose Groups



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

Primary Efficacy Endpoint: Percentage Change in LDL-C from Baseline to Day 180 (mITT Population)

Single Dose Groups: The least squares LS mean LDL-C reduction was 27.9%, 38.4% and 41.9% following a single dose of 200 mg, 300 mg and 500 mg inclisiran, respectively, compared to a 2.1% increase in the placebo group (all p<0.0001); mITT Population. The response showed dose dependency between single doses of 200 mg and 300 mg, with no additional effect at a single dose of 500 mg.

Double Dose Groups: The LS mean LDL-C reduction was 35.5%, 44.9% and 52.6% following a double dose of 100 mg, 200 mg and 300 mg inclisiran, respectively, compared to a 1.8% increase in the placebo group (all p<0.0001) for the mITT Population. The response showed dose dependency across the dose range studied (double doses of 100 mg, 200 mg and 300 mg).

As expected, the responses were greater in the double inclisiran dose groups compared to the single inclisiran dose groups with an additional reduction beyond that achieved at Day 60 from a second dose of inclisiran at Day 90. The greatest reduction in LDL-C levels at Day 180 (52.6%) was observed in association with the 300 mg dose of inclisiran administered on Day 1, followed by a second dose on Day 90. In the inclisiran 300 mg double dose group, every subject had a reduction in LDL-C level, with a mean reduction of 64.2 mg/dL at Day 180.

Category	Placebo – Single Dose N=64	Inclisiran – Single Dose			Placebo – Double Dose N=61	Inclisiran – Double Dose		
		200 mg N=60	300 mg N=60	500 mg N=60		100 mg N=59	200 mg N=60	300 mg N=59
Subjects with baseline and Day 180 assessment	64	60	60	60	61	59	60	59
Mean ± SD percent change at Day 180	2.1 ± 15.92	-28.1 ± 27.88	-38.6 ± 23.16	-41.5 ± 15.65	1.5 ± 17.80	-35.6 ± 17.70	-44.4 ± 19.11	-52.5 ± 16.36
LS mean (95% CI) percent change at Day 180	2.1 (-2.9, 7.2)	-27.9 (-33.1, -22.7)	-38.4 (-43.6, -33.2)	-41.9 (-47.2, -36.7)	1.8 (-2.6, 6.3)	-35.5 (-40.0, -31.0)	-44.9 (-49.3, -40.4)	-52.6 (-57.1, -48.1)
Difference (95% CI) from Placebo LS mean percent change at Day 180	-	-30.1 (-38.8, -21.3)	-40.5 (-49.3, -31.8)	-44.1 (-52.8, -35.3)	-	-37.3 (-44.9, -29.7)	-46.7 (-54.3, -39.1)	-54.5 (-62.1, -46.8)
Dunnett-adjusted p value	-	<0.0001	<0.0001	<0.0001	-	<0.0001	<0.0001	<0.0001

Secondary Efficacy Endpoints Based on Changes in LDL-C

Responses were dose dependent between single doses of 200 mg and 300 mg, with no apparent increase in response at a single dose of 500 mg. Responses were dose dependent between double doses of 100 mg and 300 mg. Responses were greater in the double dose groups compared to the single dose groups.

Overall, and considering the low numbers of subjects in certain risk groups, the proportion of subjects

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

achieving LDL-C <70 mg/dL appeared to be independent of baseline cardiovascular risk group suggesting the effect of inclisiran on LDL-C is independent of subject phenotype.

Secondary Efficacy Endpoint: Percentage Change in PCSK9 Levels from Baseline

Following administration of inclisiran, mean PCKS9 was reduced through Day 210 in all inclisiran dose groups and unaffected in the placebo group through Day 210.

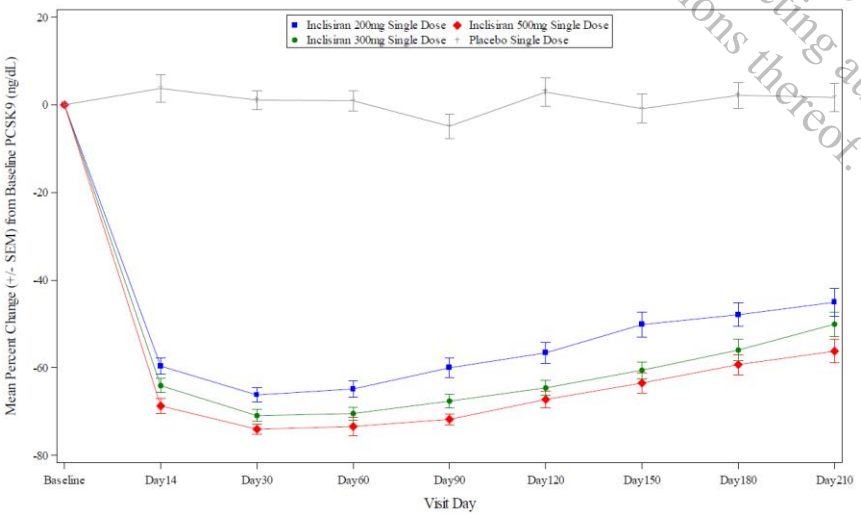
Single Dose Groups: The maximal PCSK9 reduction was observed at Day 30 (reductions of 66.2%, 70.9% and 74.0% at doses of 200 mg, 300 mg and 500 mg, respectively). PCSK9 levels were reduced through Day 210 (reductions of 45.1%, 50.1% and 56.2% at doses of 200 mg, 300 mg and 500 mg, respectively).The response showed dose dependency between single doses of 200 mg and 300 mg, with no additional effect at a single dose of 500 mg.

Double Dose Groups: The maximal PCSK9 reduction was observed at Day 120 (reductions of 60.4%, 73.0% and 74.5% at doses of 100 mg, 200 mg and 300 mg, respectively). PCSK9 levels were reduced through Day 210 (reductions of 47.0%, 63.1% and 64.6% at doses of 100 mg, 200 mg, and 300 mg, respectively). The response showed dose dependency between double doses of 100 mg and 200 mg, with little additional effect at a double dose of 300 mg.

As expected the responses were more sustained over time in the double dose groups with a greater reduction from baseline following the second dose than was achieved with the first dose for all dose groups.

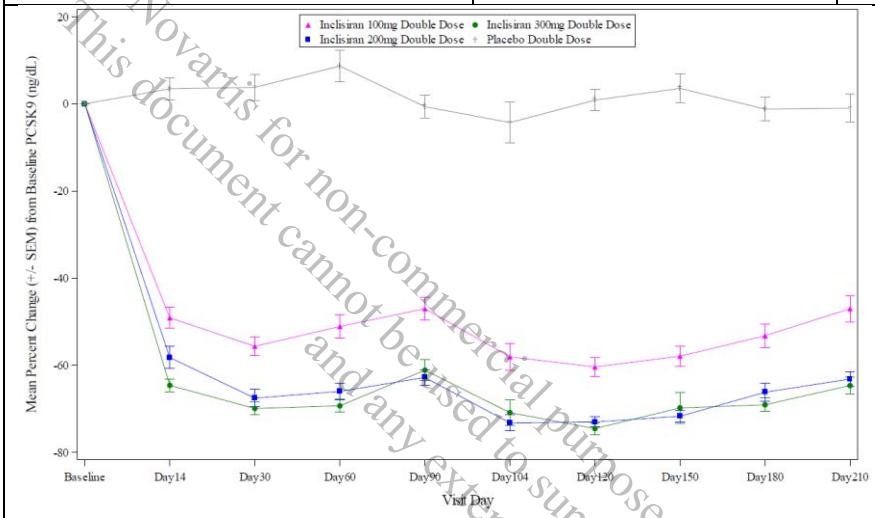
Percent Change from Baseline PCSK9 by Dose Group over Time – mITT Population

Single Dose Groups



Double Dose Groups

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



Secondary Efficacy Endpoint: Percentage Change in Other Lipids, Apolipoproteins and Inflammatory Markers from Baseline

As expected given the mode of action of the drug and the effects on PCSK9 and LDL-C, TC, non-HDL-C and ApoB were significantly reduced in all inclisiran treatment groups compared to placebo ($p < 0.0001$). The response showed dose dependency between single doses of 200 mg and 300 mg, with no additional effect at a single dose of 500 mg, and over the double dose range studied (100 mg to 300 mg).

There were no consistent dose-dependent effects of inclisiran on HDL-C, triglycerides, VLDL-C, ApoA1, Lp(a), and hsCRP.

Subgroup Analyses of Efficacy

No subgroup analyses of efficacy were planned; however, post hoc analyses were performed to evaluate the effect of inclisiran on LDL-C and on PCSKS9 by use of statins and by baseline renal function (GFR).

Although the number of subjects not on statins was small, in general, similar reductions in percent change from baseline LDL-C and PCKS9 were noted regardless of statin use across all inclisiran single and double dose groups.

Baseline GFR was selected for analysis to investigate the effect of renal function in the absence of a renal impairment study. In general, similar reductions in percent change from baseline LDL-C and PCKS9 were noted regardless of baseline renal function (GFR).

SAFETY RESULTS:

Inclisiran was well tolerated from baseline to Day 210. The incidence of SAEs and AEs was similar between placebo and inclisiran, with no clear dose-related response. There was no clear effect of inclisiran on the frequency of severe or treatment-related AEs or SAEs; however, the number of subjects experiencing these events was low. There were no differences in safety profile between the single dose and double dose groups.

Two subjects died in the study. There was one death in the 500 mg inclisiran group due to myocardial

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		
Name of Active Ingredient: Inclisiran sodium (ALN-PCSSC)		

infarction. One subject in the 200 mg inclisiran double dose group died due to device-related infection. Neither death was considered related to study drug by the investigators.

No subject withdrew from treatment due to an AE in the single dose groups. In the double dose groups, one subject in the placebo group and one subject in the inclisiran 100 mg group withdrew due to an AE.

No clear difference or dose relationship was observed between inclisiran groups and placebo for individual AE preferred terms. In both the single and double dose inclisiran groups, no AE was reported with an incidence of more than 10%.

In the inclisiran single dose groups combined the most common adverse events in decreasing order of incidence for inclisiran and placebo, respectively, were nasopharyngitis (8.6% and 6.2%, respectively), myalgia (5.4% and 4.6%), back pain (4.8% and 7.7%), cough (4.8% and 3.1%), arthralgia (3.8% and 3.1%), fatigue (3.8% and 4.6%, respectively), and headache (3.2% and 9.2%).

In the inclisiran double dose groups combined the most common adverse events in decreasing order of incidence for inclisiran and placebo, respectively, were myalgia (9.2% and 4.8%), headache (6.0% and 6.5%), diarrhea (6% and 3.2%), nasopharyngitis (5.4% and 12.9%) arthralgia (4.3% and 1.6%), and back pain (3.8% and 3.2%), osteoarthritis (3.8% and 1.6%, respectively), and dizziness (3.8% and 6.5%, respectively).

The AE profile through Day 210 was comparable in the single dose and double dose groups. The AE and SAE profile after Day 90 was similar to that before Day 90 for both single and double dose groups, and there were no apparent differences between the single and double dose groups after Day 90. No new AEs or SAEs were identified after Day 90 compared to before Day 90

The majority of AEs were reported as single cases, and all SAEs were reported as single cases, except for MI which occurred in two subjects in the 500 mg inclisiran single dose group and acute MI which occurred in two subjects in the 300 mg inclisiran double dose group.

In this study, injection site reactions including individual signs or symptoms at the injection site reported following study drug administration were collected as an AESI. Events at the injection site were reported after the first and second dose, with no clear difference or dose relationship between inclisiran groups through Day 90 after a single dose or after Day 90 through Day 210 following a second dose. No AESIs were reported for the single dose groups (single dose on Day 1) after Day 90 through Day 210. The frequency of clinically relevant injection site reactions was no different after a second dose of inclisiran (3.4%) than after the first dose (3.5%).

AEs and SAEs were similar across dose groups irrespective of statin use.

AEs and SAEs were similar across dose groups irrespective of baseline renal function (GFR) with no safety concerns observed in subjects with mild or moderate renal impairment.

No persistent and clinically relevant treatment related abnormalities were reported in any laboratory parameter. A low incidence of AST, ALT and CK rises were reported, although some of these subjects also had elevated baseline value or underlying medical conditions contributing to these elevations. There were no treatment emergent increases in bilirubin from a normal baseline and no case met the definition of Hy's Law. There were no clinically relevant or persistent changes in the inclisiran dose groups observed in any other laboratory parameters including renal function, hemoglobin, platelets, HbA1c and

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

coagulation parameters and no clinically relevant differences from placebo.

There were no vital signs or ECG findings of note and nothing was considered clinically significant.

Evaluation of potential or theoretical risks associated with existing cholesterol lowering therapies (hypersensitivity, neuropathy and neurocognitive disorders, new onset or worsening of diabetes, ophthalmological events) did not reveal any safety concerns for inclisiran. No significant differences in incidence of related AEs retrieved by predefined MedDRA search were noted between treatment and control groups.

CONCLUSION:

Overall, the data from this study indicate that inclisiran was well tolerated and resulted in robust and prolonged reductions in PCSK9 and LDL-C levels in plasma of subjects at high cardiovascular risk who had elevated LDL-C levels. Injection-site reactions, the only adverse event considered related to inclisiran, were uncommon and the frequency was no different after a second dose of inclisiran than after the first dose.

Based on these data, 300 mg has been selected as the dose to investigate further in subsequent clinical studies.

Date of the report: May 2017

Sponsor

Novartis

Novartis Study Code

MDCO-PCS-15-01 (orion1)

EudraCT Number

2015-003772-74

Swiss Authorization Date and Authorization number

Authorization Date: 09 September 2021

Authorization Number: 67836