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APPLICATION NUMBER:

214012Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	214012
Link to EDR	\\CDSESUB1\EVSPROD\NDA214012\214012.enx
Submission Date	December 23, 2019; July 2, 2020
Submission Type	505(b)(1)
Brand Name	Leqvio
Generic Name	Inclisiran
Dosage Form and Strength	Injectable solution; 284 mg (equivalent to 300 mg inclisiran sodium salt) /1.5 mL
Route of Administration	Subcutaneous
Proposed Indication	An adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low density lipoprotein cholesterol (LDL-C)
Applicant	Novartis
Associated IND	IND 127589
OCP Review Team	Sang Chung, Ph.D., Justin Earp, Ph.D., Jayabharathi Vaidyanathan, Ph.D.
OCP Final Signatory	Doanh Tran, Ph.D.

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1. EXECUTIVE SUMMARY

The applicant submitted an original New Drug Application (NDA) for inclisiran as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

Inclisiran is a small interfering ribonucleic acid (siRNA) conjugate that inhibits the hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9). The reduction of intrahepatic PCSK9 levels increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation.

LEQVIO is supplied as 1.5 mL solution containing 284 mg of inclisiran (equivalent to 300 mg inclisiran sodium salt) in a single-dose prefilled syringe.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted under NDA 214012 and recommends approval. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Data supporting effectiveness is based on the results of pivotal Phase 3 trials (ORION-9, ORION-10, and ORION-11) with supplemental clinical information from 4 Phase 1 and 3 Phase 2 trials. The observed placebo-adjusted LDL-C percentage change from baseline to Day 510 (primary end point) was -50%, -58% and -54%, in ORION-9 (subjects with HeFH), ORION-10 (subjects with ASCVD), and ORION-11 (subjects with ASCVD and risk equivalent), respectively.
General dosing instructions	The proposed dosing is 284 mg (300 mg as the salt, see composition of formulation in Appendix 4.1.) initially, at 3 months, and then every 6 months.
Dosing in patient subgroups	There was an increase in inclisiran exposure in patients with severe renal impairment (2.5-fold) or moderate hepatic impairment (2.1-fold). However, the pharmacodynamic markers including PCSK9 and LDL-C changes in these patients were comparable to those with normal renal or hepatic function. • No dose adjustment is necessary in patients with mild, moderate or severe renal impairment.

	Inclisiran was not studied in patients with end stage renal disease. • No dose adjustment is needed in patients with mild or moderate hepatic impairment. Inclisiran was not studied in patients with severe hepatic impairment. • No dose adjustments are needed for other demographics such as age, body weight, sex, and race.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed drug product (formulation and device) was used in the pivotal and supportive Phase 3 trials.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Inclisiran is a double-stranded siRNA conjugated with triantennary N-Acetylgalactosamine (GalNAc). The siRNA is to inhibit the production of PCSK9 and conjugation to GalNAc is to facilitate the hepatic uptake through the specific receptor on hepatocytes, asialoglycoprotein receptor (ASGPR). Givosiran, is an approved siRNA indicated for the treatment of acute hepatic porphyria that uses similar conjugation to GalNAc.

General clinical pharmacokinetics is as follows:

Absorption	• Inclisiran PK is dose proportional in the dose ranging from 25 mg to 800 mg based on the single ascending dose (SAD) study. • The time (Tmax) to reach maximum plasma concentration (Cmax) is approximately 4 hours following 300 mg subcutaneous (SC) injection.
Distribution	• Inclisiran is approximately 87% bound to plasma protein at 0.5 μg/mL (mean Cmax following 300 mg SC injection).
Metabolism	• Inclisiran is metabolized by (exo)nucleases. • Inclisiran is not a substrate nor is an inhibitor or inducer of major CYPs enzymes or transporters.
Elimination	• The apparent terminal half-life is approximately 7 hours (range 5-7 h) following 300 mg dose. • Approximately 17% (range 9% - 31%) of dose is eliminated as unchanged inclisiran in urine.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosage of inclisiran in combination with maximally tolerated statin therapy is 284 mg administered as a single SC injection initially, again at 3 months, and then every 6 months.

If a dose is missed by less than 3 months, administer inclisiran as soon as possible and maintain the original schedule. If a dose is missed by more than 3 months, start a new dosing schedule – administer inclisiran as soon as possible initially, again at 3 months, and then every 6 months.

After initiation of inclisiran, analyze lipid levels (b) (4).

2.2.2 Therapeutic individualization

There is no therapeutic individualization related to intrinsic (sex, race, body weight, renal impairment, and hepatic impairment) and extrinsic factors. The efficacy and safety are acceptable in the pivotal Phase 3 trials without need for individualization (dose adjustment or titration) and there were no significant covariates in the population PD analysis.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling comments reflecting trial designs, results and latest labeling guidances:

(~~strikethrough~~ text indicates deletion, and underlined text indicates addition)

Label Section		Recommendation
8.6	Renal Impairment	No dose adjustments are necessary for patients with mild, moderate, or severe renal impairment (b) (4) [see *Clinical Pharmacology (12.3)*]. (b) (4) INCLISIRAN has not been studied in patients with end state renal disease [see *Clinical Pharmacology (12.3)*].
12.1	Mechanism of Action	Inclisiran is a double-stranded small interfering RNA, conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, (b) (4) and directs catalytic breakdown of mRNA for PCSK9, (b) (4)

12.2	Pharmacodynamics	~~Following a single subcutaneous administration of 284 mg of INCLISIRAN,~~ (b) (4) ~~At Day 180,~~ (b) (4) ~~levels were still reduced by approximately~~ (b) (4) ~~%.~~ Following a dose at Day 1 and Day 90 of 284 mg of INCLISIRAN, mean serum PCSK9 levels were reduced by approximately 75% and 69% at Day 120 and~~. At~~ Day 180, respectively. (b) (4) In the (b) (4) studies, following four doses of INCLISIRAN 284 mg at Day 1, Day 90, Day 270 and Day 450, (b) (4) Cardiac Electrophysiology At a dose 3 times the maximum recommended dose, inclisiran does not prolong the QT interval to any clinically relevant extent. (b) (4)
12.3	Pharmacokinetics	*Renal Impairment* Pharmacokinetic analysis of data from a dedicated renal impairment study reported an increase in inclisiran Cmax and AUC of approximately (b) (4) to 3.3-fold and (b) (4) to (b) (4)-fold, respectively, in patients with mild, moderate or severe renal impairment relative to patients with normal renal function. Despite the higher plasma exposures, reductions in LDL-C (b) (4) were similar across all groups of renal function. (b) (4) *Hepatic Impairment* Pharmacokinetic analysis of data from a dedicated hepatic impairment study reported an increase in inclisiran Cmax and AUC of approximately 1.1 to 2.1-fold and 1.3 to (b) (4)-fold, respectively, in patients with mild and moderate hepatic impairment relative to patients with normal hepatic function. Despite the higher plasma inclisiran exposures, reductions in (b) (4) LDL-C were similar between the groups of patients administered inclisiran with normal and mild hepatic function. In subjects with moderate hepatic impairment baseline PSCK9 levels were (b) (4) lower and reductions in (b) (4) LDL-C were less than those observed in patients with normal hepatic function.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Inclisiran is the first NDA in class of siRNA targeting the hepatic PCSK9.

Although inclisiran mode of action is new (inhibition of PCSK9 translation in the hepatocytes), there is regulatory experience with anti-sense oligonucleotide (ASO) targeting the inhibition of hepatic lipoproteins in dyslipidemia as follows;

- Mipomersen, an ASO as an inhibitor of apolipoprotein B-100, was approved by the Agency dated January 29, 2013 (it has been discontinued not due to a safety reason according to information at Drugs@FDA).
- Volanesorsen, an ASO as an inhibitor of apolipoprotein C3, received a Complete Response Letter dated August 24, 2018 (b) (4)

Further, there is regulatory experience with the therapeutic target, i.e., PCSK9 inhibition, and two monoclonal antibody inhibitors of PCSK9 have been approved - alirocumab and evolocumab.

During the development of inclisiran, it was noted that there was significant temporal dissociation between PK exposure and PD changes. This was a significant challenge as the conventional exposure-response relationship was not applicable to support the proposed dosing frequency (every 6 months after the second dose at Day 90), which was to be evaluated in the pivotal Phase 3 trials without evaluation in Phase 2. As an alternative approach, the applicant proposed to apply a population assessment of PD (i.e., PCSK9 and LDL-C) using an abbreviated PK in PK/PD modeling (namely, k-PD modeling) at the End-of-Phase 2 meeting.

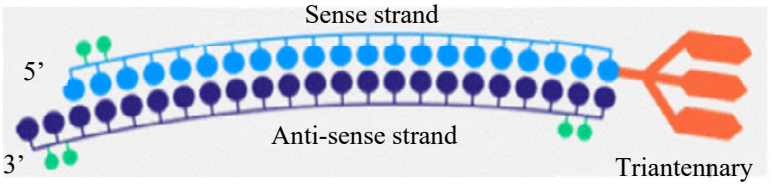
The relevant regulatory history regarding these communications is summarized below:

Communication/Meeting Type	Key Communication Points from the clinical pharmacology perspectives
EOP2 Meeting (April 6, 2017)	• Agreed to population assessment of PD (PCSK9 and LDL-C) • Recommended evaluating the to-be-marketed product in Phase 3 • Recommended evaluating drug interaction potential with statin (PK and PCSK9 at steady-state) • Recommended conducting the hepatic impairment trial
Pre-BLA Meeting (November 4, 2019)	Completeness of the application for the NDA submission including if the to-be-marketed product was used in Phase 3 trials

3.2 General Pharmacological and Pharmacokinetic Characteristics

3.2.1 Mechanism of Action:

Inclisiran is a chemically modified siRNA (21-23mer) with GalNAc conjugate on the sense strand (21mer; A-122088) (Figure 1). The GalNAc conjugate is to facilitate the hepatic update through the asialoglycoprotein receptor, which is a specific hepatic membrane receptor. The antisense strand (23mer; A-120190, active form) released from inclisiran is incorporated in the RNA-induced silencing complex and inhibits the translation of PCSK9 through the catalytic breakdown of mRNA for PCSK9. The PCSK9 controls trafficking of the hepatic LDL-C receptors, and reduced PCSK9 lowers LDL-C.



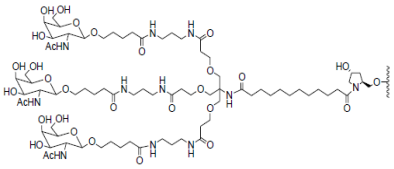


Figure 1 **Schematic summary of inclisiran structure (Molecular weight.; 16,339.51 g/mol as free acid)**
Source: Module 2.2

3.2.2 Pharmacokinetics

3.2.2.1 Absorption

The single dose PK of inclisiran following SC administration was evaluated in subjects with elevated LDL-C (Study ALN-PCSSC-001) following 25, 100, 300, 500 or 800 mg (SAD). In the same trial, the multiple dose (MD) PK was also evaluated following alternative dose regiments in a separate cohort; weekly 125 mg (QW), biweekly 250 mg (Q2W) or once in 4 weeks (Q4W) 300 mg or 500 mg.

Inclisiran plasma concentration-profiles showed apparent plateau for few hours followed by a decline in concentrations to baseline by 24 hours following administration of 300 mg dose SC (Figure 2). The median time to peak serum concentration (T_{max}) ranged from 4 to 8 hours post-dose among trials with 300 mg dose (i.e., SAD, MD, renal impairment, and hepatic impairment trials).

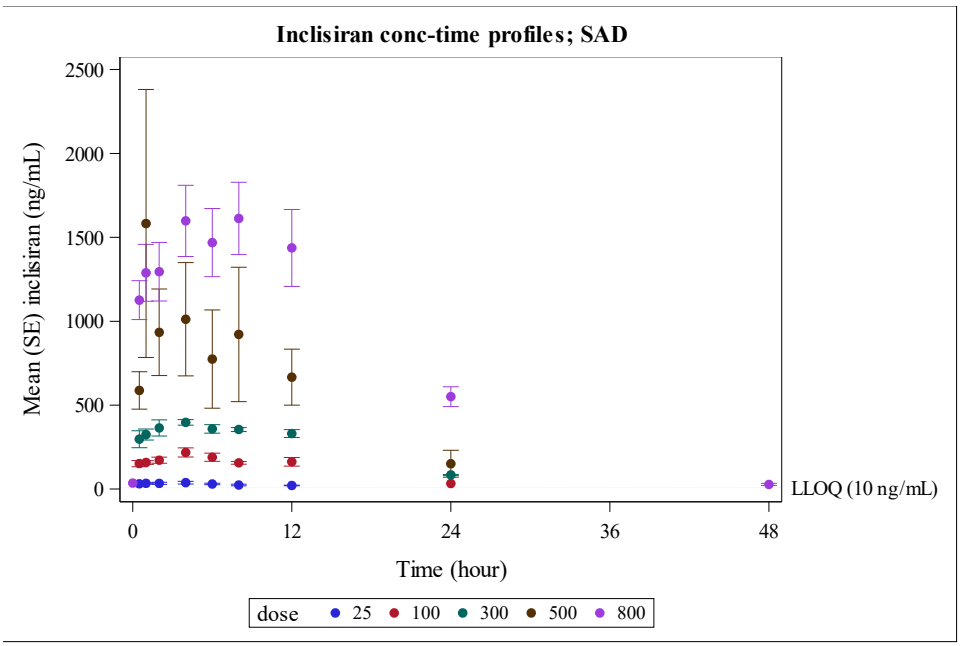


Figure 2 Mean (SE) inclisiran concentration-time profile following SAD (Study ALN-PCSSC-001)

Inclisiran PK (AUC and C_{max}) was proportional to dose (Figure 3). Based on the assessment using power model, the slopes (b) (95% CI) in the power model (i.e., PK parameter = a*Dose^b) were as follows;

- Single dose; 1.12 (0.957-1.28) and 1.14 (0.916-1.37) for AUCinf and Cmax, respectively
- Multiple dose; 1.09 (0.714-1.47) and 1.27 (0.937-1.59) for AUCinf and Cmax, respectively

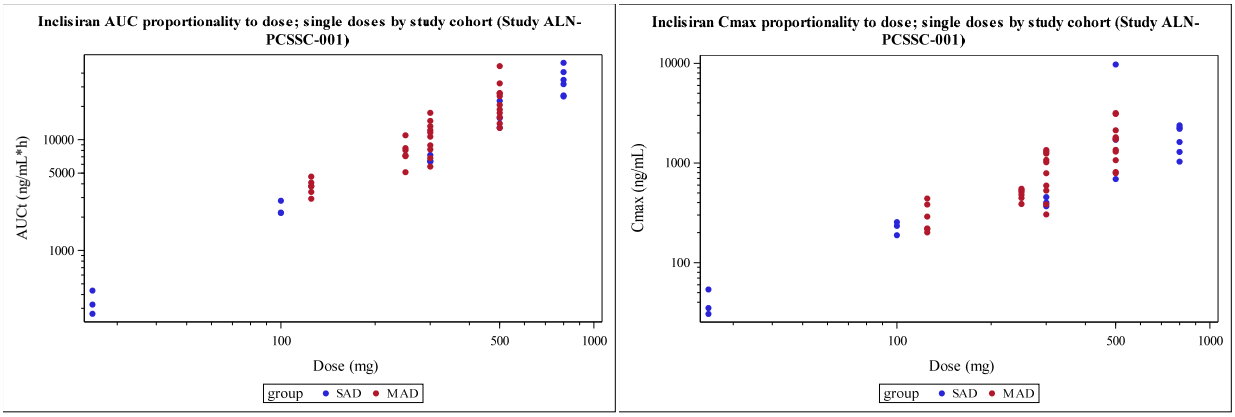
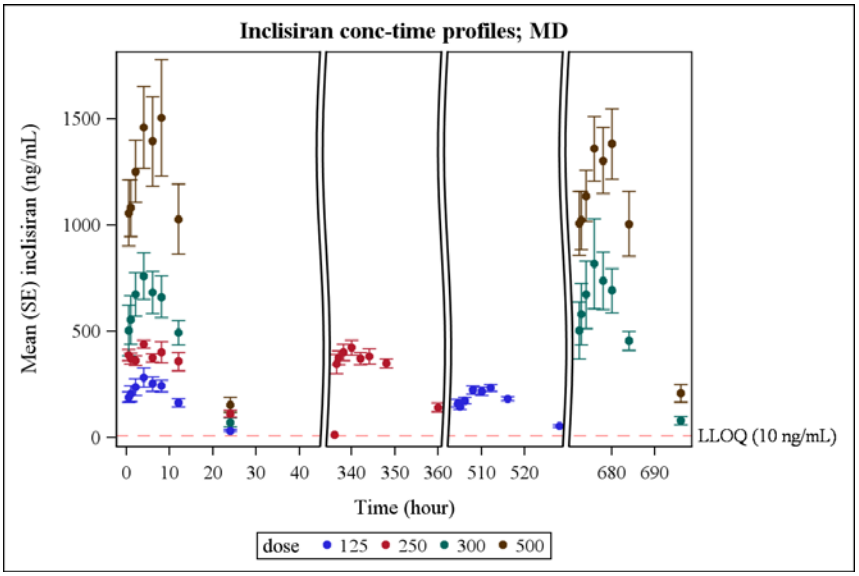


Figure 3 Inclisiran AUC (left) and Cmax (right) proportionality to dose by trial cohort; single doses (blue) and 1st dose following multiple dose study (red) (Study ALN-PCSSC-001)

During MD, there was no accumulation across different dosing regiments (e.g., four doses of 125 mg QW, two doses of 250 mg Q2W, and two doses of 300 mg or 500 mg Q4W based on the concentration-time profiles (Figure 4, upper panel) or PK parameters (Figure 4, Lower panel).



(Figure 4, upper panel)

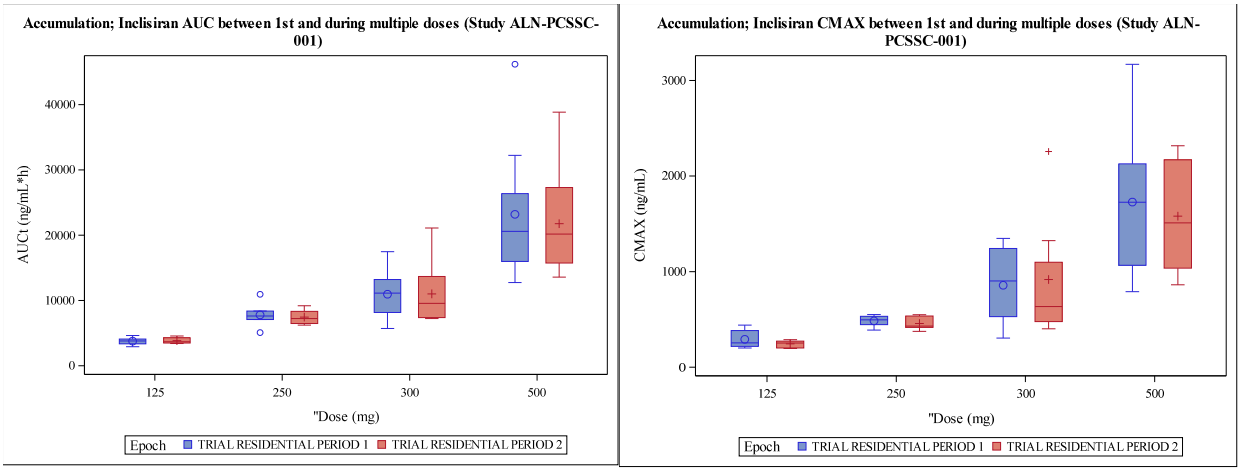


Figure 4 Mean (SE) inclisiran concentration-time profile following different MD regiments (Upper panel) and PK parameter changes during MD (Lower Panel) (Study ALN-PCSSC-001)
(Epoch; 'TRIAL RESIDENTIAL PERIOD 1'=1st dose, 'TRIAL RESIDENTIAL PERIOD 2'=2nd dose)

3.2.2.2 Distribution

Inclisiran binds to plasma protein with 87.4 % and 86.4% bound at inclisiran concentration of 0.5 and 1 µg/mL, respectively. It is expected to be significantly distributed in the liver tissues due to its targeting the hepatic uptake with GalNAc ligand, and in the kidney as it is the primary excretion route. Although a mass balance study was not conducted in human, non-clinical data showed longer T1/2 in the liver and kidney compared to that of plasma; 53-191 hours, 244-685 hours, 0.9-1.8 hours for the liver, kidney and plasma, respectively, in rats.

The estimated mean volume of distribution during the terminal phase (Vz/F) ranged from 421-553 L among trials following the 300 mg dose.

3.2.2.3 Metabolism and elimination

The primary responsible enzyme for inclisiran metabolism is (exo)nucleases. Although there were metabolites from the 3' end of the S strand following the loss of GalNAc, the major metabolites of special interests were from antisense (AS) strand from the loss of the N-1 and N-2 nucleotides from the 5' and 3' ends (i.e., AS(n-1)3', AS(n-1)5', AS(n-2)3', AS(n-2)5') due to potential pharmacologic activity.

In non-clinical models (rats and monkeys), AS(n-1) was the only primary metabolite and concentrations were several folds lower than those of inclisiran. Levels of the inclisiran metabolites were evaluated using plasma samples collected from ORION-7, the renal impairment trial. The primary metabolite (i.e., AS(n-1)) concentrations were approximately 11%, 27% and 86% to those of inclisiran at 0.5, 8 (Tmax) and 48 hours post-dose, respectively (Figure 5). The other metabolite (i.e., AS(n-2) was not detected. The applicant noted that the human AS(n-1) exposure was within the safety margin.

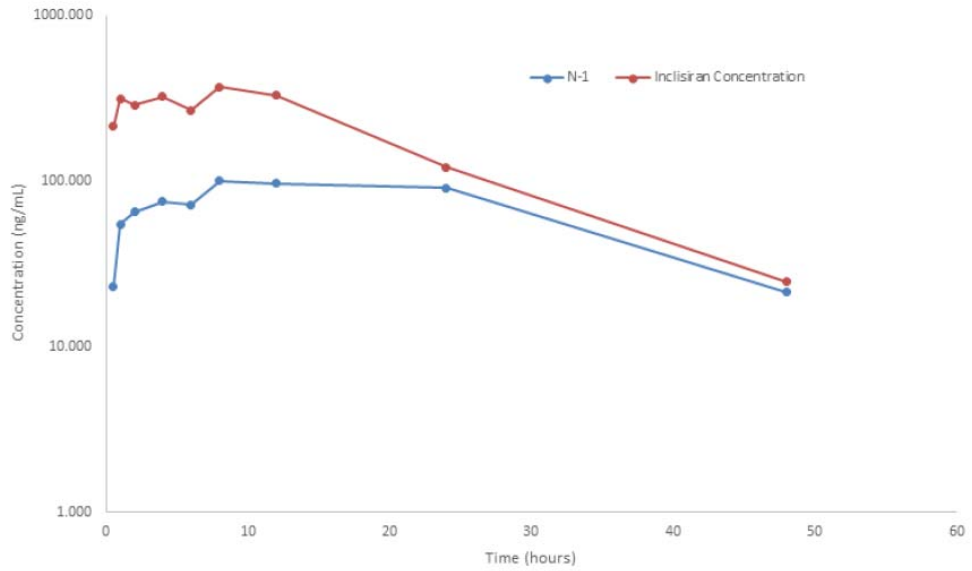


Figure 5 Concentrations of inclisiran and AS(n-1) in ORION 7

Source: Figure 6, Report 508n-1901; DMPK Report; screening and semi quantitation of AS(n-1) and AS(n-2) metabolites in human plasma from previously generated full scan LC-TOF-HRMS chromatograms

The renal excretion of inclisiran ranged from 13-21% of dose among trials following 300 mg injection. The applicant did not conduct a mass balance study. In monkey model, the renal excretion was the major route of elimination as the total radioactivity was 32% and 1.6% in the urine and feces over 7-day period, respectively, following radiolabeled [^{14}C]-inclisiran administration.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes, the clinical pharmacology information presented in this NDA provides supportive evidence of effectiveness. Refer to Section 3.3.2 for additional details.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the proposed indication as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD, who require additional lowering of LDL-C.

The recommended dose is 284 mg administered as a single SC injection initially, again at 3 months, and then every 6 months. The proposed dosing was evaluated in three Phase 3 trials with patients

The dose finding Phase 2 trial (ORION-1) evaluated the dose-response following two doses (Day 1 and Day 90) of 100 mg, 200 mg or 300 mg over 12 months in patients with ASCVD. Although

there was no apparent difference in PCSK9 reduction between 200 and 300 mg, 300 mg showed additional LDL-C reduction reaching a maximum reduction of 56% (Figure 6). Further, apparent maximum reduction was reached at 300 mg for both PCSK9 and LDL-C according to cross-study comparison of ALN-PCSSC-001 (single doses evaluated 25 mg to 800 mg) and ORION-1 (single doses evaluated 200 mg to 500 mg) (Figure 7). Therefore, the applicant selected 300 mg to evaluate its efficacy and safety in Phase 3 trials.

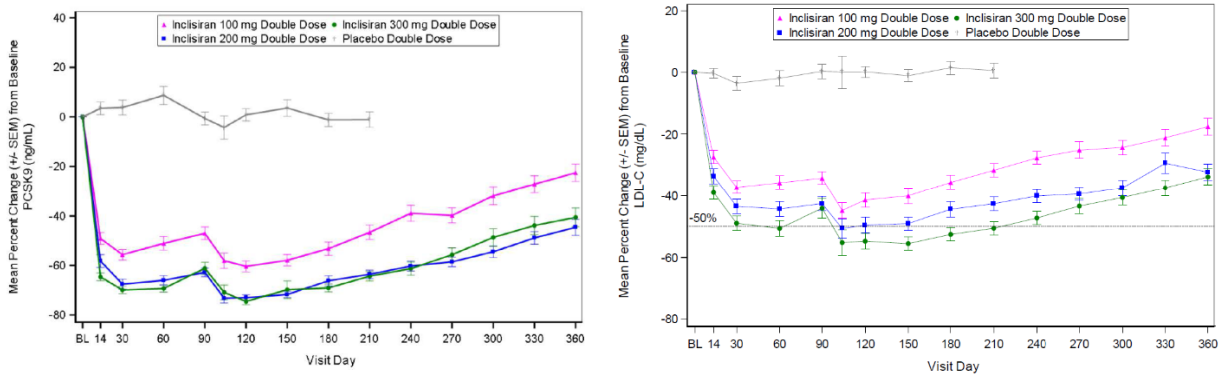


Figure 6 Mean (SE) PCSK9 (left) and LDL-C change from baseline following inclisiran dosing on Day 1 and Day 90 (ORION-1)
Source, Figure 4, Module 2.5

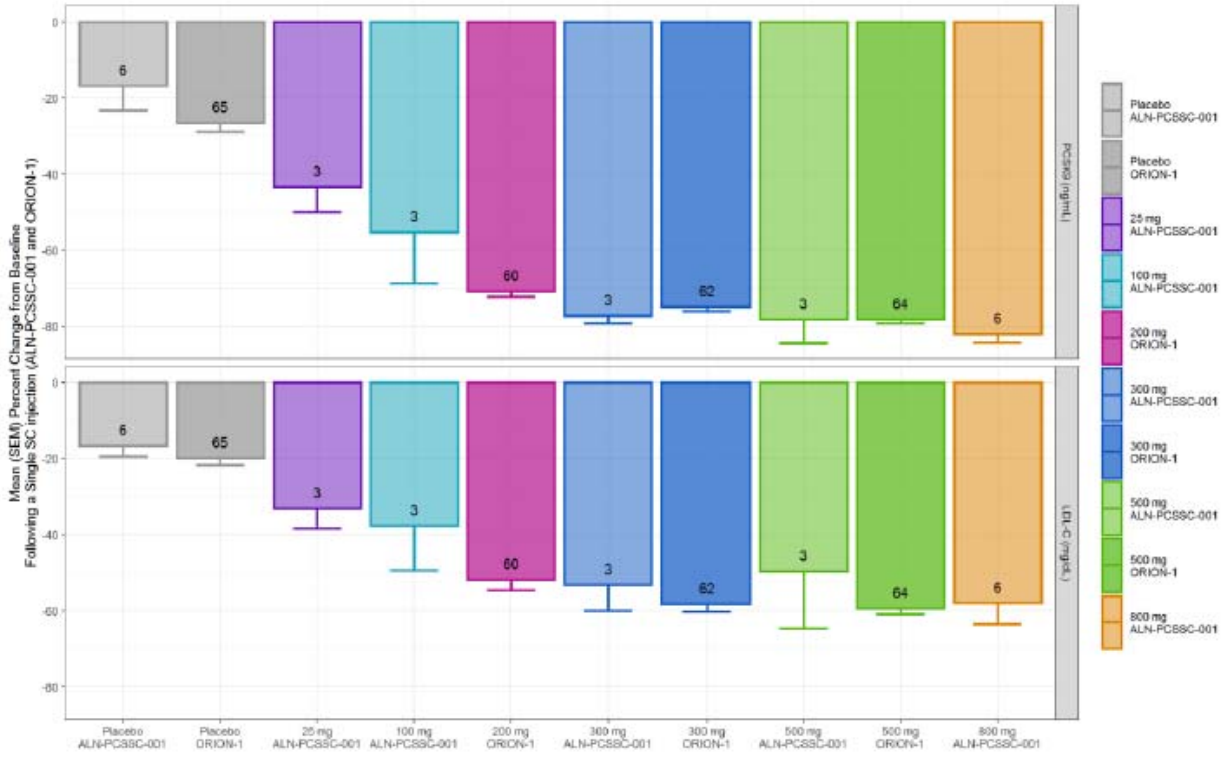


Figure 7 Mean (SE) percent change from baseline in PCSK9 (upper) and LDL-C (lower) between ALN-PCSSC-001 and ORION-1 (numbers inside bars represent the number of subjects in each group)
Source, Figure 19, Module 2.7.2

However, a dosing interval for a maintenance period after the second dose was not evaluated in Phase 2 trial. Therefore, potential scenarios of dosing frequency (e.g., 2 vs. 3 months and 4 vs. 6 months for the second and a maintenance dose, respectively) were explored using population PD approach as the conventional exposure-response analysis was not feasible due to the temporal dissociation between exposure and response. The applicant selected every 6 months after the second dose at Month 3 for the maintenance dosing interval using results of the modeling and simulation (Figure 8).

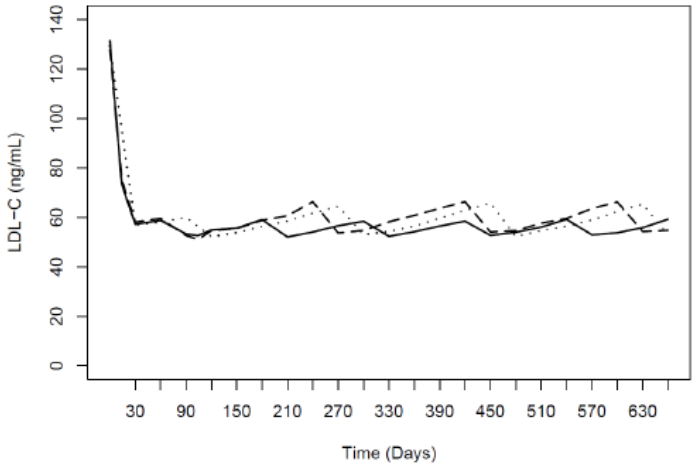


Figure 8 **Simulated LDL-C following different dosing schedules; Day 1, Day 60 and then every 4 months (solid line, schedule 1), Day 1, Day 60 and then every 6 months (broken line, schedule 2), or Day 1, Day 90, and then every 6 months (dotted line, schedule 3)**
Source, Figure 9, Module 2.7.2

The applicant evaluated the proposed dosing regimen (300 mg initially, at 3 months and then every 6 months) in 3 pivotal Phase III trials in patients with HeFH (ORION-9), ASCVD (ORION-10), or ASCVD risk equivalent (ORION-11). The primary efficacy endpoint was the percent change in LDL-C from baseline to Day 510 relative to placebo following 300 mg at Day 1, Day 90 (3 Month), Day 270 (9 Month) and Day 450 (15 Month). The typical LDL-C changes over the treatment period is shown in Figure 9. The observed primary efficacy endpoint was -50%, -58% and -54% in ORION-9, -10 and -11, respectively. The efficacy was generally consistent among different sub-groups and the covariate analysis showed that the LDL-C changes was inversely correlated with the baseline LDL-C (see the forest plot in Appendix 4.3.6.)

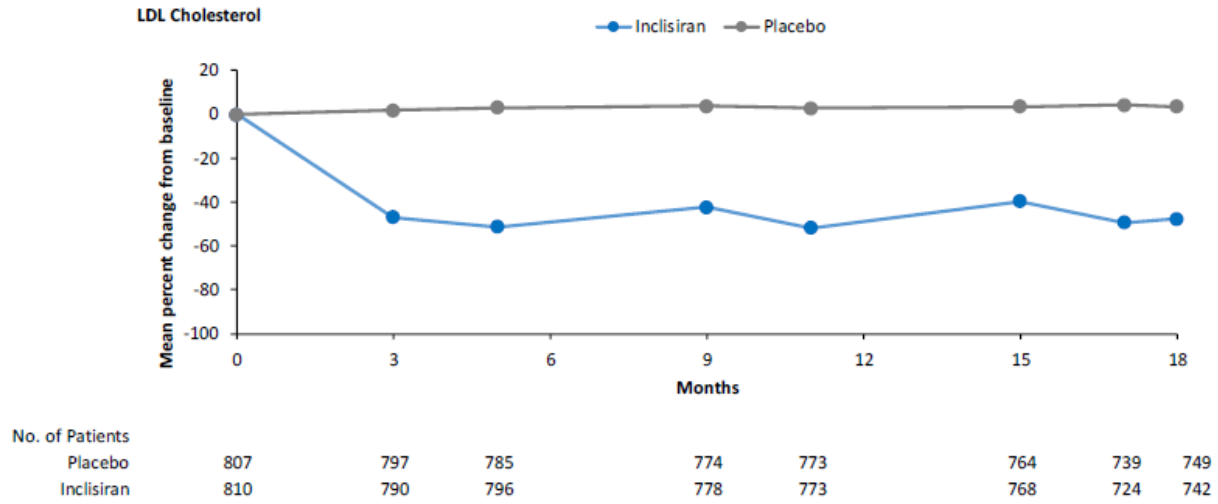


Figure 9 Observed mean percentage change from baseline in LDL-C over time (ORION-11, ITT population)
Source, Figure 7, Module 2.5

In the pooled data across all Phase 3 trial (N=3660), subjects who had at least a 50% reduction in the primary endpoint was 62% compared to 2% for those of placebo arm. Subjects who reached the threshold of 70 mg/dL was 80% for the inclisiran treatment arm compared to 16% of placebo treatment arm (Figure 10). The applicant concluded that there was no clinically relevant difference in the treatment-emergent adverse events profile between inclisiran and placebo treatments other than injection site reaction.

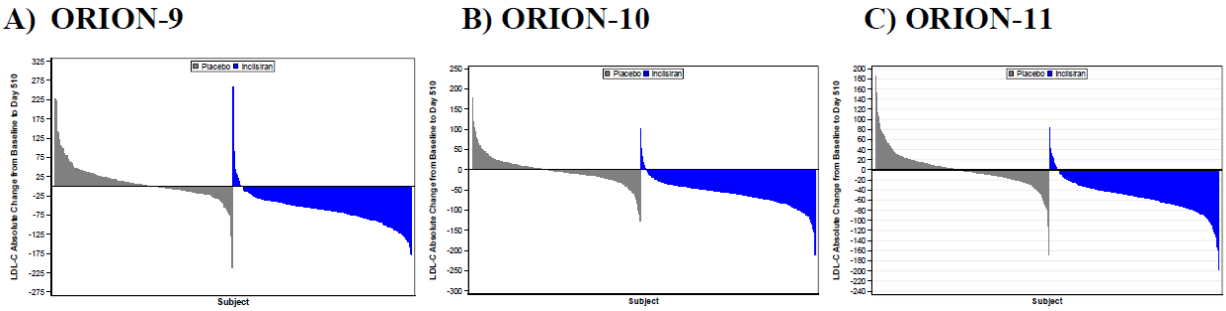


Figure 10 Waterfall plots of absolute change in LDL-C from baseline to Day 510 in each Phase 3 trials (A; ORION-9, B; ORION-10, C; ORION-11)
Source: Figure 9, Module 2.5

Missed or delayed doses:

Protocols for Phase 3 trials did not have details of missed or delayed doses as inclisiran was administered by designated staff under the supervision of the investigator at study sites. Therefore, simulations were conducted to evaluate the impact of missed or delayed doses using population PD models. Simulation scenarios were missed or delay 1, 2 or 3 months during every 6 months period. With up to a 3-month delay, median LDL-C was increased from 58.1 mg/dL to 68.2 mg/dL or 92.9 mg/dL to 105 mg/dL in subjects with ASCVD or HeFH, respectively (Table 1).

Table 1 LDL-C or PSCK9 changes with potential delayed doses up to 3 months

		PCSK9 (ng/mL)		LDL-C (mg/dL)	
		Month 21 + Dosing Delay	Month 27	Month 21 + Dosing Delay	Month 27
ASCVD	No dose delay	146 [60.0, 327]	147 [60.0, 328]	58.1 [25.9, 120]	58.1 [25.9, 120]
	1-month dosing delay	162 [63.1, 348]	134 [58.3, 308]	61.3 [27.5, 123]	56.6 [24.9, 117]
	2-month dosing delay	178 [66.6, 366]	123 [55.9, 278]	65.2 [29.4, 125]	54.4 [24.3, 113]
	3-month dosing delay	196 [70.6, 386]	110 [53.1, 247]	68.2 [31.4, 133]	51.4 [22.9, 110]
HeFH	No dose delay	222 [96.2, 417]	223 [96.1, 417]	92.9 [46.0, 169]	93.0 [46.0, 169]
	1-month dosing delay	242 [104, 436]	206 [92.9, 390]	98.6 [49.9, 173]	89.8 [43.3, 167]
	2-month dosing delay	261 [110, 458]	186 [87.6, 360]	102 [53.2, 179]	85.8 [40.8, 163]
	3-month dosing delay	279 [118, 482]	166 [81.1, 333]	105 [56.7, 182]	82.1 [38.5, 158]

Source: Table 15, Module 2.7.2

The applicant proposed labeling that inclisiran is administered maintenance dose according to the patient's original schedule if a dose is missed by less than 3 months, or start a new dosing schedule (i.e., administered immediately, again at 3 months, and then every 6 months) if a dose missed by more than 3 months.

Effect on QT/QTc interval:

The effect of inclisiran on QTc prolongation was assessed in a dedicated thorough QT study with standard study design including a supratherapeutic inclisiran dose of 900 mg, which covers potential worst-case exposure scenario (e.g., renal impairment) (ORION-12). There was no significant impact of inclisiran on the QT prolongation (Table 2). See detailed FDA analysis and review by the QT-IRT review team dated 5/13/2020 in DARRTS.

Table 2 The Point Estimates and the 90% CIs

ECG parameter	Treatment	Time	ΔΔQTcF (msec)	90% CI (msec)
QTc	Inclisiran 900 mg	4 h	2.9	(0.5 to 5.2)

Source: FDA Analysis, IRT-QT review

Immunogenicity:

There was no significant detection of anti-drug antibodies (ADA) with 1.8% of samples (n=127 from 92 patients, where some patients had repeated measures) in Phase III trials tested positive. There was no significant difference in PD profiles (PCSK9 and LDL-C), efficacy and safety for patients with positive ADA compared to those without ADA.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. Results from the clinical pharmacology trials and population PD analysis of data from Phase 3 trials indicate that dose adjustment of inclisiran is not recommended for patients based on intrinsic factors of sex, body weight, race, ethnicity, or renal or hepatic function. There was no information on patients with ESRD nor severe hepatic impairment in Phase 1 trials. Adequate clinical information was not available for labeling from Phase 3 trials due to small number of patients (i.e., patients with severe renal impairment) or absence of corresponding patients (i.e., severe hepatic impairment).

3.3.3.1 Renal Impairment

The effect of renal impairment on the PK and PD of inclisiran was evaluated following 300 mg SC injection in subjects with renal impairment categorized by creatine clearance (CLcr) (n=8, 8 and 7 for mild (CLcr, 60-89 mL/min), moderate (CLcr, 30-59 mL/min) and severe (CLcr, 15-29 mL/min) sub-group, respectively) and healthy (CLcr, ≥90 mL/min) subjects (n=8) (Study ORION-7).

The inclisiran exposure was higher in the renal impairment sub-groups compared to subjects with normal renal function (Figure 11, left). There was an increase of 53, 73, and 135% for $AUC_{0\text{-}t}$, and 133, 97 and 231% for C_{max} in the mild, moderate and severe sub-group, respectively, compared to those of healthy subjects (Table 3). Inclisiran exposure increased with a decrease in CLcr due to the renal impairment (Figure 12 right).

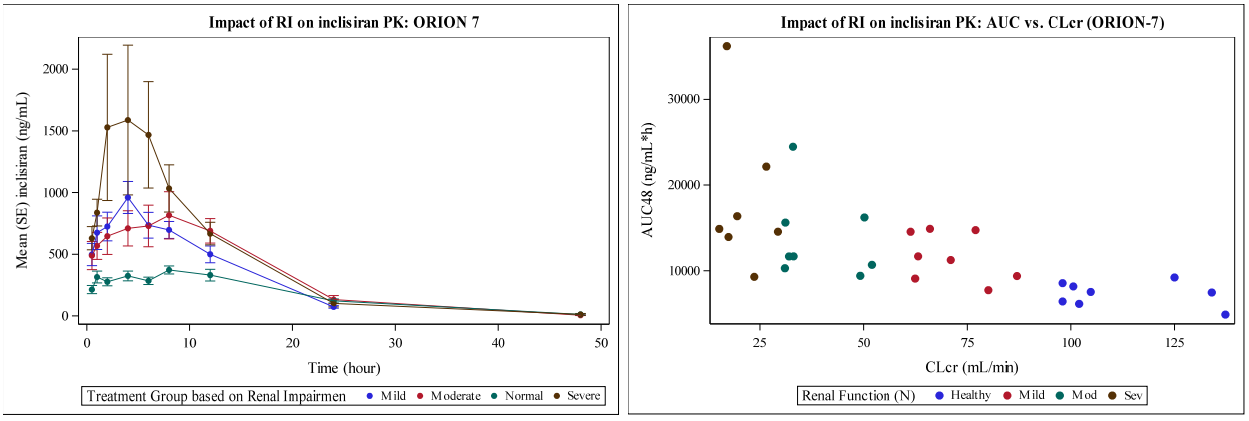


Figure 11 **Mean (SE) inclisiran concertation-time profiles in sub-groups of renal impairment (left) and relationship between AUC and CLcr (right) (ORION-7)**

Table 3 Statistical comparison of AUC and C_{max} of inclisiran in subjects with normal renal function and renal impairment sub-groups

	Mild vs Healthy		Moderate vs Healthy		Severe vs Healthy	
Parameters	**GMR**	**90% CI**	**GMR**	**90% CI**	**GMR**	**90% CI**
C_{max}, ng/mL	2.33	[1.51, 3.62]	1.97	[1.27, 3.05]	3.31	[2.10, 5.22]
AUC_{0-24}, h.ng/mL	1.75	[1.29, 2.37]	1.91	[1.41, 2.59]	2.50	[1.82, 3.42]
AUC_{0-48}, h•ng/mL	1.58	[1.22, 2.06]	1.83	[1.41, 2.37]	2.33	[1.78, 3.06]
AUC_{0-t}, h•ng/mL	1.53	[1.19, 1.97]	1.73	[1.34, 2.23]	2.35	[1.81, 3.05]
AUC_{0-inf}, h•ng/mL	1.44	[1.01, 2.07]	1.39	[0.906, 2.12]	2.23	[1.56, 3.20]

Source: Table 9, CSR

Although there was an increase in inclisiran exposure due to the renal impairment, there was no apparent PD differences in these patient groups (Figure 12, PCSK9 (left) and LDL-C (right)). The baseline PD levels tend to be lower in renal impairment sub-groups compared to those of normal sub-group (Figure 13). However, the number of subjects is too low to conclude if baseline was a significant covariate on PD changes.

In Phase 3, baseline GFR estimated using MDRD was not a significant covariate for the percent change of LDL-C reduction (n=515, 1012, 295 and 11 for normal, mild, moderate and severe sub-groups, respectively, in Efficacy Pool 1, (see the forest plot in Appendix 4.3.6.). There were no patients with end-stage renal disease (ESRD) in ORION-7 and therefore inclisiran is not recommended in patients with ESRD.

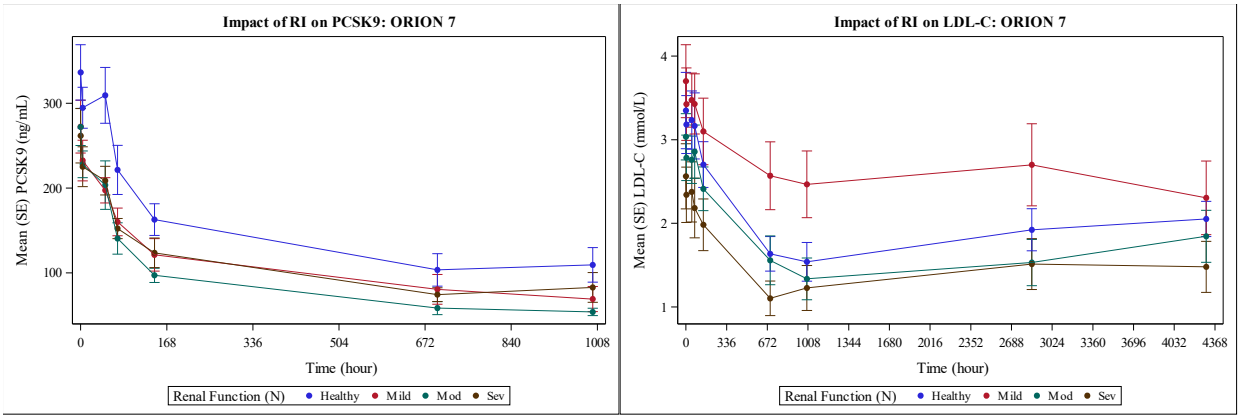


Figure 12 PD concentration-time profiles by sub-groups; PCSK9 (left) and LDL-C (right) (ORION-7)

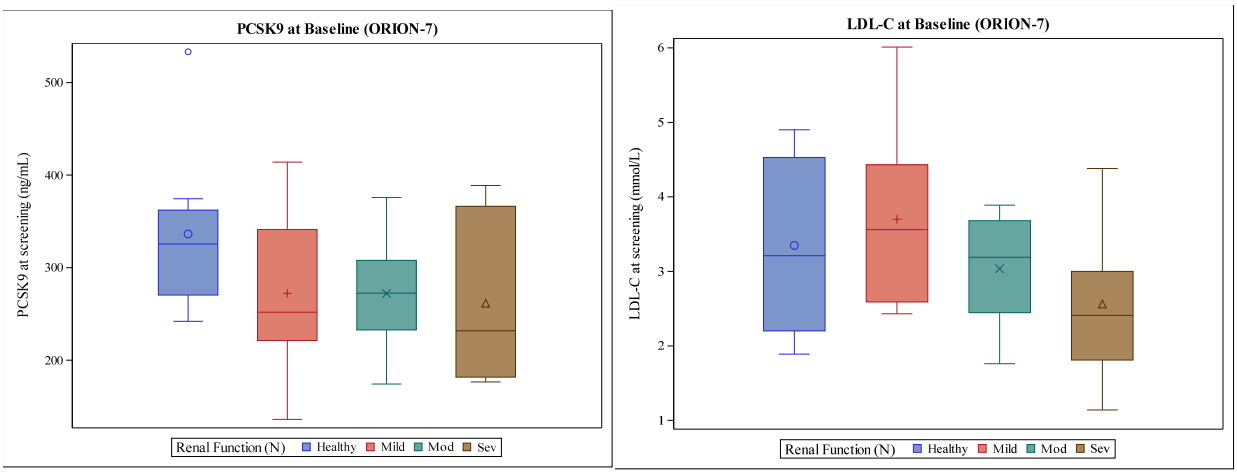


Figure 13 PD at baseline by sub-groups; PCSK9 (left) and LDL-C (right) (ORION-7)

Overall, specific dosing recommendation is not considered necessary for the exposure increase with renal impairment as 1) inclisiran exposure is below LOQ after 24 hours post-dose, 2) there was significant temporal dissociation between PK and PD, 3) there was no apparent PD difference among sub-groups, 4) renal functions defined as MDRD was not the significant covariate for the primary efficacy endpoint (% change at Day 510 from baseline) in the population PD analysis of Phase 3 data, and 5) there was no apparent AEs with special interests (e.g., myopathy).

3.3.3.2 Hepatic Impairment

The effect of hepatic impairment on the PK and PD of inclisiran was evaluated in ORION-6 following 300 mg dosing to subjects with normal hepatic function (n=12), mild (n=10) or moderate (n=6) hepatic impairment.

Inclisiran concentrations and its PK parameters were generally similar between normal hepatic function and mild impairment groups, but higher in the moderate impairment group (Figure 14).

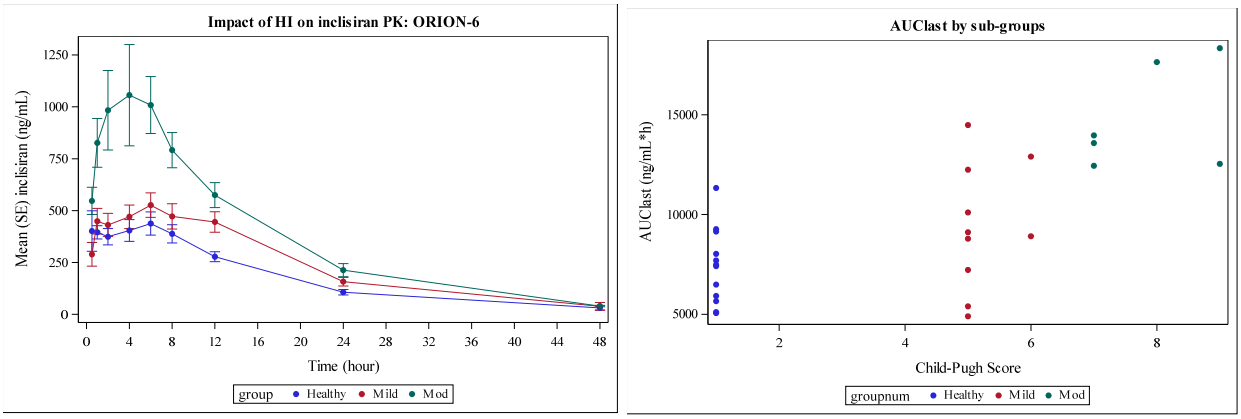


Figure 14 Inclisiran concentration-time profile in subjects with normal or hepatic impairment (left) and AUC by Child-Pugh score (right) (ORION-6)

(note; in the right panel, healthy subjects were assigned with Child-Pugh Score of 1 as the score was originally not assigned with healthy subjects.)

Compared to normal hepatic function group, inclisiran PK was similar in the mild hepatic impairment group, but approximately 2-fold higher in the moderate hepatic function group (Table 4).

Table 4 Statistical comparison of AUC and C_{max} of inclisiran in the hepatic impairment trial

	Mild vs Normal		Moderate vs Normal	
Parameters	**GMR**	**90% CI**	**GMR**	**90% CI**
Cmax, ng/mL	1.07	[0.78,1.45]	2.11	[1.47,3.03]
AUClast, h·ng/mL	1.24	[1.01,1.53]	2.03	[1.60,2.58]
AUCinf, h·ng/mL	1.33	[1.05,1.68]	2.04	[1.60,2.58]

Source: Table 2, CSR ORION 6

However, PD changes (percent change from baseline for PCSK9 and LDL-C) were comparable among sub-groups (Figure 15). Although LDL-C was lower in the moderate impairment sub-group compared to those of healthy sub-groups, LDL-C changes from baseline was comparable between two sub-groups as the baseline LDL-C was lower in the moderate impairment sub-group to that of healthy sub-group.

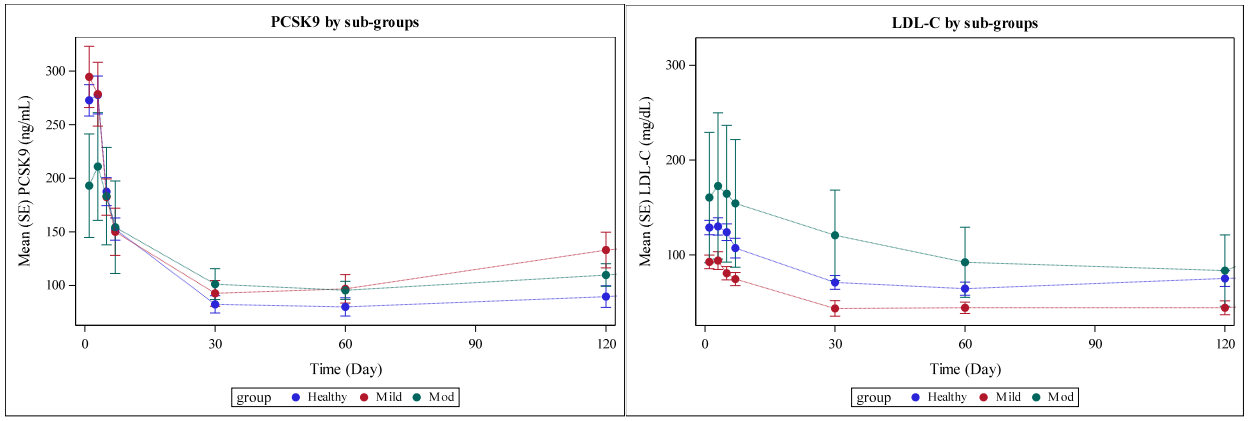


Figure 15 Mean (SE) PD concentration-time profiles by sub-groups; PCSK9 (left) and LDL-C (Study ORION-6)

In conclusion, specific dosing recommendation is not considered necessary for the exposure increase with the hepatic impairment as 1) inclisiran exposure is below LOQ after 24 hours post-dose, 2) there was significant temporal dissociation between PK and PD, 3) there were no apparent differences in LDL-C reduction (percent change from baseline) among sub-groups and 4) there was no apparent AEs with special interests (e.g., myopathy).

3.3.3.3 Race, Sex, Body mass index and Age

There was no consideration for a dose adjustment related to these covariates in Phase 3 trials. The effects of various pre-specified covariates on PD responses was assessed based on data from the three Phase 3 trials (see forest plot in Appendix 4.3.6.). Race, sex, body mass index and age were not significant covariates for PD changes.

Therefore, there is no specific dosing recommendations related to those covariates.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

No. In vitro study results indicate that inclisiran does not significantly affect major metabolic isozymes and transporters. Inclisiran is metabolized mainly by exonucleases; major CYP450 enzymes and transporters are not involved in its metabolism and elimination. Potential of PK interaction is also limited due to relatively infrequent dosing and short duration of inclisiran plasma exposure of 1 or 2 days following 300 mg.

Inclisiran is proposed as an adjunct to diet and maximally tolerated statin therapy and the sponsor evaluated the interaction potential of inclisiran with statins PK and PD. There is potential of PD interaction with statins as statins are known to induce PCSK9 levels. Further, both inclisiran and statin can reduce LDL-C through independent mechanisms. There was no consistent impact of statins on inclisiran PK (MD cohort of ALN-PCSSC-001; atorvastatin (N=7) and simvastatin (N=5)) following 300 mg or 500 mg inclisiran dosing.

The impact of inclisiran on statin PK was also evaluated in ORION-10. Sparse samples were obtained from subjects with atorvastatin 80 mg or rosuvastatin 40 mg, prior to the last inclisiran dosing at Day 450 and during a follow up visit after the last dose at Day 510. Sampling schedules were 0 to <6h, 6h to <12 h, 12 to <24 h or ≥24 hr post-statin dose. It was concluded by the applicant that there was no meaningful difference in statin concentrations between placebo and inclisiran treatment groups over the sampling period. The impact of inclisiran on statin PK information in ORION-10 was inconclusive as population modeling relied on literature parameters and trends in descriptive summary of concentrations were inconsistent among time intervals. Further, statin sampling time was not adequate to directly evaluate the effect of inclisiran on statin exposure as statin samples were collected when inclisiran is expected to be low; before inclisiran dosing (Day 450) or 60 days after the last dose (Day 510). However, there was no specific clearance mechanisms that are overlapped between inclisiran and statin PK, and inclisiran did not affect major metabolic isozymes nor transporters involve in statin disposition according to in vitro study results. Therefore, it seems reasonable to conclude that there is no meaningful drug-interaction potential in PK between inclisiran and statins.

In the analysis on pooled data of Phase 3, there was no meaningful difference in LDL-C response between on statin vs. not on statin or high intensity statin vs. not on high intensity statin (see the forest plot in Appendix 4.3.6.).

In conclusion, there is no significant PK and PD (LDL-C) drug interaction potential with inclisiran.

4. APPENDICES

4.1 Composition of formulation

Table 5 Composition of formulation
Source; Table 1, Module 2.3.P

Component, grade	Concentration (mg/mL)	Amount Per PFS	Function
Inclisiran Sodium*, In House	200	300 mg**	Drug Substance
(*corresponding to Inclisiran)	189	284 mg	Drug Substance (free acid)
Water for Injection, USP, Ph. Eur.	N/A	q.s. to 1.5 mL	Diluent
Sodium Hydroxide, NF, Ph. Eur.	N/A.	q.s. to target pH 7.0	pH adjustment
Phosphoric Acid, NF, Ph. Eur.	N/A	q.s. to target pH 7.0	pH adjustment
[redacted]			(b) (4)

USP: United States Pharmacopeia; NF: National Formulary; Ph. Eur.: European Pharmacopeia
q.s.: quantum sufficit; (b) (4)
(b) (4)

4.2 Summary of Bioanalytical Method Validation

Inclisiran was quantified by a liquid chormatography time of flight mass spectrometry (LC-TOF-MS).

Inclisiran (code name; ALN-PCSSC) is a duplex siRNA that contains an antisense (A-120190) and sense (A-122088) strand. The internal standard (IS), ALN-ASI, is a duplex RNA that contains an antisense (A-122227) and sense (A-122230) strand. The LC-TOF-MS assay quantify inclisiran concentrations by detecting the antisense and sense strand portions of the duplex. Inclisiran duplex concentrations were reported based on the antisense/sense ratio. For a ratio >1 or ≤1, the sense or antisense concentration, respectively, was reported for the duplex. For a ratio with BQL of antisense or sense, the duplex concentration was reported as BQL.

Validation of bioanalysis methods was acceptable as follows;

Standard Curve Range (ng/mL)	Duplex Strand of Inclisiran	QC Levels	Precision[a] (%CV)		Accuracy[b] (%RE)		Stability in Plasma
			Intra-day	Inter-day	Intra-day	Inter-day	
10 to 10000	A-120190	LLOQ	6.2 to 10.1	11.1	-6.8 to 11.4	5.8	Benchtop: 24 hours at ambient temperature; Freeze/thaw: 5 cycles at -20°C and -70°C; Long-term storage: 367 days at -20°C and -70°C
		Above LLOQ:	1.0 to 12.8	4.2 to 10.2	-9.1 to 11.8	0.1 to 5.7	
	A-122088	LLOQ	3.6 to 10.4	7.1	9.2 to 16.5	12.8	
		Above LLOQ	2.5 to 11.4	5.1 to 11.2	-8.0 to 11.5	0.5 to 5.6	

The quality of bioanalytical method performance was acceptable (Table 5).

Table 6 Performance summary of bioanalytical method for inclisiran

Source; Table 9, Module 2.7.1

Bioanalytical method validation report name, amendments, and hyperlinks	(b) (4)319-1418 (b) (4)319-1418 Amendment 1		
Method description	Solid phase extraction of analytes and spiked IS in human plasma samples, followed by detection of antisense and sense strands of inclisiran siRNA duplex using LC-TOF-MS		
Materials used for standard calibration curve and concentration	Inclisiran, composed of single antisense (A-120190) and sense (A-122088) strands; ALN-60519 (IS), composed of single antisense (A-122227) and sense (A-122230) strands		
Validated assay range	10 ng/mL to 10000 ng/mL		
Material used for quality controls (QCs) and concentration	Inclisiran 10 ng/mL, 30 ng/mL, 400 ng/mL, 4000 ng/mL, and 8000 ng/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents	Inclisiran: Alnylam Pharmaceuticals, Lot 982019; ALN-60519 (IS): Alnylam Pharmaceuticals, Lot 982049, 1-FIN-2086, and 982186		
Regression model and weighting	$1/x^2$		
Validation parameters	**Method validation summary**		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	
	Cumulative accuracy (%RE) from LLOQ to ULOQ	A-120190: -4.3 to 2.2 A-122088: -3.9 to 1.9	
	Cumulative precision (%CV) from LLOQ to ULOQ	A-120190: 5.4 to 9.2 A-122088: 4.4 to 7.4	
Performance of QCs during accuracy and precision runs in 5 QCs (LLOQ, low, mid, high QCs, and ULOQ)	Intra-assay accuracy (%RE)	A-120190	LLOQ: -6.8 to 11.4; Above LLOQ: -9.1 to 11.8
		A-122088	LLOQ: 9.2 to 16.5; Above LLOQ: -8.0 to 11.5
	Inter-assay accuracy (%RE)	A-120190	LLOQ: 5.8; Above LLOQ: 0.1 to 5.7
		A-122088	LLOQ: 12.8; Above LLOQ: 0.5 to 5.6
	Intra-assay precision (%CV)	A-120190	LLOQ: 6.2 to 10.1; Above LLOQ: 1.0 to 12.8
		A-122088	LLOQ: 3.6 to 10.4; Above LLOQ: 2.5 to 11.4
	Inter-assay precision (%CV)	A-120190	LLOQ: 11.1; Above LLOQ: 4.2 to 10.2
		A-122088	LLOQ: 7.1; Above LLOQ: 5.1 to 11.2
	Total error	Not applicable	
Selectivity & matrix effect	Selectivity: ≤ 20.0% LLOQ of %CV, ±20.0% of %RE for spike-in; Matrix effect: met the acceptance criteria and no significant impact on the study data		
Interference & specificity	No interference		
Hemolysis effect	No impact on assay performance		
Lipemic effect	No impact on assay performance		
Dilution linearity	%CV% (precision) ≤ 15.0%; %RE (accuracy) within ±15.0%		
Bench-top/process stability	24 hours at ambient temperature		
Freeze-Thaw stability	5 cycles at -20°C and -70°C		
Long-term storage	367 days at 20°C and -70°C		
Parallelism	Not applicable		
Carry over	No impact from carryover		

4.3 Supplemental Clinical Pharmacology Information

4.3.1. Study ALN-PCSSC-001 (SAD, MD)

Key study design (Source, Table 1, Module 2.7.6)

Primary Objective(s)	To evaluate the safety and tolerability of inclisiran when administered SC as a single dose or multiple doses to subjects with elevated LDL-C.
Study Design and Type of Control	Randomized, single-blind, placebo- controlled, SAD and MD study of inclisiran when administered subcutaneously to subjects with elevated LDL-C, with or without statin co- medication
Location	United Kingdom
Test Product(s); Dosage Regimen; Route of Administration	SAD Phase 25 mg or placebo 100 mg or placebo 300 mg or placebo 500 mg or placebo 800 mg or placebo; subcutaneous injection MD Phase (Off statin co- medication) 300 mg monthly x2 or placebo 500 mg monthly x2 or placebo 125 mg QWx4 or placebo 250 mg Q2Wx2 or placebo; subcutaneous injection
Number of Subjects	• SAD Phase 24 subjects • MD Phase 45 subjects
Healthy Subjects or Diagnosis of Patients	Healthy subjects with elevated serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening
Treatment Duration	Up to 180 days

Supplemental information (Source, CSR)

SAD: Pharmacokinetic results

Table 7 Summary of PK parameters following SAD (Source; Table 3, 2.7.2)

Dose (N)[a]	C_{max} ng/mL (SD)	T_{max}[b] ng/mL (Min-Max)	AUC_{0-inf} h*ng/mL (SD)	AUC_{0-24} h*ng/mL (SD)	CL/F L/h (SD)	V_z/F L (SD)	$t_{½}$ h (SD)	fe % (SD)
25 mg (N=3)	39.8 (12.3)	1.00 (0.50-4.00)	615[c] (NC)	470 (88.1)	40.6[c] (NC)	371[c] (NC)	6.32[c] (NC)	9.48 (2.98)
100 mg (N=3)	226 (33.9)	4.00 (0.50-4.00)	3124[c] (NC)	2804 (214)	32.0[c] (NC)	307[c] (NC)	6.64[c] (NC)	13.2 (2.68)
300 mg (N=3)	407 (43.7)	4.00 (2.00-4.00)	7576 (510)	6674 (524)	39.7 (2.62)	421 (48.8)	7.34 (0.62)	13.8 (2.97)
500 mg (N=3)	4039 (4945)	8.02 (0.50-12.00)	16,136[c] (NC)	16,985 (4925)	31.0[c] (NC)	241[c] (NC)	5.40[c] (NC)	31.2 (8.66)
500 mg (N=2)[d]	689, 1709	8.02, 12.00	NC	12,841, 22,430	NC	NC	NC	25.2, 27.2
800 mg (N=6)	1798 (565)	4.00 (0.50-12.00)	34,361 (10,940)	29,242 (8022)	24.9 (6.90)	234 (91.5)	6.32 (1.14)	20.6 (3.75)

SAD: Pharmacodynamics

Table 8 Summary of PCSK9 and LDL-C reduction* from baseline following SAD (Source; Table 14 and 15, CSR)

		ALN-PCSSC				
	Placebo (N=6)	**25 mg (N=3)**	**100 mg (N=3)**	**300 mg (N=3)**	**500 mg (N=3)**	**800 mg (N=6)**
PCKS9 percent reduction						
Day 84						
N	5	2	3	3	3	6
Mean (SD) percent reduction	0.1 (14.3)	47.3 (7.2)	29.9 (12.9)	72.6 (12.1)	68.7 (9.8)	72.2 (8.5)
Day 180						
N	NA	NA	2	3	2	4
Mean (SD) percent reduction	NA	NA	15.7 (0.2)	47.8 (24.8)	70.3 (6.6)	74.3 (13.2)
Mean (SD) percent reduction at individual nadir[a]	29.4 (9.53)	54.3 (4.75)	48.9 (27.37)	77.9 (3.49)	75.7 (11.75)	82.3 (4.85)
Mean (SD) percent reduction at group nadir[b]	17.5 (19.56)	51.2 (0.56)	41.7 (21.28)	74.0 (0.57)	77.7 (1.28)	79.4 (3.27)
Time to group nadir, days	35	42	42	42	112	98

* measured using ELISA (enzyme-linked immunosorbent assay)

		ALN-PCSSC				
	Placebo (N=6)	**25 mg (N=3)**	**100 mg (N=3)**	**300 mg (N=3)**	**500 mg (N=3)**	**800 mg (N=6)**
LDL-C percent reduction						
Day 84						
N	5	2	3	3	3	5
Mean (SD) percent reduction	7.5 (15.6)	27.9 (11.4)	36.6 (6.1)	48.4 (19.0)	47.6 (15.2)	41.9 (12.3)
Day 180						
N	NA	NA	2	3	2	4
Mean (SD) percent reduction	NA	NA	26.3 (2.1)	47.8 (0.5)	37.9 (21.7)	35.2 (16.8)
Mean (SD) percent reduction at individual nadir[a]	18.7 (5.61)	34.5 (8.62)	42.9 (15.35)	55.0 (10.03)	55.1 (19.93)	59.2 (5.00)
Mean (SD) percent reduction at group nadir[b]	8.6 (18.07)	27.9 (11.43)	38.7 (2.07)	48.4 (18.99)	55.1 (24.46)	51.8 (8.44)
Time to group nadir, days	98	84	140	84	98	35

* LDL-C was measured using a ultracentrification (beta-quantification)

MD: Pharmacokinetics

Table 9 Summary of inclisiran PK parameters following MD

Dose (N)[a]	Statin Status	C_{max} ng/mL (SD)	T_{max}[b] ng/mL (Min-Max)	$AUC_{0\text{-}inf}$ h*ng/mL (SD)	$AUC_{0\text{-}24}$ h*ng/mL (SD)	CL/F L/h (SD)	V_d/F L (SD)	$t_{½}$ h (SD)	fe % (SD)
First Dose									
125 mg QW (N=6)	Off	292 (99.1)	4.00 (2.00 - 12.00)	4138 (717)	3813 (623)	30.9 (5.30)	244 (101)	5.36 (1.57)	15.0 (3.19)
250 mg Q2W (N=6)	Off	485 (60.8)	4.00 (0.50 - 8.10)	9174 (2415)	7415 (1308)	28.8 (8.67)	389 (186)	9.06 (1.86)	12.5 (3.02)
300 mg Q4W (N=6)	Off	809 (425)	6.00 (0.50 - 12.00)	12,823 (2039)	10,068 (3196)	23.8 (3.84)	130 (44.3)	3.75 (1.11)	20.9 (5.97)
300 mg Q4W (N=4)	On	928 (375)	4.00 (2.00 - 8.00)	13,415 (1748)	12,286 (4406)	22.6 (2.92)	334 (408)	11.32 (14.7)	14.9 (7.19)
500 mg Q4W (N=6)	Off	1682 (808)	5.00 (0.50 - 8.00)	18,226 (5386)	23,287 (12,538)	29.0 (7.10)	260 (132)	6.12 (2.51)	21.7 (3.33)
500 mg Q4W (N=5)	On	1783 (910)	8.00 (0.50 - 8.00)	19,175, 22,226[b]	21,813 (7340)	26.1, 22.5[b]	153, 417[b]	4.07, 12.9[b]	15.7 (6.45)
Last Dose									
125 mg QW (N=6)	Off	244 (37.9)	8.00 (4.00 - 12.00)	4489 (798)[d]	3855 (483)	18.58 (4.10)	212 (85.4)	7.77 (1.91)	14.1 (1.70)
250 mg Q2W (N=6)	Off	457 (70.1)	3.01 (0.50 - 8.00)	17,753[d] (4287)	7450 (1125)	14.8 (3.45)	274 (82.4)	13.2 (6.93)	16.5 (1.90)
300 mg Q4W(N=6)	Off	750 (53.2)	8.00 (2.00 - 12.00)	15,586[d] (3081)	9444 (2613)	19.9 (3.95)	116, 93.3[c]	3.63, 3.54[b]	19.1 (5.93)
300 mg Q4W (N=3)	On	1252 (936)	6.00 (4.00 - 8.00)	18,860[d] (3965)	14,183 (6922)	16.4 (3.48)	165 (159)	7.36 (6.51)	16.9 (8.33)
500 mg 4W (N=6)	Off	1449 (492)	8.00 (4.00 - 12.00)	33,679[d] (16,861)	21,252 (8914)	16.1 (6.80)	120, 121[c]	3.49, 5.66[c]	20.97 (5.43)
500 mg Q4W (N=5)	On	1736 (647)	4.00 (0.50 - 8.00)	37,347[d] (6826)	22,395 (7150)	13.8 (2.95)	77.3, 87.0[c]	2.87, 4.99[c]	24.0 (15.9)

MD: Pharmacodynamics

Table 10 Summary of PCSK9 and LDL-C reduction* from baseline following MD (Source; Table 17 and 18, CSR)

	Placebo		ALN-PCSSC					
	With Statin (N=3)	Without Statin (N=8)	300 mg With Statin (N=3)	300 mg Without Statin (N=6)	500 mg With Statin (N=5)	500 mg Without Statin (N=6)	125 mg QW Without Statin (N=6)	250 mg Q2W Without Statin (N=6)
PCSK9 percent reduction								
84 days after last dose								
N	3	5	3	6	5	6	6	6
Mean (SD) percent reduction	0.5 (33.4)	-1.3 (36.7)	78.1 (3.9)	70.6 (10.9)	82.6 (9.5)	74.2 (8.3)	75.0 (7.5)	78.0 (6.8)
180 days after last dose								
N	NA	NA	1	6	4	6	6	6
Mean (SD) percent reduction	NA	NA	69.7 (NC)	62.6 (10.7)	75.9 (10.8)	72.3 (14.3)	63.3 (14.5)	67.4 (9.9)
Mean (SD) percent reduction at individual nadir[a]	42.4 (3.76)	25.3 (20.51)	86.1 (2.06)	80.4 (4.92)	88.5 (3.67)	81.5 (5.73)	83.8 (2.13)	82.7 (2.81)
Mean (SD) percent reduction at group nadir[b]		6.1 (NC)	83.6 (4.06)	73.1 (6.31)	85.2 (1.83)	79.9 (5.35)	80.3 (4.73)	79.4 (3.83)
Time to group nadir, days		91	56	56	84	84	77	35

	Placebo		ALN-PCSSC					
	With Statin (N=3)	Without Statin (N=8)	300 mg With Statin (N=3)	300 mg Without Statin (N=6)	500 mg With Statin (N=5)	500 mg Without Statin (N=6)	125 mg QW Without Statin (N=6)	250 mg Q2W Without Statin (N=6)
LDL-C percent reduction								
84 days after last dose								
N	3	5	3	6	5	6	6	6
Mean (SD) percent reduction	0.9 (33.3)	7.0 (11.6)	44.7 (21.2)	48.8 (9.0)	38.9 (13.6)	48.5 (14.2)	41.8 (8.8)	50.0 (10.5)
180 days after last dose								
N	NA	NA	1	6	4	6	6	6
Mean (SD) percent reduction	NA	NA	30 (NC)	44.3 (12.8)	44.2 (26.2)	45.3 (16.1)	34.5 (5.8)	42.1 (16.6)
Mean (SD) percent reduction at individual nadir[a]	27.7 (13.19)	19.2 (9.68)	53.8 (19.78)	64.4 (13.22)	59.9 (18.14)	56.2 (14.59)	52.1 (4.75)	60.4 (11.02)
Mean (SD) percent reduction at group nadir[b]		16.3 (NC)	46.7 (18.29)	55.7 (13.20)	48.9 (23.77)	51.9 (14.97)	44.8 (4.07)	54.8 (7.77)
Time to group nadir, days		105	70	70	140	140	63	49

Reviewer's comments: Study design and results were acceptable to support labeling as follows:

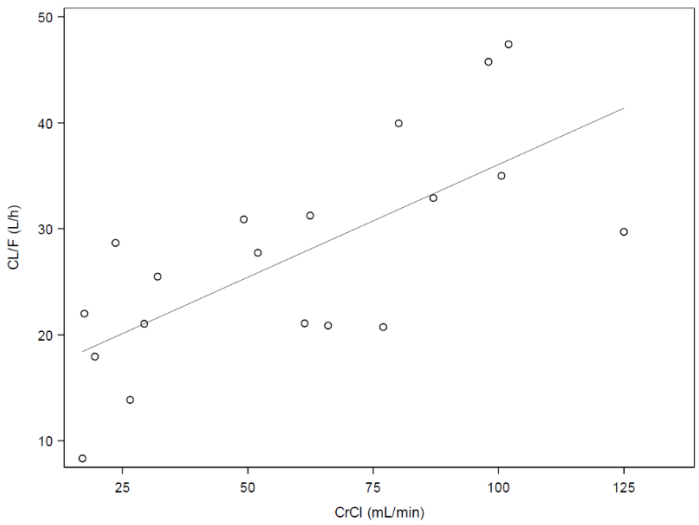
- Inclisiran PK was proportional to dose in SAD or MD
- There was no apparent accumulation
- There was significant temporal dissociation between PK and PD
- Although there were subjects with or without statins (i.e., atorvastatin or simvastatin), sample size was small to fully evaluate the effect of statins on inclisiran PK and PD, or vice versa.

4.3.2. ORION-7 (Renal impairment)

Key study design (Source, Table 1, Module 2.7.6)

Primary Objective(s)	To quantify the effect of different degrees of renal impairment on the PK of inclisiran, and to assess safety and tolerability in order to develop dosing recommendations for subjects with renal impairment.
Study Design and Type of Control	A single-dose, open-label, parallel-group study to assess the PK of Inclisiran in subjects with renal impairment compared to subjects with normal renal function.
Location	New Zealand
Test Product(s); Dosage Regimen; Route of Administration	300 mg inclisiran sodium; single dose; subcutaneous injection
Number of Subjects	31
Healthy Subjects or Diagnosis of Patients	Subjects with normal renal function and subjects with mild, moderate and severe renal impairment
Treatment Duration	Day 60 (End of study) or additional follow up till LDL-C levels of subjects returned to within 50% of the absolute reduction from Baseline up to Day 180.

Supplemental information (Source, CSR)



(CL/F=14.8+0.213*CLcr).

Figure 16 Relationship between CLcr and CL/F (Source; Figure 3, CSR)

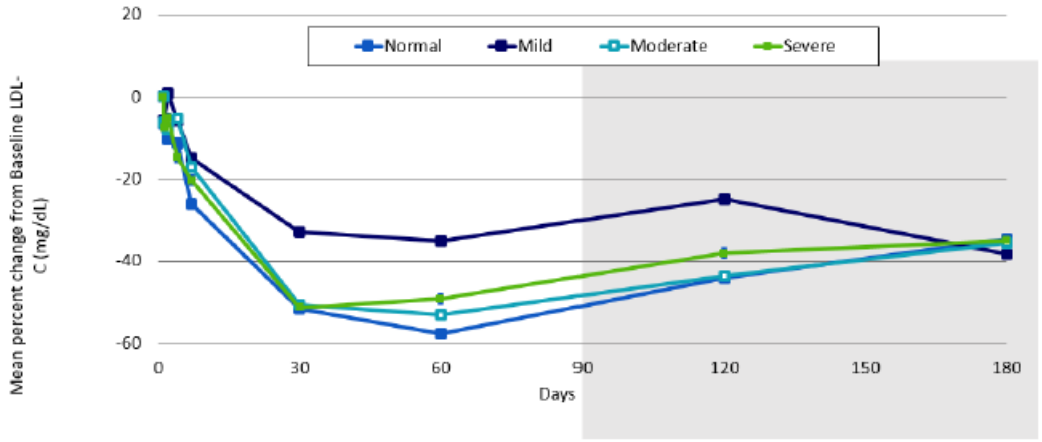


Figure 17 **Mean percent change from baseline in LDL-C by renal sub-groups (Source; Figure 6, CSR)**

Table 11 **Summary of PK parameters following 300 mg in ORION-7 (Source; Table 8, CSR)**

Group	Healthy			Mild Impairment			Moderate Impairment			Severe Impairment		
Parameters	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Plasma												
C_{max}, ng/mL	8	421	137	8	987	338	8	897	513	7	1760	1550
T_{max}, h[a]	8	8.00 (1.00, 12.00)		8	4.00 (4.00, 8.00)		8	8.00 (0.50, 12.00)		7	4.00 (2.00, 8.08)	
AUC_{0-24}, h.ng/mL	8	6170	1290	8	10900	2740	8	12400	5590	7	17000	9380
AUC_{0-48}, h•ng/mL	8	7300	1420	8	11700	2820	8	13800	4970	7	18200	8800
AUC_{0-t}, h•ng/mL	8	7030	1460	8	10900	2740	8	12300	3210	7	17700	8850
AUC_{0-inf}, h•ng/mL[b]	4	7890	1780	6	11600	3150	3	10800	1030	6	18800	9230
λ_z, 1/h[b]	4	0.0715	0.0153	6	0.146	0.0379	3	0.0973	0.0170	6	0.149	0.0892
$t_{1/2}$, h[b]	4	10.1	2.31	6	5.00	1.20	3	7.28	1.35	6	6.76	4.96
CL/F, L/h[b]	4	39.5	8.52	6	27.8	8.11	3	28.0	2.71	6	18.6	7.03
Vd/F, L[b]	4	553	29.7	6	208	98.1	3	298	84.4	6	215	228
Urine												
Ae, mg	8	40.0	10.8	8	41.2	7.29	8	20.0	16.1	7	9.49	6.58
Fe, %	8	13.3	3.62	8	13.7	2.43	8	6.68	5.38	7	3.16	2.19
CL_R, L/h	8	5.57	1.31	8	3.72	1.06	8	1.46	0.956	7	0.526	0.275

Reviewer's comments: Study design and results were acceptable to support labeling as follows:

- Inclisiran PK was increased with the renal impairment
- There was no sub-group of ESRD with dialysis including hemodialysis.
- There was significant temporal dissociation between PK and PD
- There was no clinically meaningful difference in reduction of PDs among sub-groups

4.3.3. ORION-6 (Hepatic impairment)

Key study design (Source, Table 1, Module 2.7.6)

Primary Objective(s)	To quantify the effect of different degrees of hepatic impairment Child-Pugh A and B compared to normal subjects on the PK and the PD of inclisiran in order to develop dosing recommendations for subjects with hepatic impairment.
Study Design and Type of Control	A single-dose, open label, parallel-group study to assess the PK, PD and safety of Inclisiran in subjects with hepatic impairment compared to subjects with normal hepatic function.
Location	US
Test Product(s); Dosage Regimen; Route of Administration	300 mg inclisiran sodium; single dose; subcutaneous injection
Number of Subjects	28
Healthy Subjects or Diagnosis of Patients	Subjects with mild, moderate, and normal hepatic function
Treatment Duration	180 days

Supplemental information (Source, CSR)

Table 12 Summary of PK parameters following 300 mg in ORION 6 (Source; Table 1, CSR)

Group	**Normal**			**Mild Impairment**			**Moderate Impairment**		
Parameters	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Plasma									
C_{max}, ng/mL	12	567	306	10	574	188	6	1160	526
T_{max}, h[a]	12	4.00 (0.50, 8.00)		10	6.00 (1.00, 12.00)		6	5.00 (2.00, 8.12)	
AUC_{last}, h·ng/mL	12	7380	1890	10	9410	3140	6	14800	2590
AUC_{0-24}, h·ng/mL	12	6540	1750	10	8700	2890	6	14100	2480
AUC_{0-48}, h·ng/mL	12	7840	1920	10	10500	3440	6	16100	2380
AUC_{inf}, h·ng/mL	10 [b,c]	8020	2140	6 [d,e]	10900	3720	6	16000	2340
λ_z, 1/h	10 [b,c]	0.0890	0.0400	6 [d,e]	0.0922	0.0303	6	0.120	0.0767
$t_{½}$, h	10 [b,c]	9.38	4.46	6 [d,e]	8.57	4.12	6	7.01	2.44
CL/F, L/h	10 [b,c]	37.6	9.27	6 [d,e]	29.1	11.0	6	18.1	2.44
V_d/F, L	10 [b,c]	490	215	6 [d,e]	340	148	6	183	71.3
Urine									
Ae, mg	12	50.1	14.0	10	54.4	15.5	6	85.0	20.3
Fe, %	12	17.6	4.94	10	19.2	5.45	6	29.9	7.16
CL_R, L/h	12	6.59	1.73	10	5.61	2.11	6	5.31	1.11

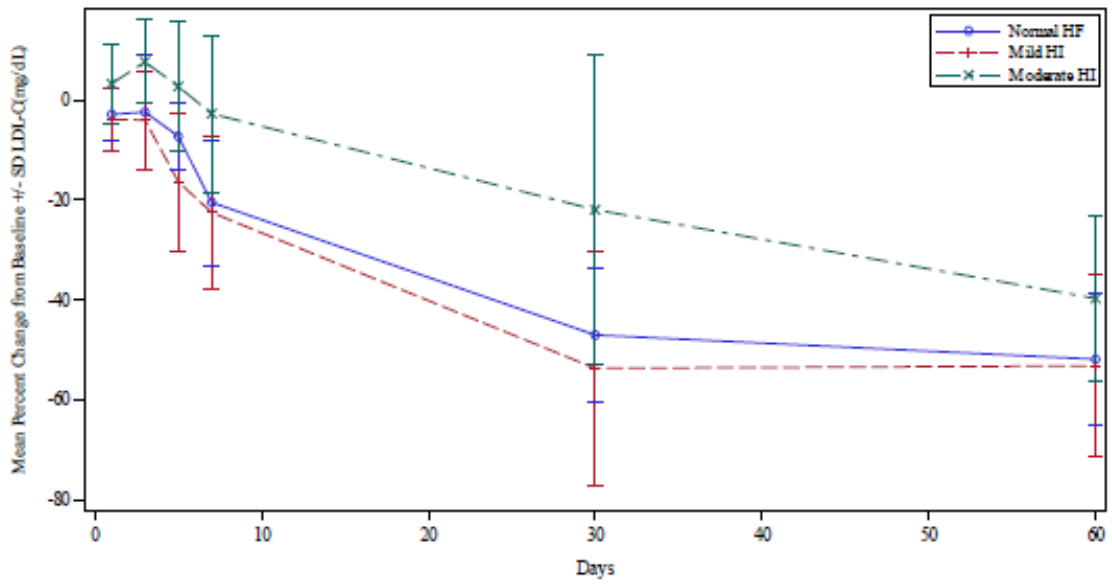


Figure 18 Mean (SD) percent change from baseline in LDL-C by hepatic sub-groups (Source; Figure 3, CSR)

Reviewer's comments: Study design and results were acceptable to support labeling as follows:

- Inclisiran PK was increased with the moderate hepatic impairment
- There was no sub-group with severe hepatic impairment
- There was significant temporal dissociation between PK and PD
- There was no clinically meaningful difference in reduction of PDs among sub-groups
- The baseline PCSK9 and LDL-C levels were lower in moderate hepatic impairment sub-group compared to those of normal sub-group.

4.3.4. ORION-12 (TQT Study)

Key study design (Source, Table 1, Module 2.7.6)

Primary Objective(s)	To assess the effect of a supratherapeutic dose of inclisiran on cardiac repolarization as assessed by the QTc interval corrected for HR using the QTcF.
Study Design and Type of Control	A randomized, double-blind, double-dummy, placebo- and positive-controlled, crossover study to assess the electrocardiographic effects of Inclisiran in healthy volunteers.
Location	US
Test Product(s); Dosage Regimen; Route of Administration	o 3 SC injections of 300 mg Inclisiran sodium and 1 placebo matched to moxifloxacin oral overencapsulated tablet o 3 SC injections of placebo solution (1.5 mL each) and 1 placebo moxifloxacin oral overencapsulated tablet o 3 SC injections of placebo solution (1.5 mL each) and moxifloxacin oral overencapsulated tablet 400 mg
Number of Subjects	48
Healthy Subjects or Diagnosis of Patients	Healthy subjects
Treatment Duration	30 days

Supplemental information (Source, CSR)

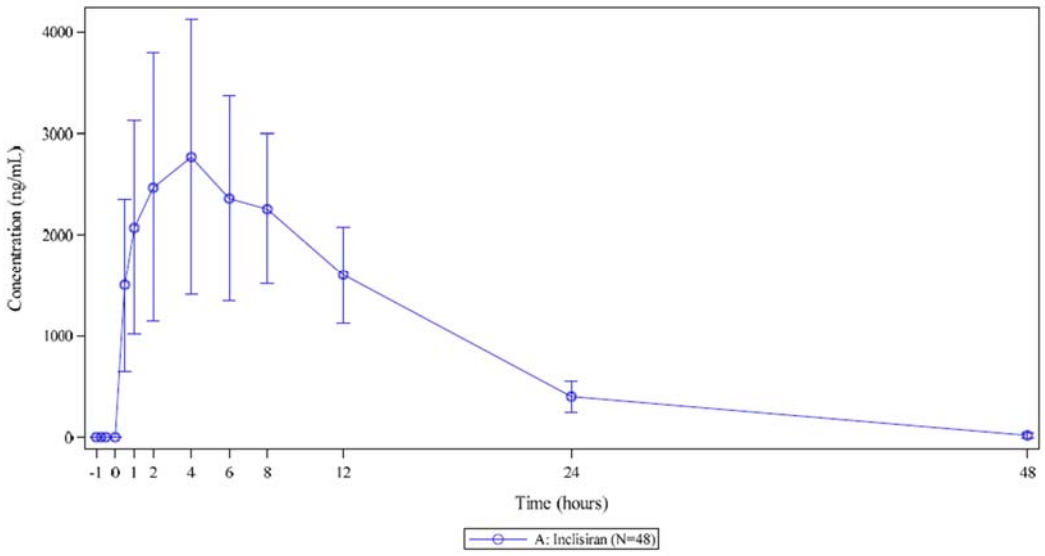


Figure 19 Inclisiran mean (SD) concentration-time profile following 900 mg (Source, Figure 14.2.1.1, CSR)

Table 13 Summary of PK parameters following 900 mg in ORION-12 (Source; Table 10, CSR)

		A: Inclisiran (N=48)	
Parameter (units)	n	Geometric Mean	Geometric CV%
AUC_{0-24} (h*ng/mL)	48	34890	29.1
AUC_{0-48} (h*ng/mL)	44	38190	25.8
AUC_{0-t} (h*ng/mL)	48	37030	24.3
AUC_{0-inf} (h*ng/mL)	42	39110	24.4
C_{max} (ng/mL)	48	2643	43.6
T_{max}[a] (h)	48	4.003[a]	0.507 - 12.0[b]
$t_{1/2}$ (h)	42	5.834	28.8
V_d/F (L)	42	183.3	47.7
CL/F (L/h)	42	21.78	24.4

Reviewer's comments: Study design and results were acceptable to support labeling as follows:

- Inclisiran PK was adequately characterized following supra-therapeutic dose.
- Inclisiran exposure following 900 mg covered potential worst situation, which was with the severe renal impairment
- There was no meaningful impact of inclisiran on QTc (See review by the QT-IRT review team dated 5/13/2020 in DARRTS)

4.3.5. Efficacy sub-group analysis – Efficacy Pool 1 (Source, Figure 8, Module 2.5)

(Note; Efficacy Pool 1 - pooled data of all 3 Phase 3 trials, ORION-9, ORION-10 and ORION-11 (N=3660), The applicant made a separate pooled data analysis for ASCVD or ASCVD risk equivalent (Efficacy Pool 2; ORION-10 and ORION-11, N=3178)).

Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C	95% CI
Overall				
Overall	1833	1827	-54.1	-56.1 to -52.0
Sex				
Male	1226	1244	-53.8	-56.2 to -51.3
Female	607	583	-54.8	-58.5 to -51.1
Age <65 yr or ≥65 yr				
<65 yr	853	884	-54.3	-57.5 to -51.2
≥65 yr	980	943	-53.7	-56.3 to -51.1
Age <75 yr or ≥75 yr				
<75 yr	1593	1575	-54.0	-56.2 to -51.8
≥75 yr	240	252	-55.0	-59.7 to -50.3
Body mass index				
≤29.7	942	888	-51.6	-54.3 to -49.0
>29.7	891	937	-56.8	-59.8 to -53.7
Race				
White	1670	1708	-54.2	-56.3 to -52.1
Black	130	102	-53.6	-63.0 to -44.1
Other	33	17	-49.8	-75.4 to -24.3
Baseline statin treatment				
On statin	1686	1675	-54.5	-56.7 to -52.4
Not on statin	147	152	-48.8	-54.0 to -43.7
Intensity of statin treatment				
High intensity statin	1356	1345	-54.6	-57.1 to -52.1
Not on high intensity statin	477	482	-52.7	-56.1 to -49.3
Lipid management treatment (LMT)				
Any statin	1686	1675	-54.5	-56.7 to -52.4
Other LMT but no statin	75	62	-53.9	-61.5 to -46.2
No LMT	72	90	-45.6	-52.8 to -38.4
Metabolic disease				
Diabetes	687	631	-56.1	-59.7 to -52.5
Metabolic syndrome	499	526	-56.2	-60.0 to -52.4
Neither	647	670	-50.6	-53.8 to -47.3
Risk category				
ASCVD	1552	1555	-55.3	-57.5 to -53.1
ASCVD equivalent	281	272	-47.1	-52.2 to -42.0
Renal function (eGFR - Cockcroft Gault)				
Normal	996	1020	-54.1	-56.9 to -51.3
Mild impairment	637	600	-53.3	-56.6 to -49.9
Moderate impairment	196	202	-56.9	-63.2 to -50.6
Baseline triglycerides in mg/dL				
≤130	918	914	-52.2	-55.0 to -49.4
>130	915	913	-55.9	-58.8 to -53.0
Baseline LDL-C in mg/dL				
≤100	927	925	-61.1	-64.2 to -58.1
>100	906	902	-46.9	-49.5 to -44.3
Baseline LDL-C quartiles in mg/dL				
≤82	455	482	-65.2	-70.1 to -60.4
>82 - ≤100	472	443	-56.9	-60.5 to -53.3
>100 - ≤129	434	465	-50.7	-54.4 to -47.1
>129	472	437	-43.1	-46.7 to -39.6
Ethnicity				
Hispanic or latino	120	116	-43.6	-52.1 to -35.0
Not hispanic or latino	1713	1711	-54.8	-56.9 to -52.7
Geographic region				
North America	826	823	-56.4	-59.4 to -53.4
Europe	859	854	-51.1	-54.2 to -48.1
South Africa	148	150	-57.6	-64.0 to -51.3

4.3.6. Statin concentrations observed in Phase 3 trial (ORION-10)

Brief description of PK data and analysis: PK analysis was based on available concentration levels of atorvastatin (40 or 80 mg) and rosuvastatin (20mg or 40 mg) collected at Day 1, Day 450 and Day 510. One blood sample was drawn at each visit for subjects receiving inclisiran or placebo injection. PK collection was done on Day 1 (baseline before initiation of treatment), Day 450 (prior to last inclisiran dosing during maintenance dosing) and Day 510 (60 days after the last inclisiran dosing).

Population PK models could not be developed with the limited numbers of statin PK samples collected per subject (i.e., 1 sample per visit) in the study, therefore the effects of inclisiran on the PK of statins were assessed by comparing the observed statin concentrations from subjects receiving inclisiran versus placebo, along with the expected concentrations simulated using published population PK models.

Table 14 Summary of observed atorvastatin (top panel) or rosuvastatin (bottom panel) concentrations

	Day 450			Day 510		
	Placebo	Inclisiran		Placebo	Inclisiran	
	n (n BLQ) Arith. Mean GeoMean	n (n BLQ) Arith. Mean GeoMean	p-value GeoMean Ratio(%) 90%CI	n (n BLQ) Arith. Mean GeoMean	n (n BLQ) Arith. Mean GeoMean	p-value GeoMean Ratio(%) 90%CI
Overall	163 (26) 10.5 (18.1) 4.58 (307)	137 (29) 12.1 (24.8) 4.81 (386)	0.531 105 (74.9, 147)	157 (23) 10.6 (19.3) 4.74 (282)	135 (27) 14.3 (32.6) 4.91 (394)	0.244 104 (74.1, 145)
0 – <6 h	41 (6) 21.1 (29.7) 7.63 (509)	28 (2) 37.8 (43.3) 18.4 (363)	0.0831 241 (114, 511)	39 (4) 20.4 (32.0) 7.35 (381)	28 (4) 47.4 (59.2) 22.9 (384)	0.0346 312 (150, 650)
6 – <12 h	30 (5) 10.5 (13.4) 7.21 (176)	31 (3) 7.30 (6.35) 5.54 (132)	0.239 76.9 (46.4, 127)	35 (5) 12.1 (15.7) 6.54 (264)	35 (3) 8.66 (10.0) 5.72 (151)	0.274 87.4 (51.0, 150)
12-<24 h	63 (9) 6.25 (8.66) 3.50 (224)	54 (16) 4.52 (10.3) 2.46 (276)	0.335 70.2 (43.0, 115)	59 (11) 5.99 (8.30) 4.11 (192)	46 (15) 4.17 (6.94) 2.67 (278)	0.223 64.9 (38.9. 108)
≥24 h	29 (6) 4.63 (6.98) 2.42 (300)	24 (8) 5.26 (10.9) 2.09 (472)	0.809 86.4 (35.4, 211)	24 (3) 3.82 (5.11) 2.00 (245)	26 (5) 4.44 (10.6) 1.65 (259)	0.790 82.9 (39.8, 173)

	Day 450			Day 510		
	Placebo	Inclisiran		Placebo	Inclisiran	
	n (n BLQ) Arith. Mean GeoMean	n (n BLQ) Arith. Mean GeoMean	p-value GeoMean Ratio(%) 90%CI	n (n BLQ) Arith. Mean GeoMean	n (n BLQ) Arith. Mean GeoMean	p-value GeoMean Ratio(%) 90%CI
Overall	63 (15) 11.9 (14.9) 9.75 (164)	54 (17) 11.4 (17.2) 11.6 (112)	0.863 119 (81.6, 174)	66 (13) 11.9 (13.1) 9.72 (140)	56 (17) 11.7 (14.6) 9.92 (226)	0.939 102 (67.6, 154)
0 – <6 h	8 (5) 11.3 (16.4) 29.3 (30.7)	9 (1) 23.6 (34.8) 16.0 (122)	0.362 54.5 (18.9, 157)	10 (3) 16.9 (19.6) 18.9 (87.0)	11 (1) 19.7 (22.8) 8.45 (859)	0.759 44.7 (10.5, 191)
6 – <12 h	15 (1) 10.3 (4.97) 10.2 (44.3)	14 (2) 15.0 (11.3) 14.7 (70.3)	0.175 143 (100, 205)	19 (4) 8.68 (7.99) 7.78 (136)	11 (2) 13.1 (12.3) 10.4 (196)	0.300 134 (60.0, 301)
12-<24 h	30 (5) 14.4 (16.8) 10.1 (213)	25 (13) 5.26 (6.77) 9.68 (57.4)	<0.01 95.9 (49.2, 187)	29 (5) 12.7 (12.3) 10.9 (121)	29 (12) 8.44 (9.95) 10.8 (115)	0.150 99.1 (60.1, 163)
≥24 h	10 (4) 7.53 (18.3) 4.36 (258)	6 (1) 10.6 (12.2) 6.21 (406)	0.698 143 (25.5, 797)	8 (1) 10.1 (16.1) 5.39 (223)	5 (2) 9.59 (16.9) 8.89 (208)	0.954 165 (30.1, 904)

(Source; Table 28 and 29, CSR)

4.3.7. Pharmacometrics Review

Population PD analyses (Module 5.3.5.3.)

There was temporal dissociation between PK and PD as inclisiran concentrations were not detectable between 24 and 48 hours following most single doses and PD changes lasted for months. A population PD model with abbreviated PK was considered to characterize the observed temporal dissociation between PK and PD as follows (Figure 20);

- A hypothetical liver effect compartment
- PCSK9 compartment with zero-order synthesis rate (KsynP) and first-order degradation rate (KdegP), and the link between the liver effect compartment and KsynP by a maximum inhibitor effect (Imax) model
- LDL-C compartment with zero-order synthesis rate (KsynL) and the first-order degradation rate (KdegL), and the link between PCSK9 and KdegL by the second Imax model.

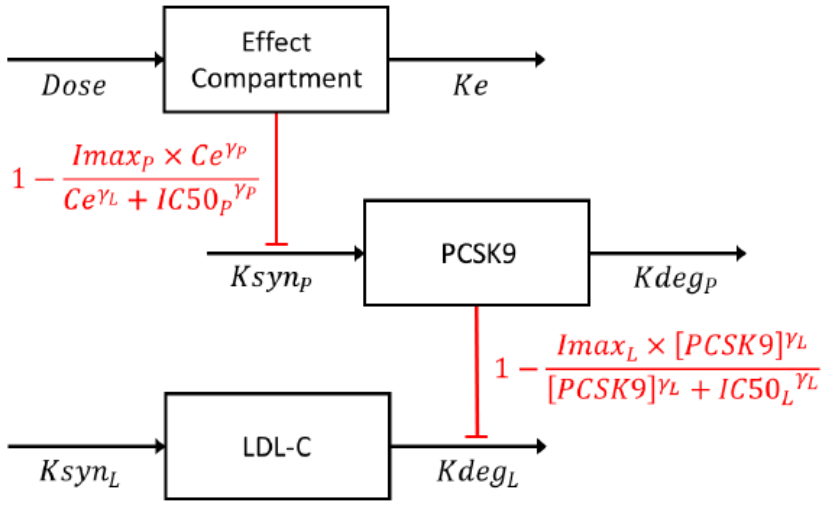


Figure 20 Schematic summary of the population PD model
Source; Figure 2, Module 5.3.5.3.

The various structural population PD models were evaluated in the model development based on available observed datasets (Table 15). The final model was selected using conventional model evaluation approaches including goodness-of-fits and visual predictive checks (Table 16).

Among 120 covariates available for the covariate analyses, the effect of covariates with clinical significance (i.e., age, gender, body weight, patient populations (ASCVD, HeFH), baseline (PCSK9, LDL-C), statins, CLcr) on the meaningful PD model parameters (i.e., IC50P, ImaxP, IC50L, ImaxL) were evaluated and determined to retain in the full covariate PD model (Table 17). The final model performance was evaluated by conventional sensitivity analysis.

Table 15 Dataset used to develop the structural population PD modeling

Study	Treatment	Overall Subjects (Excluded Subjects – Criteria #1/ (Excluded Subjects – Criteria #2)	Overall Observations (Excluded Observations - Criteria #1/ Excluded Observations - Criteria #2)	
			PCSK9	LDL-C
Phase I ALN-PCSSC-001	Placebo	18 (0/0)	286 (0/0)	287 (0/0)
	Active	51 (0/0)	1027 (0/0)	1025 (0/0)
Phase I ORION-6	Active	28 (1/0)	250 (9/0)	309 (12/0)
Phase I ORION-7	Active	31 (0/0)	216 (0/0)	275 (0/0)
Phase I ORION-12	Placebo	48 (0/0)	253 (0/0)	253 (0/0)
	Active		125 (0/0)	125 (0/0)
Phase II ORION-1	Placebo	127 (0/0)	1457 (1/0)	1458 (0/0)
	Active	370 (2/0)	5235 (48/0)	52331 (45/0)
Phase II ORION-3	Active	284 (1/0)	2696 (10/0)	3367 (14/0)
Phase III ORION-9	Placebo	240 (2/0)	1175 (12/0)	2119 (18/0)
	Active	241 (0/0)	1184 (1/1)	2135 (0/0)
Phase III ORION-10	Placebo	778 (2/1)	5794 (31/21)	6534 (13/4)
	Active	781 (4/3)	5915 (20/12)	6662 (23/14)
Phase III ORION-11	Placebo	804 (0/0)	3867 (2/2)	6993 (2/2)
	Active	811 (3/1)	3869 (12/3)	6988 (24/7)
Total	Placebo	1967 (4/1)	12,832 (46/23)	17,644 (33/6)
	Active	2361 (10/4)	20,517 (100/16)	26,117 (118/21)

Source: Appendix 1, Section 11.3

Note 1: Exclusion criteria #1: 1) overall time profiles of PD measurements if PCSK9 at baseline >1200 ng/mL and/or if LDL-C at baseline >400 mg/dL, 2) PCSK9 >1200 ng/mL at any time, 3) LDL-C >400 mg/dL at any time, and 4) treatment deviation with inconsistency in PD profiles.

Exclusion criteria #2: 1) overall time profiles of PD measurements if PCSK9 at baseline >2000 ng/mL, 2) PCSK9 >2000 ng/mL at any time, 3) LDL-C >600 mg/dL at any time, and 4) treatment deviation with inconsistency in PD profiles.

Note 2: Interim structural population PD model was fitted on all PD data from Studies ALN-PCSSC-001, ORION-7, and ORION-1; structural population PD model, full covariate PD model, and reduced covariate PD model were fitted on PD data from all studies based on exclusion criteria #1; and final population PD model was fitted on PD data from all studies based on exclusion criteria #2.

Note 3: Subjects in active group had at least one PD sample collected after inclisiran dose.

Abbreviations: LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; PD=pharmacodynamic.

Source: Table 3, Module 5.3.5.3.

Table 16 Summary of parameter estimates of the final structure model

Parameters	Estimates/ Variance (%IIV)	%RSE	95% CI	Shrinkage (%)
Ke (mg/d)	0.00711	1.4%	0.00691-0.00730	
Base PCSK9 (ng/mL)	381	0.5%	377-384	
$Kdeg_P$ (/d)	0.163	3.1%	0.154-0.173	
$IC50_P$ (mg)	48.5	2.8%	45.8-51.1	
$Imax_P$	0.887	0.3%	0.883-0.892	
Base LDL-C (mg/dL)	108	0.5%	107-109	
$Ksyn_L$(mg/dL/d)	16.6	7.9%	14.1-19.2	
$IC50_L$ (ng/mL)	124	2.6%	118-131	
$Imax_L$	1 Fix		.	
Random effects[a]				
IIV on Ke	0.204 (47.6%)	7.9%	0.173-0.236	27.8%
IIV on Base PCSK9	0.0596 (24.8%)	3.4%	0.0557-0.0635	9.3%
IIV on $IC50_P$	0.560 (86.6%)	5.7%	0.497-0.622	18.0%
IIV on Base LDL-C	0.0994 (32.3%)	2.5%	0.0945-0.104	3.8%
IIV on $IC50_L$	1.23 (155.6%)	5.9%	1.09-1.38	22.2%
Residual error				
Proportional error PCSK9	20.3%	0.8%	0.199-0.206	7.5%
Additive error LDL-C (mg/dL)	6.61	5.0%	5.97-7.26	
Proportional error LDL-C	18.2%	1.9%	0.176-0.189	

Source: Appendix 2, Section 12.2.3

a For random effects, data for variance (%IIV) are presented instead of data for estimates.

Note 1: RSE and CI were derived with the variance-covariance matrix estimated by NONMEM.

Note 2: %IIV were calculated as sqrt(exp(variance) - 1).

Note 3: ETA values of subjects in placebo group were removed for the calculation of shrinkage for PD parameters related to drug effect (ie, $IC50_L$, $IC50_P$).

Abbreviations: CI=confidence interval; ETA=inter-individual random effect; $IC50_L$=concentration of PCSK9 to achieve 50% of maximum inhibitory effect on LDL-C; $IC50_P$=concentration in effect compartment to achieve 50% of maximum inhibitory effect on PCSK9; IIV=interindividual variability; $Imax_P$=maximum inhibitory of inclisiran effect on PCSK9 levels; $Imax_L$=maximum inhibitory effect of inclisiran on LDL-C levels; $Kdeg_P$=degradation rate of PCSK9; Ke=first-order rate constant for effect compartment; $Ksyn_L$=synthesis rate of LDL-C; $Ksyn_P$=synthesis rate of PCSK9; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; PD=pharmacodynamic; RSE=relative standard error.

Source: Table 6, Module 5.3.5.3.

Table 17 Summary of parameter estimates of the final full model with covariates

Parameters	Estimates	%RSE	95% CI	SS
Ke (mg/d)	0.00736	1.80	[0.00709, 0.00760]	
Base PCSK9 (ng/mL)	385	0.235	[383, 387]	
$Kdeg_P$ (/d)	0.166	2.79	[0.158, 0.175]	
$IC50_P$ (mg)	44.6	3.86	[41.5, 48.0]	
$Imax_P$	0.881	0.329	[0.876, 0.887]	
Base LDL-C (mg/dL)	104	0.237	[104, 105]	
$Ksyn_L$(mg/dL/d)	17.3	7.90	[15.0, 20.3]	
$IC50_L$ (ng/mL)	110	4.66	[100, 120]	
$Imax_L$	1 Fix	0	[1.00, 1.00]	
Covariate Effects				
Baseline LDL-C × (age [years]/65)$^{\theta}$	-0.123	-10.8	[-0.147, -0.0963]	SS
× (baseline observed LDL-C [mg/dL]/103)$^{\theta}$	0.777	1.47	[0.755, 0.799]	SS
Baseline PCSK9 × (baseline observed PCSK9 [ng/mL]/376)$^{\theta}$	0.722	1.52	[0.701, 0.740]	SS
$IC50_L$ × (age [years]/65)$^{\theta}$	-0.723	-20.7	[-1.04, -0.441]	SS
×(1+θ) for diabetic	-0.227	-19.1	[-0.310, -0.142]	SS
×(1+θ) for HeFH	0.218	56.6	[-0.0238, 0.478]	NS
×(1+θ) for Others	-0.181	-53.7	[-0.369, 0.0186]	NS
× (LDL-C [mg/dL]/103)$^{\theta}$	-0.435	-48.5	[-0.910, -0.0704]	SS
×(1+θ) for female	0.207	37.6	[0.0669, 0.386]	SS
×(1+θ) for absence of statin	0.545	25.5	[0.310, 0.852]	SS
× (triglycerides [mg/dL]/128)$^{\theta}$	-0.51	-17.8	[-0.708, -0.351]	SS
× (WT [kg]/86)$^{\theta}$	-0.627	-26.6	[-0.924, -0.301]	SS
$IC50_P$ × (BIL [mg/dL]/0.57)$^{\theta}$	-0.415	-6.69	[-0.470, -0.360]	SS
×(1+θ) for HeFH	1.07	14.2	[0.774, 1.39]	SS
× (baseline observed PCSK9 [ng/mL]/376.2)$^{\theta}$	-1.34	-4.58	[-1.45, -1.21]	SS
×(1+θ) for presence of statin	-0.163	-24.9	[-0.240, -0.0775]	SS
× (WT [kg]/86)$^{\theta}$	-0.445	-22.4	[-0.633, -0.242]	SS
Ke ×(1+θ) for HeFH	0.203	28.6	[0.104, 0.325]	SS
×(1+θ) for Others	-0.192	-27.2	[-0.292, -0.0926]	SS
× (WT [kg]/86)$^{\theta}$	0.375	16.3	[0.251 0.500]	SS

Source: Table 7, Module 5.3.5.3.

Simulation of PD changes was performed to support the proposed maintenance dose and dosing interval (i.e., 300 mg Q6M) in Phase 3 trials as there was observations following only initial and Day 90 dosing in the dose-finding trial (Phase 2) (Figure 21). Simulation was also performed to support labeling for a missed dose (Figure 22).

The applicant explored potential scenarios for a missed dose during the maintenance period; no missed dose, missed for 3 months continue the original schedule, or missed for 3 months and start over the dosing schedule (Table 18).

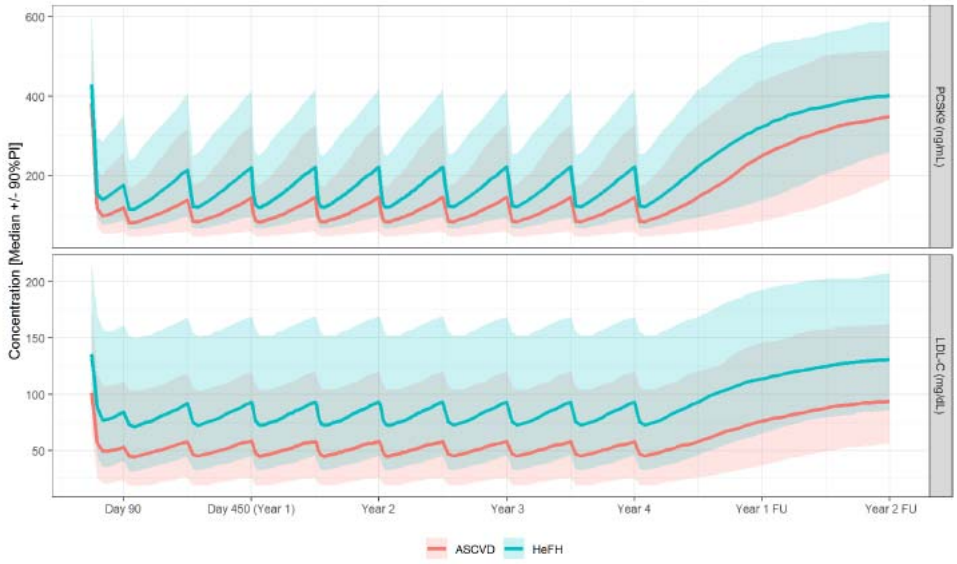


Figure 21 Simulated PD changes following the proposed dosing regimen in Phase 3 trials using the final population PD model
Source; Figure 15, Module 5.3.5.3.

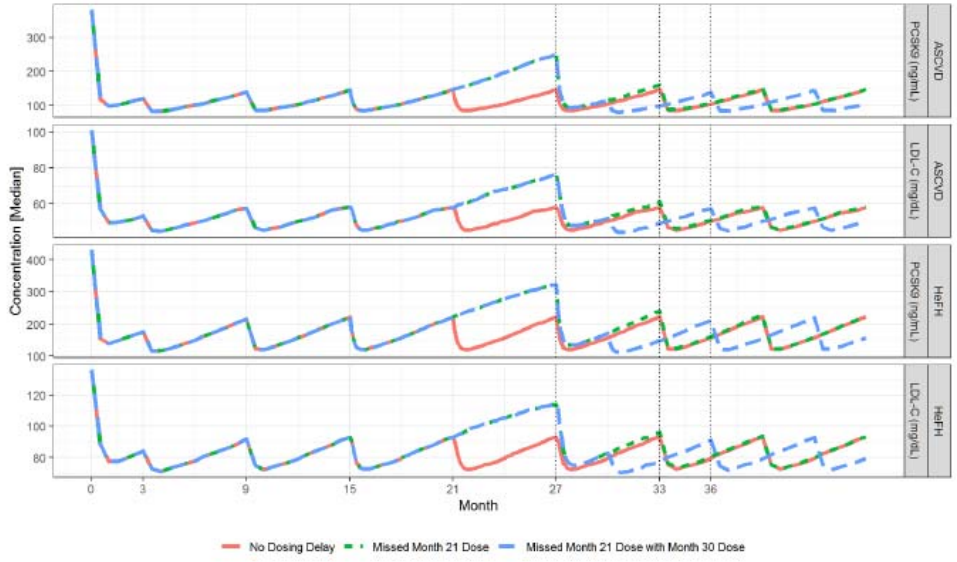


Figure 22 Simulated PD changes following with or without a missed dose for 6 months and potential scenarios
Source; Figure 19, Module 5.3.5.3.

Table 18 Descriptive summary of percent change from baseline of PCSK9 or LDL-C in simulation with time deviation at Month 21

		PCSK9 (ng/mL)		LDL-C (mg/dL)	
		Month 21+Time Deviation	Month 27	Month 21+Time Deviation	Month 27
ASCVD	**No dosing delay**				
	Mean (CV)	-57.8 (33.4%)	-57.8 (33.4%)	-41.6 (43.4%)	-41.5 (43.5%)
	Median [90% PI]	-61.0 [-82.1, -18.4]	-61.1 [-82.1, -18.4]	-42.2 [-69.9, -10.6]	-42.3 [-69.8, -10.5]
	One month dosing delay				
	Mean (CV)	-53.8 (38.3%)	-61.1 (29.1%)	-38.7 (47.4%)	-43.9 (40.3%)
	Median [90% PI]	-56.9 [-81.1, -13.8]	-64.1 [-82.8, -24.4]	-38.7 [-68.4, -8.21]	-45.1 [-71.1, -12.9]
	Two months dosing delay				
	Mean (CV)	-49.8 (43.5%)	-64.4 (24.9%)	-35.8 (51.8%)	-46.3 (37.4%)
	Median [90% PI]	-51.8 [-79.9, -9.87]	-67.8 [-83.4, -31.2]	-35.2 [-66.5, -6.12]	-47.6 [-72.0, -15.4]
	Three months dosing delay				
	Mean (CV)	-45.9 (49.0%)	-67.6 (20.9%)	-32.9 (56.5%)	-48.6 (35.0%)
	Median [90% PI]	-47.1 [-79.0, -7.10]	-70.9 [-84.0, -40.0]	-31.5 [-64.7, -4.96]	-49.9 [-73.7, -19.2]
HeFH	**No dosing delay**				
	Mean (CV)	-46.0 (44.6%)	-46.0 (44.7%)	-30.9 (57.6%)	-30.8 (57.7%)
	Median [90% PI]	-45.8 [-77.3, -12.7]	-45.6 [-77.3, -12.7]	-27.8 [-62.7, -6.16]	-27.8 [-62.6, -6.16]
	One month dosing delay				
	Mean (CV)	-41.5 (51.4%)	-49.9 (38.8%)	-27.9 (63.4%)	-33.4 (53.0%)
	Median [90% PI]	-40.4 [-75.6, -8.91]	-50.3 [-78.4, -17.9]	-24.4 [-60.5, -5.07]	-31.2 [-64.3, -7.58]
	Two months dosing delay				
	Mean (CV)	-37.3 (58.4%)	-54.0 (33.2%)	-25.1 (69.6%)	-36.1 (48.8%)
	Median [90% PI]	-35.0 [-73.2, -6.56]	-55.1 [-79.4, -23.1]	-20.4 [-58.5, -3.68]	-35.1 [-65.6, -8.94]
	Three months dosing delay				
	Mean (CV)	-33.4 (65.5%)	-58.3 (28.2%)	-22.6 (76.1%)	-38.8 (45.2%)
	Median [90% PI]	-30.3 [-70.7, -4.44]	-60.5 [-80.6, -28.9]	-17.7 [-56.4, -2.57]	-38.0 [-67.8, -11.4]

Reviewer's comments:

- The parameter estimates of the final structural model (Table 15) and the full model with covariates provided reasonable precision (%RSE) and shrinkage (Table 16).
- Simulation results were acceptable to support the proposed maintenance dose (300 mg Q6M, Figure 19) at the End-of-Phase 2 meeting as results reasonably showed PCSK9 and LDL-C reduction as expected from observations in early clinical trials.
- The simulation result indicates that efficacy is comparable between 'missed for up to 3 months and continue the original schedule' and 'missed for more than 3 months and restart the dosing schedule' (Table 18). Therefore, the proposed labeling based on the simulation is acceptable.

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/s/

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10/13/2020 11:20:08 AM

DOANH C TRAN
10/13/2020 11:36:00 AM