NOVARTIS

Sponsor

Novartis

Novartis Study Code

ALN-PCSSC-001

EudraCT Number

Not applicable

Swiss Authorization Date and Authorization number

Authorization Date: 09 September 2021
Authorization Number: 67836

Medicinal product name, including dosage strength and pharmaceutical form

The investigational drug ALN-PCSSC was to be supplied as a sterile, nominally 200 milligram/milliliter (mg/mL) solution for subcutaneous (SC) injection.

Active substance name

ALN-60212

Trial title as per latest protocol version, including all changes and short description

A Phase 1, Randomized, Single-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneously Administered ALN-PCSSC in Subjects with Elevated Low-Density Lipoprotein Cholesterol

Trial drug

ALN-PCSSC

Investigators

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Information on study centres

2 study centers in the United Kingdom

Publication, particularly title, publisher and year of publication

n/a

Trial duration

Date first subject enrolled (randomized): 09 December 2014
Date last subject last visit: 20 November 2015

Trial phase, trial type

Phase 1

Trial objectives

Primary objective(s)

- To evaluate the safety and tolerability of ALN-PCSSC when administered subcutaneously as a single dose or multiple doses to subjects with elevated low-density lipoprotein cholesterol (LDL-C)

Secondary objective(s)

- To characterize the pharmacokinetics (PK) of ALN-PCSSC
- To evaluate the pharmacodynamic (PD) effect of ALN-PCSSC on serum levels of LDL-C
- To evaluate the PD effect of ALN-PCSSC on plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9)

Exploratory Objective(s)

- To evaluate the change from baseline in lipid parameters and the lipoprotein profile
- To evaluate the PD effect of ALN-PCSSC when administered to subjects who were on or off statin co-medication

Test methods

This was a randomized, single-blind, placebo-controlled, single ascending dose (SAD) and multiple dose (MD) study of ALN-PCSSC when administered subcutaneously to subjects with elevated LDL-C, with or without statin co-medication. The study was designed to evaluate the safety, tolerability, PK, and PD of ALN-PCSSC in 2 phases: a SAD phase and an MD phase.
In addition to the planned cohorts, the protocol permitted the enrollment of up to 2 optional cohorts in both the SAD and MD (either on or off statins co-medication) phases. Three of these 4 optional cohorts were enrolled, including 1 cohort in the SAD phase to expand the 800 mg ALN-PCSSC cohort and 2 cohorts in the MD phase that examined alternative dose regimens (weekly [QW] and biweekly [Q2W] regimens) in subjects who were off statin co-medication.

Planned and actual number of analysed patients

Planned: Up to 76 subjects were expected to be enrolled in the study.

Actual:

• SAD phase cohorts: 24 subjects

• MD phase cohorts: 45 subjects

<u>Diagnosis and inclusion criteria</u>

Inclusion Criteria for All Subjects in the SAD and MD Cohorts

1. Male and female subjects, aged 18 to 60 years, inclusive; subjects in the MD cohorts may have been enrolled up to, and including, age 75.
2. Body mass index (BMI) between 18 and 30 kilogram/ meter square (kg/m^2), inclusive.
3. Serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening.
4. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
5. Adequate complete blood counts (CBCs) (if outside the reference range, CBC values that were not clinically relevant and were acceptable to the Investigator).
6. Female subjects must have been of non-childbearing potential:
   - Natural (spontaneous) postmenopausal defined as amenorrhea for 12 months without an alternative medical cause with a screening follicle-stimulating hormone (FSH) level >25 IU/L (or at the local laboratory levels for post menopause).
   - Premenopausal with irreversible surgical sterilization by bilateral oophorectomy or bilateral salpingectomy (with or without hysterectomy), but not tubal ligation, or hysterectomy at least 6 months before screening.
7. Male subjects must have used acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of study drug until 90 days following administration of the last dose of study drug. One of the following acceptable methods of contraception was utilized:
   - Condom and occlusive cap ([diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository).
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The subject's female partner used oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The subject's female partner used medically prescribed topically applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The subject's female partner had undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) must have been used.
   - The subject's female partner had undergone documented placement of an intrauterine device or intrauterine system. In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must have been used.
   - True abstinence: when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception.

Abstinent subjects had to agree to use 1 of the above-mentioned contraceptive methods if they started sexual relationships during the study and for up to 90 days after the last dose of study drug.

8. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent.
9. Non-smokers and non-nicotine users for at least 90 days before screening.

Additional Inclusion Criteria for Subjects in the SAD and Non-statin MD Cohorts

1. Healthy as determined by pre-study medical history, physical examination, clinical laboratory assessments, and 12-lead electrocardiogram (ECG).

Additional Inclusion Criteria for Subjects in the Statin MD Cohorts

1. On a stable dose of statin medication for ≥30 days before screening with no planned dose change during study participation.

<u>Information on study medication, particularly dosage, route of administration, batch number</u>

ALN-PCSSC is comprised of a synthetic, chemically modified small interfering RNA (siRNA) targeting PCSK9 mRNA with a covalently attached triantennary GalNAc ligand (ALN-60212) that is formulated in water. The investigational drug, ALN-PCSSC, supplied as a sterile 200-mg/mL solution for SC injection, batch B140356.

<u>Duration of treatment</u>

In the SAD phase of the study, subjects with LDL-C ≥2.6 mmol/L (≥100 mg/dL) who were not on statin medication were enrolled in a total of 6 cohorts. Each cohort was composed of 4 subjects randomized 3:1 to receive a single dose of ALN-PCSSC or placebo, respectively.

In the MD phase of the study, subjects with LDL-C ≥2.6 mmol/L (≥100 mg/dL) were enrolled in 6 cohorts (including 4 cohorts of subjects without statin co-medication and 2 cohorts of subjects with statin co-medication). Each cohort was composed of 8 subjects randomized 3:1 (in blocks of 4 subjects) to ALN-PCSSC or placebo, respectively. Subjects enrolled in the planned monthly cohorts received a total of 2 doses. Subjects enrolled in the optional cohorts in the MD phase received ALN-PCSSC or placebo according to a dosing regimen of QW for a total of 4 doses or Q2W for a total of 2 doses.

Subjects were screened from -45 to -2 days before first study drug administration in the MD phase. Eligible subjects were admitted to the clinical study site on Day -1 for continued eligibility checks and pretreatment assessments. Subjects were randomized on Day 0 of the residential period and received an initial dose of ALN-PCSSC or placebo. Subjects were discharged from the clinical study site on Day 1 after completing the 24-hour postdose follow-up assessments. Subjects in the monthly cohorts were re-admitted to the clinical study site on Day 27 for the second and final dose of ALN-PCSSC or

placebo on Day 28, and discharged on Day 29 after completing the 24-hour postdose follow-up assessments. Subjects in the QW cohort were re-admitted to the clinical study site on Day 20 for the fourth and final dose of ALN-PCSSC or placebo on Day 21, and discharged on Day 22. Subjects in the Q2W cohort were re-admitted to the clinical study site on Day 13 for the second and final dose of ALN-PCSSC or placebo on Day 14, and discharged on Day 15.

Information on comparators, particularly dosage, route of administration, batch number

Placebo was supplied by the clinical study site as sterile normal saline 0.9% for SC injection.

Evaluation criteria, particularly efficacy and safety

Safety:
Safety evaluations include clinical laboratory safety tests (hematology, biochemistry, coagulation, cytokine panel, drugs of abuse and alcohol parameters: and urinalysis), vital signs (oral body temperature, blood pressure, heart rate, and respiration rate), physical examinations, 12-lead ECG, adverse event (AE) monitoring, and concomitant medications, body weight/height.

Pharmacodynamics:
Blood samples for determination of PCSK9 protein concentration and LDL-C (β-quantification) concentrations were collected at the time points listed in the Schedules of Assessments. Plasma samples were analyzed using an enzyme-linked immunosorbent assay to determine PCSK9 protein concentration. Serum samples were analyzed using preparative ultracentrifugation (β-quantification) to determine LDL-C concentration.

Exploratory biomarkers (lipid parameters) were analyzed from the sample obtained for LDL-C (β-quantification) concentrations. Lipid parameters included, but were not limited to, TC, HDL-C, non-HDL-C, very LDL, apolipoprotein B, apolipoprotein A1, triglycerides, and lipoprotein (a).

Fasting blood samples for lipoprotein profile (LDL particle) analysis via nuclear magnetic resonance spectroscopy were collected at the times points listed in the Schedules of Assessments.

Additional blood samples for analysis of PCSK9 effect on hepatocyte-derived proteins and/or the induction of antibodies were collected at the time points listed in the Schedule of Assessments.

Aliquots of serum and plasma samples were obtained and frozen to permit future analysis of the effect of ALN-PCSSC on the expression of these exploratory biomarkers.

Pharmacokinetics:

Blood samples were collected for assessment of PK parameters and possible metabolite analysis at the time points listed in the Schedules of Assessments. Urine samples for determination of ALN-PCSSC concentration and possible metabolite analysis were obtained from the total urine sample collected at the time points listed in the Schedules of Assessments. Plasma and urine samples for determination of ALN-PCSSC concentration were analyzed at a central laboratory by a GLP-validated liquid chromatography-mass spectroscopy method.

Statistical method

Data listings were provided for all subjects. For continuous data, summary statistics included the arithmetic mean, arithmetic standard deviation, standard error of the mean [SEM], median, quartiles, minimum, maximum, and number; for log-normal data, the geometric mean and geometric coefficient of variation (CV%) were also presented. For categorical data, frequency counts, percentages, and number were presented. For categorical data, frequency counts, percentages, and number were presented. Data listings were provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses were only performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data were used.
For vital signs, serum biochemistry, hematology, coagulation, urinalysis, cytokine, and hs-CRP data, baseline was defined as the last observed value prior to the first dose of study drug.

For ECG data, baseline was defined as last observed value (mean of triplicate) prior to the first dose of study drug.

Mean change from baseline was the mean of all individual subjects' change from baseline values were calculated. Each individual change from baseline was calculated by subtracting the individual subject's baseline value from the value at the time point. The individual subject's change from baseline values was used to calculate the mean change from baseline using a SAS® procedure such as Proc Univariate.

Mean percent change from baseline was the mean of all individual subjects' percent change from baseline values were calculated. Each percent change from baseline was calculated by subtracting the individual subject's baseline value from the value at the desired time point and then dividing this calculated value by the individual subject's baseline value and multiplying by 100. These individual subjects' percent changes from baseline values were used to calculate the mean percent change from baseline using a SAS® procedure such as Proc Univariate.

Relative change from baseline was calculated as the actual value divided by baseline.

Relative to baseline and placebo was calculated by dividing the individual subject's relative change from baseline by the mean relative change from baseline of the placebo group at that time point.

Onset times post dose were calculated from the last dose administered. For the MD phase, onset times were also calculated from the first dose administered.

Missing values were not imputed.

Data analysis was performed using SAS® Version 9.3.

Analysis Data Model (ADaM) datasets were prepared using Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Version 2.1, and CDISC ADaM Implementation Guide Version 1.0. OpenCDISC Version 1.5 was utilized to ensure compliance with CDISC standards.

Summary and conclusion, particularly results on efficacy and safety:

Study ALN-PCSSC-001 was a randomized, single-blind, placebo-controlled, SAD and MD study of ALN-PCSSC when administered subcutaneously to subjects with elevated LDL-C, with or without statin co-medication. The study was designed to evaluate the safety, tolerability, PK, and PD of ALN-PCSSC in 2 phases: a SAD phase and an MD phase.

In the SAD phase, dose-dependent reduction in LDL-C concentrations was observed up to 300mg ALN-PCSSC, at which there was a plateauing of dose effect. Reductions in LDL-C from baseline were maintained through Day 180, the last day measured, in all ALN-PCSSC treatment groups, except for the 25 mg dose. The largest mean percent reduction in LDL-C from baseline at the individual nadir was observed at 800 mg ALN-PCSSC (59.2%). The largest mean percent reduction from baseline at the group nadir was observed at 500 mg ALN-PCSSC (55.1% at Day 98).

Consistent with LDL-C reductions, a dose-dependent reduction in PCSK9 concentrations was observed up to 300 mg ALN-PCSSC, at which there was a plateauing of dose effect, and reductions from baseline were maintained through Day 180, the last day measured, at all doses >100 mg. The largest mean percent reduction in PCSK9 from baseline at the individual nadir was observed at 800 mg ALN-PCSSC (82.3%). The largest mean percent reduction from baseline at the group nadir was observed at 800 mg ALN-PCSSC (79.4% at Day 98).

In the SAD phase, dose-dependent reductions from baseline were observed in total cholesterol, non-HDL-C, and apolipoprotein B, with a plateauing of dose effect observed at 300 mg ALNPCSSC. Reductions were also observed in lipoprotein (a) beginning at 100 mg ALN-PCSSC.

In the MD phase, a reduction in LDL-C and PCSK-9 concentrations was observed with ALN-PCSSC treatment, with similar effects observed for all dose groups and dose

frequencies. Reductions from baseline were maintained through 180 days after the last dose for all ALN-PCSSC doses. The largest mean percent reduction in LDL-C from baseline at the individual nadir (64.4%) and at the group nadir (55.7% at Day 70) was observed at 300 mg ALN-PCSSC with no statin. The largest mean percent reduction in PCSK9 from baseline at the individual nadir (88.5%) and at the group nadir (85.2% at Day 84) was observed at 500 mg ALN-PCSSC with statin.

The mean percent reductions in LDL-C at the individual and group nadirs were similar within 300 mg and 500 mg dose levels regardless of statin co-medication use, and the time to group nadir was the same at each dose level. The mean percent reductions in PCSK9 at the individual nadirs were similar within 300 mg and 500 mg dose levels regardless of statin co-medication use, and the time to group nadir was the same at each dose level. There was a difference in the percent reduction in PCSK9 at the group nadir within the 300 mg and 500 mg dose levels based on statin co-medication use, with a greater reduction observed in subjects with statin comedication use.

In the MD phase, a total of 24 of 32 subjects who received ALN-PCSSC achieved LDL-C ≤70 mg/dL during the study compared with 1 of 11 subjects who received placebo. The longest median continuous time subjects achieved this level was 196 days, which was observed at 500 mg ALN-PCSSC with no statin.

Greater reductions from baseline in total cholesterol, non-HDL-C, apolipoprotein B, and lipoprotein (a) were observed for ALN-PCSSC treatment groups compared to placebo. The PK of ALN-PCSSC was generally dose proportional and consistent across dose regimens and days. Plasma concentrations were not measurable 48 hours post-dose following administration of highest single dose of 800 mg. No accumulation was observed upon repeated dosing. Generally, <25% of the dose was recovered in urine. There was no clinically relevant change in exposure when statins were co-administered.

Single doses of ALN-PCSSC were well tolerated. All TEAEs were mild or moderate. No individual study drug-related TEAE was reported for more than 1 subject.

Multiple doses were well tolerated across doses and regimens with or without statin use. One subject who received 500 mg ALN-PCSSC with statin, had a severe TEAE of GGT increased that resolved within 29 days and was associated with clinically significant elevations of ALT, AST, and ALP. These elevations were attributed by the Investigator to statin use. The most common study drug-related TEAE in the MD phase was injection site rash (3 subjects), which were mild and resolved during the study. Hyperpigmentation was observed around the rash site in 2 of these subjects.

No subject in either phase had an ISR that met protocol-specified CTCAE criteria, and no subject died or had any other SAE or TEAE leading to discontinuation of study drug. No trends were observed in laboratory abnormalities, vital signs, ECGs, or physical examination findings.

Overall, the data from this study indicate that ALN-PCSSC was generally well tolerated and resulted in substantial LDL-C and PCSK9 reduction

Trial report date

14 June 2016