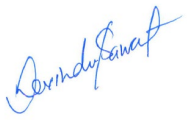
Form 30
The Patents ACT, 1970
(39 of 1970)
And
THE PATENTS RULES, 2003
TO BE USED WHEN NO OTHER FORM IS PRESCRIBED
[See sub-rule (2) of Rule 8]

1. Name of the Applicant/Patentee/Other	**IONIS PHARMACEUTICALS, INC**
2. Complete address including postal index number/code and State along with e-mail ID, telephone, mobile and fax number	2855 Gazelle Court, Carlsbad, CA 92010, USA
3. Application No. /Patent no.	**201847020374**
4. Relevant section/ rules	Section 14
5. Purpose of request	Written submission to the Hearing
6. Details of request	Written submission to the Hearing
7. To be signed by Agent	
8. Name of the Natural person who has signed along with designation and official seal, if any.	**Devinder Singh Rawat** **IN/PA No. 2594** **Of Anand And Anand Advocates** **Attorney for the applicant**
	To, The Controller of Patents, The Patent Office, Delhi

THROUGH E-FILING MODULE

Our Ref.: 28117/P-3 **May 04, 2024**

CONTROLLER OF PATENTS
THE PATENT OFFICE
DELHI

Re.: Indian Patent Application No.	**:**	**201847020374**
Date of Filing	**:**	**MAY 31, 2018**
Title of Invention	**:**	**MODULATING APOLIPOPROTEIN (A) EXPRESSION**
Applicant	**:**	**IONIS PHARMACEUTICALS, INC.**
Date of Hearing	**:**	**April 22, 2024**
Extension for Written Submission	**:**	**No**
Written Submission Due Date	**:**	**May 6, 2024**
Controller in Charge	**:**	**Akash Kumar**

Hearing Submission

Respected Sir,

Thank you very much for scheduling a hearing on April 22, 2024, in respect of the above application. Our submissions to the objections raised by the Learned Controller in the Hearing Notice are as follows:

A. REPLY ON OBJECTIONS:

1) <u>Inventive Step</u>

The controller has alleged that the present invention lacks inventive step in view of the following documents:

- *D1: US2015/0126720 A1*
- *D2: SOTIRIOS TSIMIKAS ET AL: "Antisense therapy targeting apolipoprotein(a): a randomized. Double-blind. placebo-controlled phase 1 study". LANCET. vol. 386. no. 10002. Pages 1472-1483*

The Applicant respectfully disagree with the opinion of the Learned Controller and submits that the presently amended claims are novel and inventive in view of the cited documents.

The pending claims recites to a pharmaceutical composition comprising ISIS 681257, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition contains from 75 mg to 85 mg of the oligomeric compound.

The Applicant submits that the cited prior art does not provide any teaching in the direction of the claimed invention.

D1 does not teach or suggest a pharmaceutical composition according to the claims as amended. D1 teaches that ISIS 681257 was subcutaneously administered to 8-week-old female mice at 0.3, 1, 3, or 10mg/kg, but fails to provide any teaching or suggestion regarding an amount suitable for humans, let alone a pharmaceutical composition containing the specific dosage of 75 mg to 85 mg of ISIS 681257 as instantly claimed.

Moreover, an ordinarily skilled artisan would not have had a reasonable expectation of success in developing the now claimed composition for treatment at specific dosage amounts based on the teachings of D1.

a) First, D1 only teaches doses suitable in mice.
b) Second, D1 only teaches that ISIS 681257 was more potent with a longer duration of action than ISIS 494372 in female mice.

The Applicant respectfully submits that, optimizing the dose for antisense oligonucleotides (ASOs) was and is not routine. In particular, the development of the correct dosing of GalNAc conjugated ASOs in humans was not routine at the filing date: GalNAc conjugated ASOs are still a developing field of medicine to this date, and only recently the first GalNAc conjugated siRNA agents (not even an ASOs!) have been approved. Accordingly, an ordinarily skilled artisan has no past experience nor any literature available, at the time of filing of the present application to guide the development of the correct dosing amount for a GalNAc conjugated ASO.

The Applicant submits that D1 provides no guidance to arrive at the specific dosage of 75 mg to 85 mg of ISIS 681257 in humans as claimed. Indeed, a dosage amount found suitable in mice may not directly correlate to a suitable regimen in humans. Accordingly, the ordinary skilled artisan would not have had a reasonable expectation of success in developing the specific claimed composition because doing so would have required excessive experimentation.

D2 does not cure the deficiencies of D1. D2 merely teaches administering ISIS 494372 to a human at 100mg per day at days 1, 3, 5, 8, 15 and 22 for a total dose exposure of 600 mg over a 3-week period. See D2, at 1478. An ordinarily skilled artisan would not have had a reasonable expectation of success in developing the now claimed composition based on the teachings of D2. D2 only teaches administration of ISIS 494372.

As disclosed in D1, ISIS 494372, having different internucleoside linkages and nucleoside modifications and also lacking a GalNAc moiety, is a different oligomeric compound from ISIS 681257. See D1, at Example 89, Table 92.

In fact, D2 teaches away from a pharmaceutical composition comprising ISIS 681257, or a pharmaceutically acceptable salt thereof, for treating or preventing a disease or condition related to apolipoprotein(a) (apo(a)) and/or lipoprotein(a) (Lp(a)) in a human, wherein: (i) the treatment or prevention comprises administering from 75 mg to 85 mg of the oligomeric compound to the human during the a dosing period; and (ii) the dosing period is one month.

Indeed, D2 teaches that a single dose of ISIS 494372 (50–400 mg) did not decrease Lp(a) concentrations at one month. See D2, at page 1478. An ordinarily skilled artisan looking to treat or prevent a disease by reducing the production of apo(a) in the liver and as a consequence, the level of Lp(a) lipoprotein in blood would not expect from the teachings of D2 that a dosage less than 400 mg, let alone an amount from 75 mg to 85 mg as claimed, would decrease Lp(a) concentrations at one month. The Applicant submits that a person skilled in art would not have had a reasonable expectation of success in developing the now claimed composition based on the teachings of D2 because D2 teaches that a significantly higher dose and more frequent dosing period than claimed would be expected to achieve efficacy with ISIS 494372, let alone with the structurally different compound, ISIS 681257.

While D1 discloses that ISIS 681257 was more potent with a longer duration of action than ISIS 494372 in female mice, neither D1 nor D2 provide any teaching or suggestion of the surprising potency in humans. As shown in Examples 1 and 2 of the present application, a ≥ 30-fold improvement in potency in humans was observed for oligomeric compound ISIS 681257 in sterile saline solution. Indeed, an ordinarily skilled artisan considering D1 and D2 could not have predicted the unexpected ≥ 30-fold improvement observed in humans for ISIS 681257. In light of these surprising results, when treating humans, ISIS 681257 and its salts can be administered at a significantly lower dose and/or less frequently than expected based on the earlier in vivo testing.

Therefore, the presently claimed invention provides one or more improvements in treating humans including reduced cost of treatment, improved patient compliance, reduced volume of administered medicinal product and/or potentially reduced risk of potential adverse events via lower dose administration regimens.

In the instant case, the claimed compositions and their results would be unpredictable based on the teachings of the prior art. Thus, Applicant submits that the claims are inventive over D1 and/or D2. Reconsideration and withdrawal of the rejection are requested.

Clinical trial data given in the specification:

The clinical results presented herein for ISIS 681257 are surprising, because earlier experiments involving both the unconjugated compound (ISIS 494372 also having the nucleobase sequence TGCTCCGTTGGTGCTTGTTC (SEQ ID NO.: **1)** and a 5-10-5 gapmer motif, and the GalNAc conjugated compound **(ISIS** 681257) had suggested that the GalNAc conjugated compound would have significantly lower potency and/or a shorter duration of action in humans than was observed following the first dosing of humans reported herein *(e.g.* see Examples 89, 100 and 108 of **WO**2014/179625 (equivalent D1 US2015/0126720) and Tsimikas et al.,(D2, Lancet, 2015 Oct 10; 386:1472-83).

Example 1: ISIS 681257 Clinical Trial

As described herein, a double-blinded, placebo-controlled, dose-escalation Phase 1 study was performed on healthy volunteers with elevated Lp(a) to assess safety, tolerability, pharmacokinetics **(PK)** and pharmacodynamics **(PD)** after administration of single and multiple doses of **ISIS** 681257. **ISIS** 681257 was previously disclosed in WO 2014/179625 and is also described hereinabove. **ISIS** 681257 has been shown to be potent in inhibiting Lp(a) and tolerable when administered to non-human subjects. This subsequent study revealed unexpectedly improved properties of ISIS 681257 when administered to human subjects.

Table 2: Dose-dependent Change in Lp(a) after a Single Dose of ISIS 681257

	% Change from Baseline							
Cohort	Day 2	Day 4	Day 8	Day 15	Day 30	Day 50	Day 70	Day 90
Placebo	-1.7	-2.4	-9.6	0.3	6.8	-14	-9	3.9
A	4	-5	-16	-20	-26	-	-	-
B	7	8	2	-22	-33	-	-	-
C	-2	-13	-33	-41	-43	-35	-26	-26
D	-21	-35	-50	-70	-79	-71	-52	-46
E	-11	-25	-50	-76	-85	-75	-61	-44

The above results were surprising, because earlier experiments involving both the unconjugated compound **(ISIS** 494372) and the GalNAc conjugated compound **(ISIS** 681257) had suggested that the GalNAc conjugated compound would have significantly lower potency and/or a shorter duration of action in humans than was observed following the first dosing of humans reported herein *(e.g.* see Examples 89, 100 and 108 of **WO** 2014/179625 and Tsimikas *et al.*, Lancet, 2015 Oct 10; 386:1472-83). In light of these surprising results, when treating humans, the GalNAc conjugated compound **(ISIS** 681257, or a salt thereof) can be administered at lower doses and/or less frequently than expected based on the earlier *in vivo* testing of the GalNAc conjugated compound. This can provide one or more very

significant improvements in treating humans, *e.g.* reduced cost of treatment, improved patient compliance, reduced volume of administered medicinal product and/or potentially reduced risk of potential adverse events via lower dose administration regimens.

Additional Data:

The Applicant submits that the currently Phase 3 trial utilizing an 80 mg QM is ongoing.

Further, Phase 2b trial data published in New England Journal of Medicine, Jan 16, 2020 (Annexure 1). The attention of the Ld. Controller is drawn to page 253, LHC,

The result indicates that "*At the highest cumulative dose regimen, which was equivalent to 80 mg monthly, 98% of patients attained a lipoprotein(a) level of 50 mg per deciliter (125 nmol per liter) or lower, a target value supported by European and U.S. guidelines and by empirical data from patients treated with statins. We found reductions in levels of oxidized phospholipids on apolipoprotein B and oxidized phospholipids on apolipoprotein(a), both of which are proinflammatory components that are present on lipoprotein(a) and on apolipoprotein(a) and are linked to a higher atherothrombotic risk. Finally, we noted reductions in LDL cholesterol and apolipoprotein B in patients receiving APO(a)-LRx, beyond those achieved with aggressive background lipid-lowering therapy*".

In light of the above, the Applicant submits that the present invention is inventive and therefore reconsideration of the objection is requested.

2) Non-Patentability

a) Para 2 of FER is maintained, As, the amended claims 1-2 and 5-13 are not patentable under section 3(e) as the composition claimed is is just an admixture of various ingredients without any demonstrated synergistic effect.

The Applicant submits that as demonstrated in above section, the dosage regime of 75 to 85 mg, as demonstrated, in the specification, (preclinical data) and clinical data of phase 2b indicate the surprising effect in the reductions of LDL cholesterol and apolipoprotein B in patients receiving APO(a)-LRx (ISIS 681257, or a salt thereof)

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

3) Sufficiency of Disclosure u/s 10(4):

a) Para 3(I) of FER is maintained as the applicant's reply is not satisfactory for the amended claims 1-2 and 5-13 pertaining to a pharmaceutical composition are not enabled in the specification via working example. Hence, these claims do not meet the requirement of 10(4) (b) of the Patents Act, 1970.

The Applicant submits that pending claims are fully supported by the patent specification. In this regard, reference has been made to the Example 1 and 2 describing different dosage regime.

In view of the above reconsideration of the objection is requested.

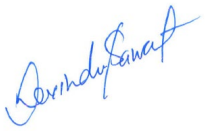
4) <u>Formal Requirement:</u>

Fees for 2 newly added claims (Rs 3,200) has to be paid.

The Applicant has paid the fee for the extra two claims. A copy of the CBR is enclosed.

In view of revisions to claims and our submissions made hereinabove and during the hearing on **April 22, 2024** we request the Learned Controller to kindly allow the application to proceed for grant.

Yours faithfully,



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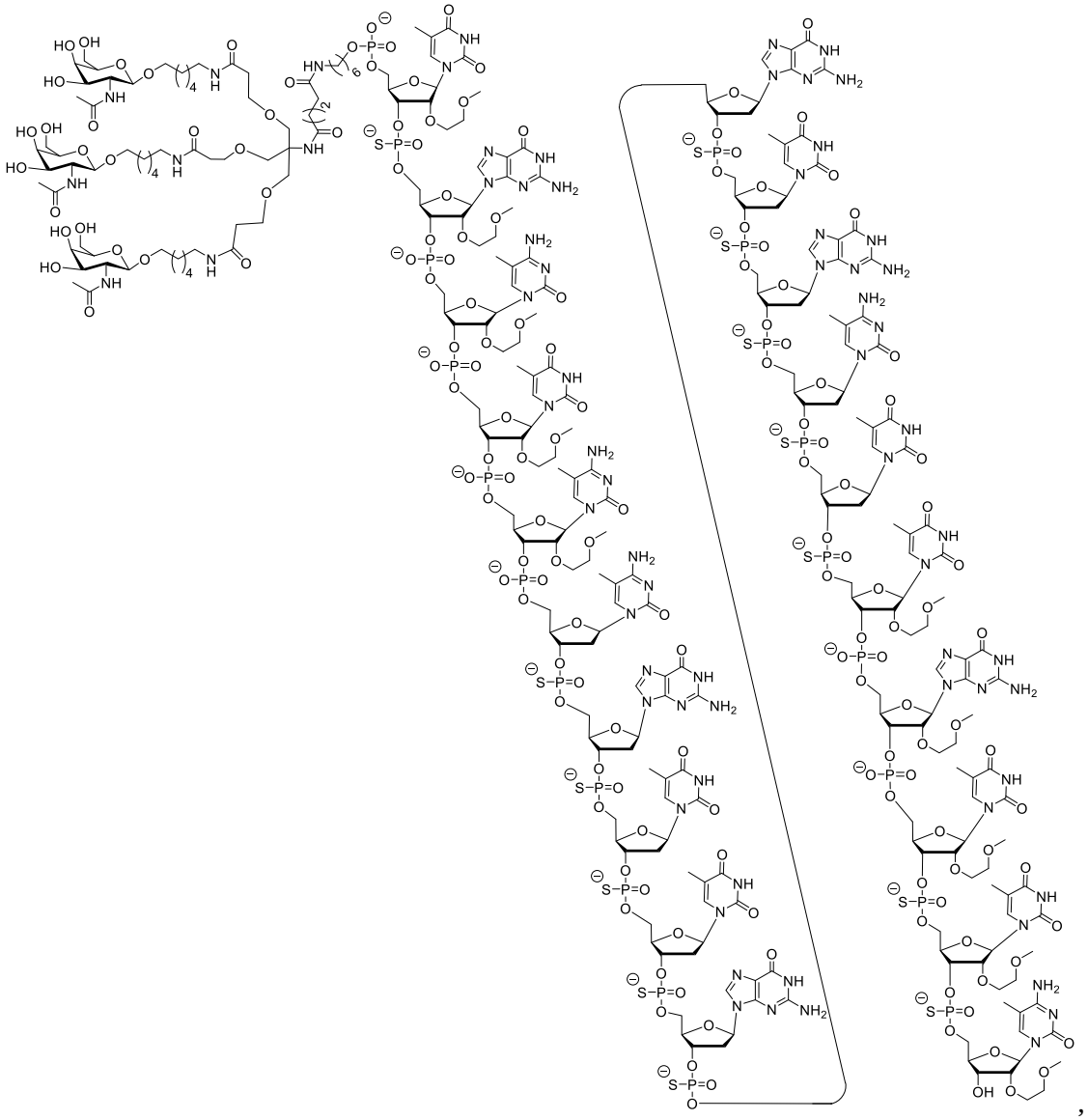
Attorney for the applicant

Encl.:

- Pending Claims
- Annexure 1, NEJM, Jan 2020
- CBR receipt of extra two claim fee

We Claim:

1. A pharmaceutical composition comprising an oligomeric compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent, wherein the oligomeric compound has the following structure



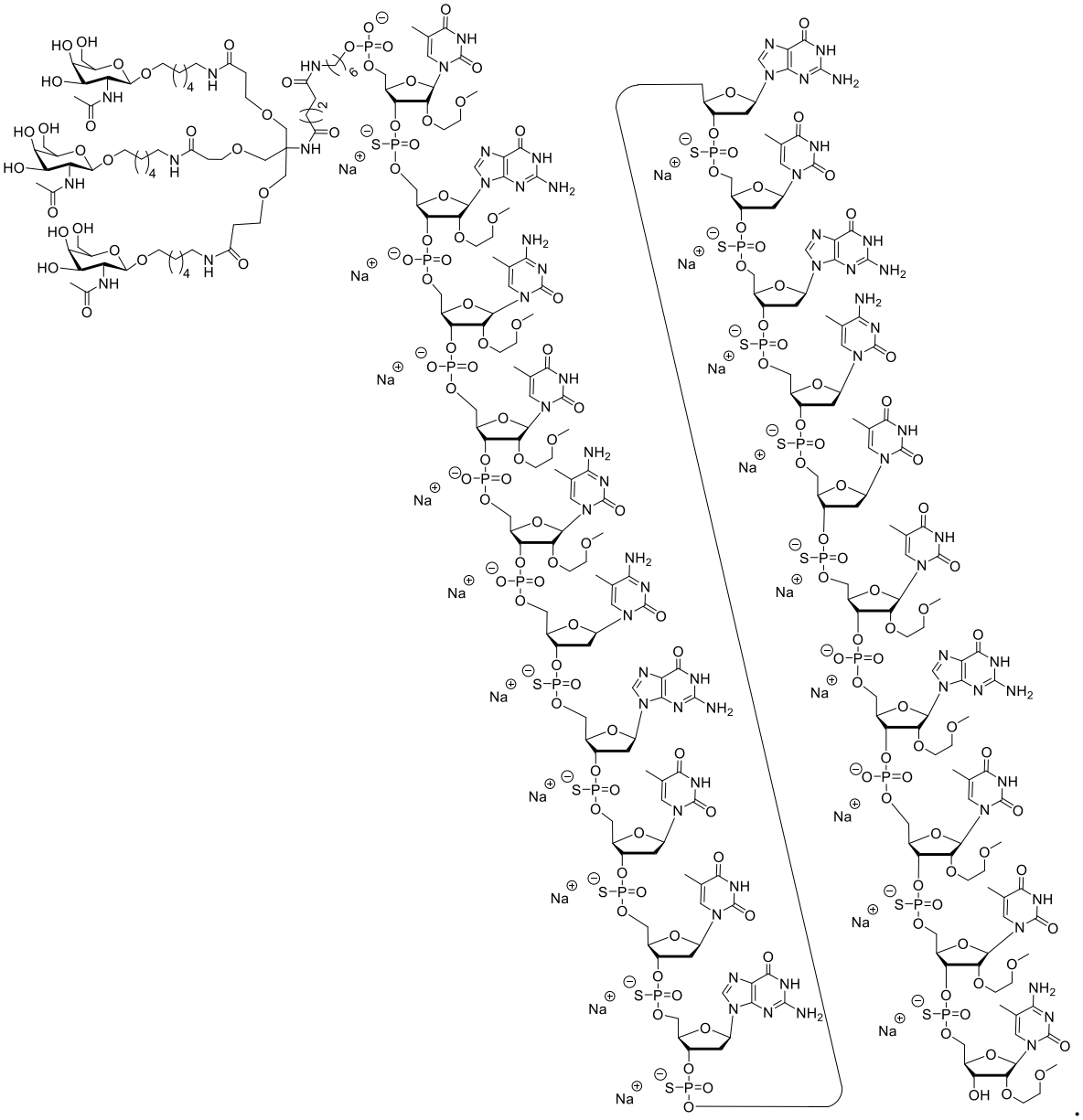
and wherein the pharmaceutical composition contains from 75 mg to 85 mg of the oligomeric compound, and wherein the pharmaceutically acceptable carrier or diluent is a sterile liquid.

Former 114-128. Cancelled

2. The pharmaceutical composition as claimed in claim 1, wherein the composition comprises 80mg of the oligomeric compound.

3. The pharmaceutical composition as claimed in claim 1 or 2, wherein the oligomeric compound is a sodium salt.

4. The pharmaceutical composition as claimed in any of claims 1 to 3, wherein the oligomeric compound has the following structure:



5. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the composition contains 1 mL of the sterile liquid.

6. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the pharmaceutical composition contains 0.8 mL of the sterile liquid.

7. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the pharmaceutical composition contains 0.5 mL of the sterile liquid.

8. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the pharmaceutical composition contains 0.4 mL of the sterile liquid.

9. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the pharmaceutical composition contains 0.25 mL of the sterile liquid.

10. The pharmaceutical composition as claimed in any one of claims 1 to 4, wherein the pharmaceutical composition contains 0.2 mL of the sterile liquid.

11. The pharmaceutical composition as claimed in any of claims 1 to 10, wherein the sterile liquid is water.

12. The pharmaceutical composition as claimed in any of claims 1 to 10, wherein the sterile liquid is water with a sodium phosphate buffer.

13. The pharmaceutical composition as claimed in any of claims 1 to 10, wherein the sterile liquid is water with a sodium phosphate buffer and sodium chloride.

Dated this 31st day of May, 2018.

Devinder Singh Rawat
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ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

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ABSTRACT

BACKGROUND

Lipoprotein(a) levels are genetically determined and, when elevated, are a risk factor for cardiovascular disease and aortic stenosis. There are no approved pharmacologic therapies to lower lipoprotein(a) levels.

METHODS

We conducted a randomized, double-blind, placebo-controlled, dose-ranging trial involving 286 patients with established cardiovascular disease and screening lipoprotein(a) levels of at least 60 mg per deciliter (150 nmol per liter). Patients received the hepatocyte-directed antisense oligonucleotide AKCEA-APO(a)-L_{Rx}, referred to here as APO(a)-L_{Rx} (20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week), or saline placebo subcutaneously for 6 to 12 months. The lipoprotein(a) level was measured with an isoform-independent assay. The primary end point was the percent change in lipoprotein(a) level from baseline to month 6 of exposure (week 25 in the groups that received monthly doses and week 27 in the groups that received more frequent doses).

RESULTS

The median baseline lipoprotein(a) levels in the six groups ranged from 204.5 to 246.6 nmol per liter. Administration of APO(a)-L_{Rx} resulted in dose-dependent decreases in lipoprotein(a) levels, with mean percent decreases of 35% at a dose of 20 mg every 4 weeks, 56% at 40 mg every 4 weeks, 58% at 20 mg every 2 weeks, 72% at 60 mg every 4 weeks, and 80% at 20 mg every week, as compared with 6% with placebo (P values for the comparison with placebo ranged from 0.003 to <0.001). There were no significant differences between any APO(a)-L_{Rx} dose and placebo with respect to platelet counts, liver and renal measures, or influenza-like symptoms. The most common adverse events were injection-site reactions.

CONCLUSIONS

APO(a)-L_{Rx} reduced lipoprotein(a) levels in a dose-dependent manner in patients who had elevated lipoprotein(a) levels and established cardiovascular disease. (Funded by Akcea Therapeutics; ClinicalTrials.gov number, NCT03070782.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Tsimikas at the Sulpizio Cardiovascular Center, Vascular Medicine Program, University of California, San Diego, 9500 Gilman Dr., La Jolla, California 92093, or at stsimikas@health.ucsd.edu.

*A list of the AKCEA-APO(a)-L_{Rx} Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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N Engl J Med 2020;382:244-55.
DOI: 10.1056/NEJMoa1905239

Lipoprotein(a) is composed of a low-density lipoprotein (LDL)–like moiety bound covalently to apolipoprotein(a).[1,2] Lipoprotein(a) potentially contributes to cardiovascular disease through proatherogenic effects of its LDL-like moiety, proinflammatory effects of its oxidized phospholipid content, and prothrombotic effects through its inactive, plasminogen-like protease domain on apolipoprotein(a). Mechanistic, epidemiologic, and genetic evidence reported over the past 20 years provides support for the idea that elevated plasma lipoprotein(a) is an independent genetic risk factor for cardiovascular disease and calcific aortic-valve stenosis.[3,4] In contrast, genetically determined low levels of lipoprotein(a) (<30 mg per liter [<75 nmol per liter]) are associated with a decreased risk of cardiovascular disease but not of other non–cardiovascular disease adverse phenotypes.[5]

There are currently no approved pharmacologic therapies that specifically target lipoprotein(a). Antisense oligonucleotides (ASOs) inhibit the production of apolipoprotein(a) in the hepatocyte, the source of approximately 99% of plasma lipoprotein(a).[6] Preclinical proof-of-concept studies have established that ASOs targeting hepatic *LPA* messenger RNA (mRNA) specifically reduce plasma levels of lipoprotein(a).[7,8] Subsequent phase 1 and 2 studies of a non–hepatocyte-targeted, second-generation ASO showed lowering of lipoprotein(a) levels in healthy participants who had elevated lipoprotein(a), as well as in patients with established cardiovascular disease and elevated plasma levels of lipoprotein(a).[9,10] Advances in directing ASOs to hepatocytes by conjugation with a triantennary *N*-acetylgalactosamine ($GalNAc_3$) moiety, a high-affinity ligand for the asialoglycoprotein receptor on the surface of hepatocytes, have resulted in large increases (by a factor of 15 to 30) in their potency,[10] with implications for improvements in the side-effect profile and safety of ASOs.[11,12] AKCEA-APO(a)-L_{Rx} — here referred to as APO(a)-L_{Rx} and previously called IONIS-APO(a)-L_{Rx} — is a $GalNAc_3$-conjugated 2′-methoxyethyl chimeric second-generation ASO drug targeted to *LPA* mRNA. In a phase 2a trial, APO(a)-L_{Rx} was shown to result in a dose-dependent reduction of 66 to 92% in circulating lipoprotein(a) in participants with elevated lipoprotein(a) levels.[10] The long half-life of APO(a)-L_{Rx} (approximately 1 month) that was observed in that trial prompted us to consider longer dosing intervals in the trial we report here.

METHODS

TRIAL DESIGN

We conducted this phase 2, dose-ranging, randomized, double-blind, placebo-controlled trial evaluating APO(a)-L_{Rx} at 30 sites in five countries. Patients were randomly assigned to one of five groups; within each group, randomization was performed in a 5:1 ratio (APO(a)-L_{Rx}:placebo) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The patients in each group were given one of five regimens, with APO(a)-L_{Rx} or placebo administered subcutaneously, for a minimum of 6 months: APO(a)-L_{Rx} at a dose of 20 mg every 4 weeks, 40 mg every 4 weeks, 60 mg every 4 weeks, 20 mg every 2 weeks, or 20 mg every week or physiologic saline placebo. By week 25, the groups receiving monthly doses would have reached 6 months of exposure (after the week 21 dose); however, the groups receiving doses every 2 weeks or every week would have reached only 5.5 and 5.75 months of exposure, respectively. Therefore, the timing of the analysis of the primary efficacy end point was moved to week 27 for these groups.

To collect additional long-term safety and efficacy data, treatment was continued up to 1 year or until the last enrolled patient had reached 6 months of treatment. The post-treatment follow-up period lasted 16 weeks to account for the long half-life of the drug.[11] Site visits were scheduled to occur every 4 weeks to collect efficacy and safety data. Platelet counts and renal-function tests were performed every 2 weeks, and liver-function tests were performed every 2 weeks for the first 3 months and monthly thereafter throughout the treatment period. The platelet count was analyzed simultaneously by both central and local laboratories, and APO(a)-L_{Rx} or placebo could be administered only if recent (within 14 days) platelet-count results were available. Monitoring and stopping rules, which were prespecified in the protocol (available at NEJM.org), included threshold limits on platelet count and renal and liver function.

Akcea Therapeutics sponsored the trial and was responsible for its conduct and oversight, the collection and management of the data, and the statistical analyses and data interpretation.

The protocol was approved by the relevant health authorities, institutional review boards, and ethics committees. An academic author and an author who is an employee of the sponsor wrote the first draft and last submitted draft of the manuscript and vouch for the completeness and accuracy of the data and for fidelity of the trial to the protocol. All the authors participated in revising the manuscript.

ELIGIBILITY

Patients who were 18 to 80 years of age and had established cardiovascular disease and an elevated screening plasma lipoprotein(a) level (≥60 mg per deciliter [150 nmol per liter]) were eligible for enrollment. Patients who were being treated with lipid-lowering medications could be enrolled if they had been on a stable drug regimen for 4 weeks before screening and were expected to remain on that regimen during the trial. Exclusion criteria included acute coronary syndrome, major cardiac surgery, or stroke or transient ischemic attack within 6 months before screening; coronary, carotid, or peripheral revascularization, major noncardiac surgery, or lipoprotein apheresis within 3 months before screening; heart failure of New York Heart Association (NYHA) class IV; uncontrolled hypertension (systolic blood pressure, >160 mm Hg; or diastolic blood pressure, >100 mm Hg); an estimated glomerular filtration rate of less than 60 ml per minute; a ratio of urine protein (in milligrams) to creatinine (in grams) of 250 or greater; a ratio of urine albumin (in milligrams) to creatinine (in grams) of 100 or greater; an alanine aminotransferase or aspartate aminotransferase level exceeding twice the upper limit of the normal range; an alkaline phosphatase or total bilirubin level exceeding the upper limit of the normal range; a platelet count lower than the lower limit of the normal range; a history of major bleeding or high risk of bleeding diathesis; and use of anticoagulant drugs. Additional details, including those of the laboratory measurements, are provided in the Supplementary Appendix. Trial participants provided written informed consent.

END POINTS

The primary efficacy end point was the percent change in lipoprotein(a) level from baseline to the primary analysis time point at 6 months of exposure (week 25 or week 27) in each APO(a)-L_{Rx} group as compared with the pooled placebo group. The unranked secondary end points, which were analyzed in the same way, were the percent change from baseline in LDL cholesterol level, the percent of patients with a plasma lipoprotein(a) level of 50 mg per deciliter (125 nmol per liter) or lower, the percent of patients with a plasma lipoprotein(a) level of 30 mg per deciliter (75 nmol per liter) or lower, the percent change from baseline in apolipoprotein B level, the percent change from baseline in the level of oxidized phospholipids on apolipoprotein B, and the percent change from baseline in the level of oxidized phospholipids on apolipoprotein(a).

STATISTICAL ANALYSIS

The power calculations are shown in the Supplementary Appendix. All efficacy analyses were performed with the full analysis set, defined as all patients who had undergone randomization and had received at least one dose of APO(a)-L_{Rx} or placebo. The primary end point and secondary end points for oxidized phospholipids on apolipoprotein B, oxidized phospholipids on apolipoprotein(a), LDL cholesterol, and apolipoprotein B were analyzed with the use of an analysis of covariance model with treatment groups as factors and the log-transformed baseline value for each respective measure as covariate. Responder analyses (i.e., in which each patient is considered as either having a response or having no response) were performed with the use of a logistic-regression model with the log-transformed baseline level of lipoprotein(a) as the concomitant variable. Missing data for the primary and secondary efficacy end points were handled with a multiple-imputation model containing baseline and postbaseline values, stratified according to treatment group. The imputations were performed for postbaseline values by the Markov chain Monte Carlo method. Supportive efficacy analyses over time, including primary and secondary efficacy data with data collected beyond the primary analysis time point, were performed with a mixed model of repeated measurements. Because of the exploratory nature of this phase 2 trial, the P values and widths of the 95% confidence intervals were not adjusted for multiplicity. All safety analyses were performed in the safety population, defined as all patients who underwent randomization and received at least one dose of APO(a)-L_{Rx} or placebo.

RESULTS

PATIENTS

Of the 459 patients who underwent assessment for eligibility, 286 were randomly assigned to one of five APO(a)-L_{Rx} regimens or placebo (Figs. S1 and S2). The first patient underwent randomization on March 27, 2017, and the last patient underwent randomization on January 16, 2018.

The mean (±SD) duration of treatment was 31.6±11.5 weeks (median, 32.1) among patients who received APO(a)-L_{Rx} and 31.2±12.0 weeks (median, 34.0) among those who received placebo. Approximately 60% of patients were younger than 65 years, and more than 30% were women (Table 1). By protocol design, all patients had established atherosclerotic cardiovascular disease, most commonly coronary artery disease; 4.5% had both carotid and peripheral artery disease. Between 35% and 54% of patients in each group had premature coronary artery disease, defined as a first cardiovascular event before 55 years of age for men and before 65 years of age for women. A majority of patients had a family history of coronary artery disease, and approximately one third had familial hypercholesterolemia. At trial entry, approximately 80 to 90% of the patients were receiving statin therapy, 50% were receiving ezetimibe, and 20% were receiving a PCSK9 inhibitor.

At baseline across all groups, median levels of lipoprotein(a) ranged from 205 to 247 nmol per liter (the upper limit of the normal range is 30 mg per deciliter [75 nmol per liter]),[13] median levels of oxidized phospholipids on apolipoprotein B ranged from 20.3 to 24.6 nmol per liter (the top quartile in the general population is >8 nmol per liter), and median levels of oxidized phospholipids on apolipoprotein(a) ranged from 61.9 to 67.3 nmol per liter (the top quartile in the general population is >20 nmol per liter). Mean LDL cholesterol levels ranged from 67.6 to 89.3 mg per deciliter (1.75 to 2.31 mmol per liter). Mean estimated corrected LDL cholesterol levels ranged from 40.8 to 56.4 mg per deciliter, if it is assumed that 30% of lipoprotein(a) mass is cholesterol.[14]

MEAN PERCENT CHANGE IN LIPOPROTEIN(A) LEVEL

At 6 months of exposure (25 or 27 weeks), dose-dependent mean percent reductions in lipoprotein(a) from baseline were noted in all the APO(a)-L_{Rx} groups, with decreases of 35% at a dose of 20 mg every 4 weeks, 56% at 40 mg every 4 weeks, 58% at 20 mg every 2 weeks, 72% at 60 mg every 4 weeks, and 80% at 20 mg every week, as compared with 6% for the pooled placebo group (P value range for the comparison with placebo, 0.003 to <0.001) (Fig. 1A). The two regimens of the same monthly dose (40 mg) — 40 mg every 4 weeks and 20 mg every 2 weeks — lowered lipoprotein(a) to similar extents. The lipoprotein(a)-lowering effect was noted within the first month and reached near-maximal effect by week 16 (Fig. 1B). In addition, dose-dependent absolute reductions in lipoprotein(a) levels were observed in all the APO(a)-L_{Rx} groups (Table 2). The lipoprotein(a) levels returned to baseline within 16 weeks after the last dose (Fig. S3), a finding consistent with previous observations.[10] The mean percent changes in the lipoprotein(a) level in individual patients in each treatment group are shown in waterfall plots in Figure S4.

PERCENT OF PATIENTS ATTAINING PRESPECIFIED LIPOPROTEIN(A) LEVELS

The percent of patients with a lipoprotein(a) level of 50 mg per deciliter (125 nmol per liter) or lower at 6 months of exposure was 23% in the group that received 20 mg of APO(a)-L_{Rx} every 4 weeks, 63% in the group that received 40 mg every 4 weeks, 65% in the group that received 20 mg every 2 weeks, 81% in the group that received 60 mg every 4 weeks, and 98% in the group that received 20 mg every week. The corresponding odds ratios for this end point in comparison with the placebo group were 5.0 (95% confidence interval [CI], 1.2 to 21.0), 31.1 (95% CI, 7.3 to 131.4), 43.8 (95% CI, 9.8 to 195.0), 122.8 (95% CI, 24.0 to 627.4), and 1124.6 (95% CI, 109.3 to 11,571) (Fig. 1C).

The percent of patients with a lipoprotein(a) level of 30 mg per deciliter (75 nmol per liter) or lower at 6 months of exposure ranged from 6% in the group that received 20 mg every 4 weeks to 71% in the group that received 20 mg every week. The odds ratios for this end point in comparison with the placebo group were 7.3 (95% CI, 0.3 to 155.3) for 20 mg every 4 weeks, 27.9 (95% CI, 1.5 to 521.5) for 40 mg every 4 weeks, 59.9 (95% CI, 3.2 to 1128.0) for 20 mg every 2 weeks, 113.9 (95% CI, 6.2 to 2098.5) for 60 mg every 4 weeks, and 347.0 (95% CI, 18.3 to 6597.9) for 20 mg every week.

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Patients at Baseline.*

Characteristic	APO(a)-L_{Rx}						Pooled Placebo (N=47)
	20 mg Every 4 Wk (N=48)	40 mg Every 4 Wk (N=48)	20 mg Every 2 Wk (N=48)	60 mg Every 4 Wk (N=47)	20 mg Every Wk (N=48)	Pooled (N=239)	
Age — yr	60.0±9.6	61.3±10.6	57.9±11.5	62.2±9.7	58.9±8.0	60.1±10.0	59.9±10.5
Age <65 yr — no. (%)	32 (67)	28 (58)	30 (62)	25 (53)	35 (73)	150 (63)	28 (60)
Age <50 yr — no. (%)	9 (19)	8 (17)	15 (31)	6 (13)	9 (19)	47 (20)	11 (23)
Female sex — no. (%)	19 (40)	12 (25)	17 (35)	14 (30)	20 (42)	82 (34)	15 (32)
White race — no./total no. (%)†	44 (92)	45 (94)	47 (98)	47 (100)	47 (98)	230 (96)	46 (98)
Cardiovascular risk factors — no. (%)							
Hypertension	28 (58)	35 (73)	34 (71)	31 (66)	25 (52)	153 (64)	30 (64)
Type 2 diabetes	7 (15)	8 (17)	5 (10)	4 (9)	6 (12)	30 (13)	10 (21)
Family history of coronary artery disease	34 (71)	31 (65)	33 (69)	29 (62)	34 (71)	161 (67)	37 (79)
Familial hypercholesterolemia	13 (27)	14 (29)	13 (27)	10 (21)	15 (31)	65 (27)	16 (34)
Current smoker	8 (17)	4 (8)	2 (4)	2 (4)	4 (8)	20 (8)	1 (2)
Body-mass index‡	29.0±4.51	27.2±3.52	28.7±4.18	28.5±3.96	28.7±4.89	28.4±4.25	27.6±4.25
Coronary artery disease — no. (%)	44 (92)	45 (94)	45 (94)	46 (98)	44 (92)	224 (94)	45 (96)
Premature coronary artery disease§	21 (44)	26 (54)	17 (35)	18 (38)	23 (48)	105 (44)	22 (47)
Myocardial infarction	25 (52)	25 (52)	31 (65)	20 (43)	27 (56)	128 (54)	27 (57)
Carotid artery disease — no. (%)	13 (27)	12 (25)	10 (21)	11 (23)	14 (29)	60 (25)	9 (19)
Peripheral artery disease — no. (%)	9 (19)	10 (21)	4 (8)	1 (2)	5 (10)	29 (12)	4 (9)
Stroke or TIA — no. (%)	6 (12)	6 (12)	7 (15)	4 (9)	5 (10)	28 (12)	8 (17)
Aortic-valve stenosis of grade 2 or higher — no. (%)	5 (10)	3 (6)	3 (6)	1 (2)	3 (6)	15 (6)	2 (4)
History of lipoprotein apheresis — no. (%)	1 (2)	2 (4)	2 (4)	1 (2)	2 (4)	8 (3)	2 (4)

Lipid-lowering therapy — no. (%)							
Statin therapy	42 (88)	44 (92)	43 (90)	44 (94)	44 (92)	217 (91)	39 (83)
High intensity	36 (75)	31 (65)	30 (62)	37 (79)	32 (67)	166 (69)	32 (68)
Moderate or low intensity¶	6 (12)	13 (27)	13 (27)	7 (15)	12 (25)	51 (21)	7 (15)
Ezetimibe	25 (52)	25 (52)	23 (48)	19 (40)	23 (48)	115 (48)	23 (49)
PCSK9 inhibitor	8 (17)	11 (23)	9 (19)	10 (21)	13 (27)	51 (21)	10 (21)
Platelet aggregation inhibitors — no. (%)	47 (98)	47 (98)	46 (96)	47 (100)	48 (100)	235 (98)	43 (91)
Median lipoprotein(a) level (IQR) — nmol/liter	246.6 (179.2–300.8)	220.0 (176.5–283.3)	238.2 (183.7–298.4)	204.5 (163.8–286.5)	233.7 (193.1–275.3)	224.3 (177.2–286.9)	231.6 (194.9–317.7)
Median OxPL-apoB level (IQR) — nmol/liter	24.6 (18.1–33.1)	23.1 (16.2–32.5)	23.9 (17.9–29.2)	20.3 (16.6–28.5)	23.7 (17.2–30.7)	23.3 (17.4–30.5)	21.2 (17.2–31.5)
Median OxPL-apo(a) level (IQR) — nmol/liter	66.3 (57.8–75.0)	65.9 (56.6–71.9)	67.3 (60.8–73.2)	61.9 (53.4–72.7)	67.1 (60.0–74.6)	65.8 (58.6–73.8)	69.2 (59.6–76.5)
Total cholesterol level — mg/dl	166.0±38.6	154.4±52.1	146.7±36.3	142.9±32.4	154.4±34.7	154.4±39.8	154.4±33.6
LDL cholesterol level — mg/dl	89.3±37.1	77.4±39.5	74.4±28.8	67.6±28.3	76.1±28.4	77.0±33.3	79.4±29.2
Estimated LDL-Ccorr — mg/dl‖	56.4±39.5	49.8±39.1	45.2±27.6	40.8±28.3	46.7±30.1	47.8±33.5	47.6±30.1
Apolipoprotein B level — mg/dl	80.7±23.6	71.9±23.4	69.3±19.8	68.5±18.8	70.6±19.2	72.2±21.3	73.8±16.9
HDL cholesterol level — mg/dl	54.1±15.5	54.1±19.3	54.1±19.3	50.3±11.6	58.0±19.3	54.1±19.3	50.3±19.3
Median triglyceride level (IQR) — mg/dl	97 (44–230)	97 (35–283)	106 (35–204)	106 (53–567)	89 (35–266)	97 (35–567)	106 (35–576)
hsCRP level — mg/liter	2.9±5.3	2.3±4.5	1.6±2.5	2.0±2.5	2.2±4.4	2.2±4.0	2.4±4.4

* Plus–minus values are means ±SD. To convert the values for lipoprotein(a) to nanomoles per liter, multiply by 2.5. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, hsCRP high-sensitivity C-reactive protein, IQR interquartile range, LDL low-density lipoprotein, OxPL-apoB oxidized phospholipids on apolipoprotein B, OxPL-apo(a) oxidized phospholipids on apolipoprotein(a), and TIA transient ischemic attack.

† Race was reported by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Premature coronary artery disease was defined as disease that occurred before the age of 55 years in men and before the age of 65 years in women.

¶ This category includes patients who were not treated with statins.

‖ The LDL cholesterol level corrected for lipoprotein(a) (LDL-Ccorr) was calculated as the LDL cholesterol level minus the lipoprotein(a) mass multiplied by 0.3.

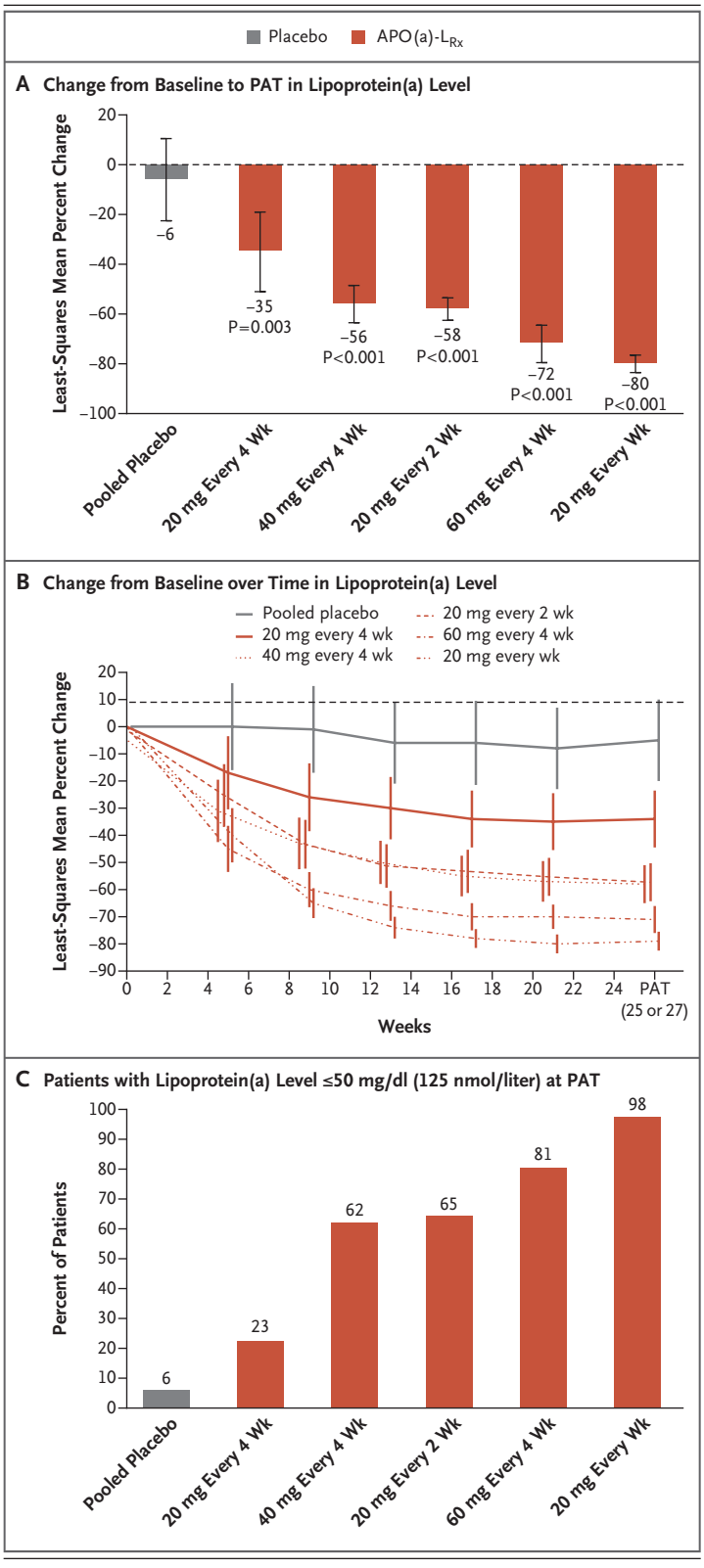

Figure 1. Effect of APO(a)-L_{Rx} on Lipoprotein(a) Level.

Panel A shows the least-squares mean percent changes from baseline to the primary analysis time point (PAT) (i.e., 6 months of exposure [at week 25 in the groups that received monthly doses and at week 27 in the groups that received more frequent doses]). I bars denote 95% confidence intervals. Panel B shows the least-squares mean percent changes from baseline in lipoprotein(a) over time. Error bars denote 95% confidence intervals. Panel C shows the percent of patients with lipoprotein(a) levels of less than 50 mg per deciliter (125 nmol per liter) in each group at the primary analysis time point.

OTHER PRESPECIFIED MEASURES

At 6 months of exposure, we observed mean reductions in levels of oxidized phospholipids on apolipoprotein B and levels of oxidized phospholipids on apolipoprotein(a) in all APO(a)-L_{Rx} groups. The mean percent reductions in oxidized phospholipids on apolipoprotein B were 37% at a dose of 20 mg every 4 weeks, 57% at 40 mg every 4 weeks, 64% at 20 mg every 2 weeks, 79% at 60 mg every 4 weeks, and 88% at 20 mg every week, as compared with a 14% increase in the placebo group. The ratios of geometric mean reductions from baseline (APO(a)-L_{Rx}:placebo) were 0.55 (95% CI, 0.38 to 0.81), 0.37 (95% CI, 0.26 to 0.54), 0.32 (95% CI, 0.22 to 0.46), 0.18 (95% CI, 0.13 to 0.27), and 0.11 (95% CI, 0.07 to 0.16) in the groups that received 20 mg every 4 weeks, 40 mg every 4 weeks, 20 mg every 2 weeks, 60 mg every 4 weeks, and 20 mg every week, respectively. (A ratio of geometric means of <1 indicates a larger reduction from baseline in the APO(a)-L_{Rx} group than in the placebo group.)

The mean percent reductions in oxidized phospholipids on apolipoprotein(a) were 28% at a dose of 20 mg every 4 weeks, 49% at 40 mg every 4 weeks, 45% at 20 mg every 2 weeks, 63% at 60 mg every 4 weeks, and 70% at 20 mg every week, as compared with a 20% decrease in the placebo group. The ratios of the geometric mean reductions from baseline (APO(a)-L_{Rx}:placebo) were 0.91 (95% CI, 0.68 to 1.21), 0.64 (95% CI, 0.48 to 0.86), 0.69 (95% CI, 0.52 to 0.92), 0.46 (95% CI, 0.35 to 0.62), and 0.38 (95% CI, 0.28 to 0.51) for 20 mg every 4 weeks, 40 mg every 4 weeks, 20 mg every 2 weeks, 60 mg every

Table 2. Absolute Change from Baseline at 6 Months of Exposure.*

Measure	APO(a)-L_{Rx}					Pooled Placebo (N=47)
	20 mg Every 4 Wk (N=48)	40 mg Every 4 Wk (N=48)	20 mg Every 2 Wk (N=48)	60 mg Every 4 Wk (N=47)	20 mg Every Wk (N=48)	
Lipoprotein(a) — nmol/liter	−95.9±94.4	−116.9±71.7	−130.3±66.1	−149.5±67.4	−187.8±80.3	−15.2±34.6
Lipoprotein(a) — mg/dl	−38.4±7.7	−46.8±28.7	−52.1±26.4	−59.8±27.0	−75.1±32.1	−6.1±13.8
OxPL-apoB — nmol/liter	−8.0±10.3	−11.3±11.0	−12.2±7.9	−14.9±10.3	−20.1±8.5	3.7±8.1
OxPL-apo(a) — nmol/liter	−16.8±14.3	−24.5±20.1	−25.9±17.2	−33.3±16.8	−41.6±16.5	−12.3±14.7
LDL cholesterol — mg/dl	−5.6±27.4	−13.5±30.1	−13.2±19.8	−8.2±17.3	−16.4±14.8	−1.2±17.8
Apolipoprotein B — mg/dl	−2.2±17.4	−8.3±18.2	−6.3±11.6	−3.9±13.5	−10.9±10.9	0.6±12.0
Total cholesterol — mg/dl	−3.9±32.1	−11.6±32.1	−11.6±24.4	−3.9±23.2	−11.6±20.9	−3.9±21.3
HDL cholesterol — mg/dl	0.0±6.2	0.0±9.7	3.7±8.9	3.7±11.6	3.7±10.1	0.0±6.6
Triglycerides — mg/dl	−8.9±32.8	−8.9±31.0	0.0±52.3	0.0±50.5	−8.9±41.6	0.0±51.4
hsCRP — mg/liter	−0.9±4.24	−0.7±4.24	−0.3±2.84	−0.5±2.22	−0.1±6.30	−0.8±5.13

* Plus–minus values are means ±SD. The primary analysis time point was at 6 months of exposure: week 25 in the groups that received monthly doses and week 27 in the groups that received more frequent doses. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

4 weeks, and 20 mg every week, respectively (Table 2 and Fig. S5A and S5B). We found mean reductions from baseline to 6 months in apolipoprotein B levels (ideal levels are <80 mg per deciliter in high-risk patients) and in laboratory-measured LDL cholesterol levels in all treatment groups (Table 2 and Fig. S5C and S5D). Waterfall plots of individual patients' percent changes from baseline in levels of oxidized phospholipids on apolipoprotein B, oxidized phospholipids on apolipoprotein(a), apolipoprotein B, and LDL cholesterol are shown in Figures S6 through S9.

SAFETY ANALYSES

Adverse events occurred in 90% of patients receiving APO(a)-L_{Rx} and in 83% of those receiving placebo during the treatment period; most of the events were mild or moderate (Table 3). Serious adverse events occurred in 10% of the patients receiving APO(a)-L_{Rx} and in 2% of those receiving placebo. Neither the overall incidence of adverse events nor the incidence of serious adverse events showed a dose-dependent pattern (Table 3). Overall, 5% of patients who received APO(a)-L_{Rx} and 4% of those who received placebo discontinued participation in the trial owing to adverse events. The most frequent adverse events leading to discontinuation among patients who received APO(a)-L_{Rx} were myalgia or arthralgia or postinjection general discomfort (malaise). No patients discontinued participation for protocol-defined reasons. Injection-site reactions, the most frequently reported adverse event, occurred in 27% of the patients who received APO(a)-L_{Rx} and in 6% of those who received placebo during the trial. Approximately 7% of injections were associated with injection-site reactions irrespective of the dose or regimen (Table 3). These reactions were mostly mild, and the most common was erythema (26%). One patient discontinued treatment with APO(a)-L_{Rx} because of injection-site reactions.

Other adverse events that occurred in more than 10% of patients who received APO(a)-L_{Rx} and were more frequent than in the placebo group were urinary tract infection (13% vs. 6%), myalgia (12% vs. 11%), and headache (11% vs. 8%). The incidence of influenza-like symptoms was similar in the APO(a)-L_{Rx} group and the placebo group (7% and 6%, respectively). Platelet-count monitoring that was conducted every 2 weeks did not reveal a dose- or time-dependent effect of APO(a)-L_{R}, and no patient had a platelet count lower than 100,000 per cubic millimeter (Table 3

Table 3. Adverse Events and Laboratory Measurements during the Treatment Period.*

Event or Measurement	APO(a)-L_{Rx}					Pooled Placebo (N = 47)
	20 mg Every 4 Wk (N = 48)	40 mg Every 4 Wk (N = 48)	20 mg Every 2 Wk (N = 48)	60 mg Every 4 Wk (N = 47)	20 mg Every Wk (N = 48)	
Adverse events						
Any adverse event — no. of patients (%)	46 (96)	42 (88)	41 (85)	43 (91)	42 (88)	39 (83)
Mild	26 (54)	21 (44)	25 (52)	18 (38)	21 (44)	22 (47)
Moderate	14 (29)	18 (38)	14 (29)	20 (43)	19 (40)	15 (32)
Severe	6 (12)	3 (6)	2 (4)	5 (11)	2 (4)	2 (4)
Serious adverse event — no. of patients (%)	6 (12)	7 (15)	3 (6)	6 (13)	3 (6)	1 (2)
Adverse event leading to treatment discontinuation — no. of patients (%)	2 (4)	0	1 (2)	3 (6)	6 (12)	2 (4)
Death — no. of patients (%)	0	0	0	1 (2)	1 (2)	0
Injection-site reaction — no. of patients (%)†	5 (10)	15 (31)	11 (23)	12 (26)	22 (46)	3 (6)
Injections leading to injection-site reaction — no. of injections/total no. (%)	6/393 (1.5)	36/438 (8.2)	59/819 (7.2)	34/396 (8.6)	126/1495 (8.4)	3/720 (0.4)
Influenza-like symptoms — no. of patients (%)‡	0	4 (8)	4 (8)	6 (13)	2 (4)	3 (6)
Laboratory measurements — no. of patients (%)§						
Platelet count						
<140,000/mm^3¶	3 (6)	8 (17)	3 (6)	3 (6)	8 (17)	7 (15)
<100,000/mm^3	0	0	0	0	0	0
ALT level >3× ULN	0	0	0	0	0	0
AST level >3× ULN	0	0	1 (2)	0	0	0
eGFR decrease of >25% from baseline‖	2 (4)	1 (2)	0	1 (2)	3 (6)	3 (6)
eGFR decrease of >40% from baseline‖	1 (2)	0	0	0	0	0
Urine albumin (mg):creatinine (g) ratio >250	1 (2)	0	0	1 (2)	1 (2)	3 (6)
Urine protein (mg):creatinine (g) ratio >500	1 (2)	0	0	2 (4)	1 (2)	2 (4)
24-hr creatinine clearance decrease of >40% from baseline**	0	1 (2)	1 (2)	0	0	0
24-hr creatinine clearance <45 ml/min/1.73 m^2	0	0	0	0	0	0
24-hr urine protein >1 g	0	0	0	0	0	0

* The treatment period was defined as the period from the first dose through one dosing interval after the last dose. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Category includes any adverse event at the injection site persisting for at least 2 days.
‡ Category includes any of the following adverse events starting on the day of the injection or the next day: influenza-like illness, chills, myalgia, arthralgia, pyrexia, feeling hot, or a body temperature increase.
§ Values were confirmed by a second measurement within 1 week. In cases in which a second measurement was not available, the result was considered confirmed.
¶ Category includes patients who had two occurrences of the platelet count.
‖ The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.
** This event was due to prerenal causes in the patient who received 40 mg every 4 weeks and was due to incomplete 24-hr urine collection in the patient who received 20 mg every 2 weeks.

and Fig. S10). No patient had liver or renal toxic effects that met the predetermined thresholds for treatment discontinuation. There were no clinically significant changes in other laboratory measures (including coagulation panel), vital signs, or electrocardiographic measures. High-sensitivity C-reactive protein (CRP) levels were measured as a safety outcome to gauge potential proinflammatory effects of APO(a)-L_{Rx}. Baseline high-sensitivity CRP levels were between 2 and 3 mg per liter across the groups (Table 1). The absolute mean changes in the high-sensitivity CRP level at 6 months of exposure were −0.9±4.2 mg per liter in the group that received 20 mg every 4 weeks, −0.7±4.2 mg per liter in the group that received 40 mg every 4 weeks, −0.3±2.8 mg per liter in the group that received 20 mg every 2 weeks, −0.5±2.2 mg per liter in the group that received 60 mg every 4 weeks, and −0.1±6.3 mg per liter in the group that received 20 mg every week, as compared with −0.8±5.2 mg per liter in the pooled placebo group.

Two deaths occurred during the trial, both in patients receiving APO(a)-L_{Rx}. One patient in the group that received 60 mg every 4 weeks died in a road traffic accident, and one patient in the group that received 20 mg every week committed suicide as a result of depression.

DISCUSSION

APO(a)-L_{Rx} treatment resulted in dose-dependent reductions in lipoprotein(a) levels in patients with cardiovascular disease; these reductions were significant at all doses studied, with a mean 80% reduction at the highest dose (20 mg weekly). At the highest cumulative dose regimen, which was equivalent to 80 mg monthly, 98% of patients attained a lipoprotein(a) level of 50 mg per deciliter (125 nmol per liter) or lower, a target value supported by European[15] and U.S.[16] guidelines and by empirical data from patients treated with statins.[17] We found reductions in levels of oxidized phospholipids on apolipoprotein B and oxidized phospholipids on apolipoprotein(a), both of which are proinflammatory components that are present on lipoprotein(a) and on apolipoprotein(a) and are linked to a higher atherothrombotic risk.[18-20] Finally, we noted reductions in LDL cholesterol and apolipoprotein B in patients receiving APO(a)-L_{Rx}, beyond those achieved with aggressive background lipid-lowering therapy.

The patients enrolled in this trial all had established cardiovascular disease, even though two thirds of the patients were under 65 years of age, which is generally younger than is typical in cardiovascular trials. This age profile was consistent with the lipoprotein(a) level being genetically determined and therefore a lifelong risk factor. Other ways in which the patients in the pooled trial population differed from participants in other cardiovascular trials were the relatively high percentages of patients with premature cardiovascular disease (40%) and familial hypercholesterolemia (approximately 30%) and the relatively low body-mass index and likelihood of having type 2 diabetes. That 97% of the patients were white is a limitation of the trial.

Patients with elevated lipoprotein(a) levels often cannot reach very low LDL cholesterol levels even with aggressive LDL-lowering therapy, because lipoprotein(a) cholesterol is comeasured with LDL cholesterol.[21] Consistent with this observation is the fact that, in the current trial, mean LDL cholesterol levels at baseline were approximately 70 to 80 mg per deciliter despite treatment with up to three drugs. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, patients in whom very low LDL cholesterol levels could not be achieved had markedly elevated lipoprotein(a) levels.[22] Most LDL-lowering drugs do not substantially lower lipoprotein(a), and statins often have a neutral or modest lipoprotein(a)-increasing effect.[17,23]

Evidence from studies of primary prevention indicate that elevated lipoprotein(a) levels are associated with an increased atherothrombotic risk — in particular, an increased risk of myocardial infarction.[4] The role of lipoprotein(a) in the context of secondary prevention remains controversial. Although meta-analyses have intrinsic limitations, we would note that in a patient-level meta-analysis of statin outcomes trials that included 5751 events and 95,576 person-years at risk, the risk of elevated lipoprotein(a) was almost linearly associated with the risk of cardiovascular disease, and lipoprotein(a) levels greater than 50 mg per deciliter (125 nmol per liter) among patients who were taking statins were associated with significantly higher risk.[17] Furthermore, a recent analysis of data from the placebo group in the FOURIER trial showed that higher levels of lipoprotein(a) are associated with

an increased risk of cardiovascular events in patients with established cardiovascular disease, irrespective of LDL cholesterol levels.[24]

Among lipoproteins, lipoprotein(a) is the highest-capacity carrier of oxidized phospholipids,[25] which are responsible for many of its proinflammatory effects.[26-28] In our trial, dose-dependent reductions were noted in oxidized phospholipids on apolipoprotein B and oxidized phospholipids on apolipoprotein(a) in plasma which, we posit, reflects effects of APO(a)-L_{Rx} on the oxidized phospholipid content of lipoprotein(a). In previous studies, oxidized phospholipids on apolipoprotein B, primarily reflecting the oxidized phospholipid content of lipoprotein(a), predicted first and recurrent myocardial infarction, stroke, and aortic stenosis.[18-20]

The reduction in LDL cholesterol and apolipoprotein B levels by ASOs targeting *LPA* mRNA, in the presence of aggressive lipid-lowering therapy, has been documented in previous studies.[9,10] Such findings may indicate that, when the synthesis of apolipoprotein(a) is inhibited in the liver, apolipoprotein B lipoproteins — which would otherwise be destined to become lipoprotein(a), with relatively low plasma clearance as a result of weak interactions with the LDL receptor — are converted to LDL particles with relatively strong affinity for the LDL receptor and hence a relatively quick and efficient clearance from the blood.[10]

We did not observe marked changes in platelet, renal, or liver function, nor a between-group difference in the risk of influenza-like symptoms. The most common adverse events among patients who received APO(a)-L_{Rx} were injection-site reactions, which were generally mild.

Elevated levels of lipoprotein(a) are a cardiovascular risk factor for which no effective pharmacological therapy currently exists. In this trial, we found that APO(a)-L_{Rx} provided potent reductions in levels of lipoprotein(a) in patients with cardiovascular disease.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: the Divisions of Cardiovascular Medicine (S.T.) and Endocrinology and Metabolism (J.L.W.), University of California, San Diego, La Jolla, and Ionis Pharmaceuticals, Carlsbad (S.T., S.X., N.J.V.) — both in California; Akcea Therapeutics, Boston (E.K.-P., J.G., L.O.); Polyclinic for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, Cologne, Germany (I.G.-B.); Montreal Heart Institute, Université de Montréal, Montreal (J.-C.T.); Excel Medical Clinical Trials, Boca Raton, FL (S.J.B.); the Department of Endocrinology and Metabolism, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität Berlin, Berlin Institute of Health, Berlin (E.S.-T.), and the Division of Geriatrics, University Medicine Greifswald, Greifswald (E.S.-T.) — both in Germany; the Center for Preventive Cardiology, Knight Cardiovascular Institute, Oregon Health and Science University, Portland (M.D.S.); the Department of Vascular Medicine, Academic Medical Center, Amsterdam (E.S.S.); the Division of Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City (P.M.M.); and the Department of Clinical Biochemistry and the Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev (B.G.N.), and the Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen (B.G.N.) — all in Denmark.

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4. Relevant section/ rules	Section 14
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