**Original Research**

Pharmacokinetics, Pharmacodynamics, and Tolerability of Olpasiran in Healthy Japanese and Non-Japanese Participants: Results from a Phase I, Single-dose, Open-label Study

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**ABSTRACT**

**Purpose:** Olpasiran, an N-acetyl galactosamine-conjugated, hepatocyte-targeted, small interfering RNA, is being developed to reduce plasma lipoprotein (Lp)-(a) concentration by directly targeting the LPA gene. This study evaluated the pharmacokinetics, pharmacodynamics, and tolerability of a single SC injection of olpasiran in healthy, Japanese and non-Japanese participants.

**Methods:** In this Phase I, open-label, parallel-design study, Japanese participants were randomized in a 1:1:1:1 ratio to receive a single 3, 9, 75, or 225 mg dose of olpasiran. Non-Japanese participants received a single 75 mg dose of olpasiran. The primary end points were pharmacokinetic parameters, including Cmax, AUCinf, tmax, and t1/2. Tolerability and change in Lp(a) concentration were also assessed.

**Findings:** A total of 27 enrolled participants had a mean (SD) age of 48.0 (12.5) years. Olpasiran Cmax and AUCinf were increased in an approximately dose-proportional manner in the Japanese groups. Mean (SD) Cmax values were 242 (121.0) and 144 (71.3) ng/mL, and mean (SD) AUCinf values were 3550 (592.0) and 2620 (917.0) h-ng/mL, in the Japanese and non-Japanese groups, respectively, given 75 mg of olpasiran. Median tmax ranged from 3.0 to 9.0 hours and mean (SD) t1/2 ranged from 4.0 (0.3) to 6.9 (1.6) hours across all groups. The maximal Lp(a) reduction occurred at day 57, with mean (SD) Lp(a) percentage reductions from baseline ranging from 56.0% (21.0%) to 99.0% (0.2%). A reductions in Lp(a) was observed as early as day 4. All adverse events were mild in severity, with no serious or fatal adverse events. No clinically important changes in tolerability-related laboratory analytes or vital signs were observed.

**Implications:** In this population of healthy Japanese participants, dose-proportional increases in exposure and reduced Lp(a) in a dose-dependent manner were found with single 3, 9, 75, and 225 mg doses of olpasiran. The magnitude and durability of Lp(a) reductions were similar between the Japanese and non-Japanese groups. Olpasiran was well tolerated, with no clinically important adverse events or laboratory or vital sign abnormalities. (Clin Ther. 2022;000:1–11.) © 2022 Amgen Inc. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

**Keywords:** Japanese adults, Lipoprotein(a), olpasiran, Pharmacokinetics, Tolerability, Small interfering RNA.

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**Accepted for publication July 16, 2022**

https://doi.org/10.1016/j.clinthera.2022.07.008

0149-2918/S - see front matter

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is among the most significant health problems in Japan, with stroke and ischemic heart disease being the second and third leading causes of mortality, respectively. Although lipid-lowering therapies have improved ASCVD-related outcomes, residual risk persists and the cost burden is still high in the Japanese population. Lipoprotein (Lp)-(a) is composed of a low-density lipoprotein–like particle containing apolipoprotein (apo) B-100 that is covalently bound to a unique glycoprotein apo(a). It has been reported that the plasma Lp(a) level is primarily determined by the LPA gene encoding apo(a) and is not significantly influenced by dietary or environmental factors. Over the past decade, epidemiologic evidence and genomic studies have shown that an elevated plasma Lp(a) level is associated with an increased risk for coronary heart disease and atherosclerosis-related disorders. Prospective studies and mendelian randomization analyses have supported a causal role of Lp(a) level in ASCVD and a shorter lifespan. Even though Lp(a) serum concentrations vary greatly across racial groups, the associated ASCVD risk appears similar. Japanese lipid guidelines affirm that Lp(a) is an independent risk factor for ASCVD.

Currently, effective Lp(a)-reducing therapies that specifically target Lp(a) are lacking. Lipid-modulating agents such as niacin and proprotein convertase subtilisin/kexin type 9 inhibitors have shown modest Lp(a)-lowering effects. Nucleic acid–based drugs, including antisense oligonucleotides and small interfering (si)-RNA, represent first-in-class therapeutics that specifically target LPA transcripts for degradation. With olpasiran, an N-acetyl galactosamine (GalNAc)-conjugated, hepatocyte-targeted siRNA, serum Lp(a) was reduced by >98% transiently and by >85% for >5 weeks after a single SC injection in transgenic mice. In cynomolgus monkeys, a >80% reduction in serum Lp(a) concentration for up to 45 days after nadir was found with a single SC 3 or 10 mg/kg dose of olpasiran. In a first-in-human (FIH) clinical study in participants with elevated baseline Lp(a) levels (>70 nmol/L), a dose-dependent reduction in Lp(a) level was found with a single SC 3, 9, 30, 75, or 225 mg injection of olpasiran, with a maximal mean percentage change from baseline ranging from −71% to −97% across all dose cohorts. Olpasiran was well tolerated, with no clinically relevant changes in tolerability-related parameters. The present Phase I, open-label, parallel-group, single-dose study was designed to evaluate the pharmacokinetic and pharmacodynamic (PK/PD) characteristics and tolerability of a single SC injection of olpasiran at four dose levels (3, 9, 75, and 225 mg) in healthy Japanese participants and at one dose level (75 mg) in healthy non-Japanese participants with no study entry criterion regarding baseline Lp(a) level.

PARTICIPANTS AND METHODS

Study Design and Treatment

This Phase I, open-label, parallel-group, single-dose study was conducted at two centers in the United States. The primary objective was to characterize the PK properties of olpasiran after a single SC administration in Japanese and non-Japanese participants. The secondary objective was to assess the tolerability of olpasiran. Enrolled participants were 18 to 60 years of age, with a body mass index between 18 and 32 kg/m². Japanese participants were first-generation Japanese, defined as having four grandparents, biological parents, and participants born in Japan. Key exclusion criteria included a history or clinical evidence of peripheral neuropathy, bleeding diathesis or any coagulation disorder, diabetes mellitus, unstable medical condition, a history of malignancy of any type, and/or use of apheresis as lipid-reducing therapy at screening or any medications within 14 days before dosing and during the study. No entry threshold criterion regarding Lp(a) level was applied in this study.

Healthy Japanese participants were randomly assigned, in a 1:1:1:1 ratio, to receive a single SC dose of open-label olpasiran at 3, 9, 75, or 225 mg. Healthy non-Japanese participants received a single SC dose of open-label olpasiran at 75 mg (Figure 1). The selection of doses was based on available PK, PD, and tolerability data from an ongoing FIH study (NCT03626662). The selected doses were predicted to provide a dynamic range of data to support a robust evaluation of the exposure–response relationship for olpasiran in Japanese and non-Japanese participants. These dose levels were also supported by conservative dose margins based on the no-observed-adverse-effect level in rats and cynomolgus monkeys (150 mg/kg). The lowest (3 mg) and highest (225 mg) doses were 3000- and 40-fold lower, respectively, than the no-observed-adverse-effect level on a dose (mg/kg) basis, assuming an adult body weight of 60 kg. The 75 mg dose was associated with near-maximal Lp(a) reductions that were anticipated to translate into clinically meaningful
reductions in cardiovascular events. Thus, these dose levels provided an assessment of tolerability and PK data on olpasiran as well as an evaluation of the magnitude and durability of Lp(a) response in Japanese and non-Japanese participants.

All procedures in this study were conducted in accordance with International Council for Harmonisation and the Declaration of Helsinki guidelines. The study protocol, all amendments, and the informed-consent form were reviewed and approved by an institutional review board at each study center. All participants provided informed consent prior to any study-related procedures.

PK Assessments
Blood samples for PK assessments were collected at predose and 30, 60, 180, 360, and 720 minutes postdose on day 1 also on days 2, 3, 4, 7, 15, 29, and 57. PK parameters included AUC, AUC$_{\text{last}}$, AUC$_{\text{inf}}$, dose-normalized AUC$_{\text{inf}}$ (DN_AUC$_{\text{inf}}$, calculated as AUC$_{\text{inf}}$ divided by the actual dose), C$_{\text{max}}$, dose-normalized C$_{\text{max}}$ (DN_C$_{\text{max}}$, calculated as C$_{\text{max}}$ divided by the actual dose), t$_{\text{max}}$, and t$_{1/2}$. These parameters were estimated using noncompartmental analysis. Concentrations below the lower limit of quantification (<0.400 ng/mL) were set to 0 prior to data analysis. Actual doses administered and actual sampling times were used in the noncompartmental analysis, and nominal times (hours postdose) were used for data presentation. Any PK profiles with an $R^2$ value of <0.7 and %AUC extrapolated >20% were excluded from the AUC$_{\text{inf}}$ and t$_{1/2}$ calculations. Terminal half-life (t$_{1/2}$x) was estimated via linear regression based on data points selected during the log-linear phase of the PK profile that represented the overall effective elimination half-life. Phoenix WinNonlin software version 8.3.2 was used as part of a validated Pharsight Knowledgebase Server system version 4.0.4 (Certara, Princeton, New Jersey). Mean PK graphs were plotted using SigmaPlot software version 14.0 (Systat Software Inc, San Jose, California).

PK Analytical Assay
In a validated quantitative assay designed to detect olpasiran concentrations in human serum, the analyte in calibration standards, quality controls, and samples was hybridized to two complimentary oligonucleotides. One of the oligos (capture probe) was labeled with biotin to permit capture of the complex on a streptavidin-coated Meso Scale Discovery plate (Meso Scale Diagnostics, Rockville, Maryland). The second oligo (detection probe) was labeled with digoxigenin. The hybridized analyte was transferred to the Meso Scale Discovery plate and detected with an anti-digoxigenin antibody, which was labeled with ruthenium. After the addition of read buffer, the plate was read in a Meso Scale Discovery Sector S 600 plate reader. The calibration standards ranged from 0.400 to 500 ng/mL. This assay required a minimum of 20 μL of human serum aliquot. Samples were kept frozen at −80°C ± 10°C prior to analysis. A four-parameter, logistic, 1/response²-weighted, least-squares regression algorithm was used to quantitate unknown samples. A sample analysis was conducted at PPD Laboratories (Richmond, Virginia).

Lp(A) Analytical Assay
Plasma Lp(a) level was measured by a validated double monoclonal antibody–based ELISA method developed by the Northwest Lipid Metabolism and Diabetes Research Laboratories at the University of Washington (Seattle, Washington). In brief, Lp(a)
molecules were first captured by monoclonal antibody a-6 in assay plates, then detected by monoclonal antibody a-40. The detecting antibody a-40 is specific to a unique epitope in apo(a) K4 type 9, without any cross-reactivity to K4 type 2 repeats, and therefore is independent of apo(a) size polymorphism. Lp(a) concentrations are reported in nmol/L.

Tolerability Assessment

Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities version 23.0. Tolerability assessments included physical examination (including assessment for peripheral neuropathy), hypersensitivity reactions, ECG assessment, laboratory tests (including liver function tests), renal function tests, coagulation and hematologic parameters, glucose, and metabolic acidosis (if needed). All TEAEs and the use of concurrent medication were collected for the duration of the study, up to and including day 225 or the end-of-study visit. Bioanalytical testing for anti-olpasiran antibodies was not conducted because there were no unexpected PK or PD findings or safety signals that warranted further investigation by characterizing drug immunogenicity.

Study End Points

The primary end points were PK parameters, including Cₘₐₓ, tₘₐₓ, t₁/₂, and AUC. The secondary end points were TEAEs and changes in tolerability-related laboratory results and vital signs. Exploratory end points were changes in plasma Lp(a) and biomarkers, including, but not limited to, total cholesterol and cholesterol fractions (very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apoA1, and total apoB).

Statistical Analysis

The pharmacokinetic analysis set (PAS) included all dosed participants in whom at least one PK parameter or end point could be adequately estimated. The safety analysis set (SAS) included all participants who were enrolled and received at least one dose of olpasiran. The PAS was used for assessing primary and exploratory end points, while the SAS was used for assessing secondary end points. With a total of 20 to 30 total participants receiving olpasiran, there was a 64% to 79% risk for detecting an adverse event (AE) with a true prevalence rate of 5% or greater. With 16 to 24 Japanese participants receiving olpasiran, there was a 56% to 71% risk for detecting an AE with a true prevalence rate of 5% or greater.

All data were analyzed descriptively. Descriptive statistics on continuous measurements include means, medians, SDs, and ranges; and categorical data summarized using frequency counts and percentages. Descriptive statistics by treatment group are reported for PK, PD, vital signs, and clinical laboratory data. The prevalences of TEAEs were tabulated by system organ class and preferred term and further classified by treatment group.

RESULTS

Baseline Demographic and Clinical Characteristics

Between April 2019 and May 2020, a total of 27 participants were enrolled and received a single dose of olpasiran. Four participants (14.8%) were discontinued due to withdrawal of consent from the study. All 27 participants were included in the SAS and the PAS. Baseline demographics and clinical characteristics are summarized in Table 1. The mean (SD) ages were 51.5 (9.6) years in the collective Japanese group and 36.0 (14.8) years in the non-Japanese group. In the collective Japanese group, 52.4% were men; in the non-Japanese group, all participants were men. The mean (SD) body mass index values were 23.5 (3.1) kg/m² in the Japanese group and 25.6 (3.0) kg/m² in the non-Japanese group. Five participants (18.5%) used at least one concurrent medication during the study (3 participants used paracetamol and 2 participants used hydrocortisone).

Pharmacokinetics

The serum olpasiran concentration–time profiles are presented in Figure 2, and the estimates of PK parameters are listed in Table II. The PAS comprised 378 samples from all 27 participants. A total of 15 samples (4.0%) were excluded from serum concentration–time summary statistics due to actual time deviations of ≥20% from nominal time and unscheduled visits.

Exposure, as assessed by Cₘₐₓ and AUCᵢₙᵣ, was increased in an approximately dose-proportional manner in the Japanese cohorts (Table II). With a 3-fold change in the olpasiran dose level, from 3 to 9 mg, Cₘₐₓ and AUCᵢₙᵣ values were changed by 2.7- and 3.2-fold, respectively. Similarly, with a 3-fold change in dose

Table I. Baseline demographics and clinical characteristics. Results expressed as mean (SD) for continuous variables and frequency (percentage) for categorical variables.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Olpasiran 3 mg (n = 6)</th>
<th>Olpasiran 9 mg (n = 6)</th>
<th>Olpasiran 75 mg (n = 5)</th>
<th>Olpasiran 225 mg (n = 4)</th>
<th>Overall (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.0 (4.6)</td>
<td>49.0 (9.7)</td>
<td>45.2 (13.7)</td>
<td>56.3 (4.9)</td>
<td>51.5 (9.6)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>2 (33.3)</td>
<td>3 (50.0)</td>
<td>5 (100)</td>
<td>1 (25.0)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>22.7 (3.7)</td>
<td>24.1 (2.7)</td>
<td>23.7 (3.4)</td>
<td>23.4 (3.7)</td>
<td>23.5 (3.1)</td>
</tr>
<tr>
<td>Hispanic/Latino, no. (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td>Asian: 6 (100)</td>
<td>6 (100)</td>
<td>5 (100)</td>
<td>4 (100)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Black or African American: NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>White: NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Other: NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Lp(a), mean (SD), nmol/L</td>
<td>41.1 (34.4)</td>
<td>96.9 (71.0)</td>
<td>32.9 (45.2)</td>
<td>34.7 (18.8)</td>
<td>33.0 (39.9)</td>
</tr>
<tr>
<td>Lp(a), median (Q1, Q3), nmol/L</td>
<td>30.6 (18.5, 46.1)</td>
<td>105.4 (23.8, 160.7)</td>
<td>7.3 (3.9, 42.6)</td>
<td>35.4 (18.8, 50.6)</td>
<td>19.9 (10.0, 30.4)</td>
</tr>
</tbody>
</table>
| BMI = body mass index; Lp(a) = lipoprotein (a); NA = not applicable.

level, from 75 to 225 mg, the C<sub>max</sub> and AUC<sub>inf</sub> values were changed by 2.3- and 4.1-fold, respectively. Dose-normalized AUC<sub>inf</sub> values were generally similar across all dose levels. Mean (SD) C<sub>max</sub> was 144 (71.3) ng/mL, and mean (SD) AUC<sub>inf</sub> was 2620 (917.0) h·ng/mL, in the 75 mg non-Japanese cohort. Mean C<sub>max</sub> and AUC<sub>inf</sub> values were 1.68- and 1.35-fold higher, respectively, in the 75 mg Japanese cohort than in the 75 mg non-Japanese cohort.

Across dose levels in the Japanese cohorts, the median t<sub>max</sub> ranged from 3.0 to 9.0 hours and mean (SD) t<sub>1/2</sub> values ranged from 4.0 (0.3) to 6.9 (1.6) hours. In the 75 mg Japanese and non-Japanese cohorts, median t<sub>max</sub> values were 3.0 and 3.5 hours, respectively, and mean (SD) t<sub>1/2</sub> values were 4.8 (1.0) and 6.4 (1.4) hours, respectively.

Pharmacodynamics

The mean (SD) baseline Lp(a) values across all cohorts ranged from 32.9 (45.2) to 96.9 (71.0) nmol/L, and the median (Q1, Q3) baseline Lp(a) values ranged from 7.3 (3.9, 42.6) nmol/L to 105.4 (23.8, 160.7) nmol/L. Lp(a) was reduced in a dose-dependent manner with a single SC injection of olpasiran, with greater magnitudes of Lp(a) suppression and extended periods of sustained maximal suppression achieved with higher doses. Maximal Lp(a) reductions occurred at day 57, with mean (SD) Lp(a) percentage reductions from baseline ranging from 56.0% (21.0%) to 99.0% (0.2%) (Figure 3). Reductions in Lp(a) were observed as early as day 4. From days 29 to 225, Lp(a) reductions were sustained, with mean percentage reductions of ≥68% at the 75 mg dose (in both the Japanese and...
Figure 2. Mean (SD) serum olpasiran concentration–time profiles, by dose level, on linear and semi-logarithmic scales. Inset shows the same data, magnifying the values through day 7.

non-Japanese cohorts) and ≥90% at the 225 mg dose. Mean Lp(a) percentage reductions returned to within 50% of baseline by day 225 in the 3 and 9 mg dose cohorts.

The overall mean reductions in Lp(a) concentration after a single dose of 75 mg olpasiran were similar between the Japanese cohort and the non-Japanese cohort. In both groups, the same mean baseline Lp(a) level (33 nmol/L) and the same mean percentage reduction from baseline in Lp(a) at day 57 (95%) were observed.

T tolerability

A summary of TEAEs during the study is provided in Table III. All AEs were mild in severity. There were no serious or fatal AEs. In the 9 mg cohort, 1 participant had headache on days 1 and 2 which resolved on day 4, and 1 participant had vitreous floaters on day 30 which resolved on day 93. All other AEs were considered by the investigator as unrelated to olpasiran use. Two participants (33.3%) in the 3 mg cohort, 4 participants (66.7%) in the 9 mg cohort, and 3 participants (75.0%) in the 225 mg cohort

Table II. Olpasiran PK properties, by dose level. Data are given as mean (SD), except for $t_{\text{max}}$, which is presented as median (range).

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>$t_{\text{max}}$, h</th>
<th>Cmax, ng/mL</th>
<th>DN_Cmax, ng/mL/mg</th>
<th>AUCinf,* h-ng/mL</th>
<th>DN_AUCinf, h-ng/mL/mg</th>
<th>AUClast, h-ng/mL</th>
<th>$t_{1/2}$,* h</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Japanese subjects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg</td>
<td>6</td>
<td>3.0 (1.0–6.0)</td>
<td>13.1 (3.99)</td>
<td>4.35 (1.33)</td>
<td>114† (39.8)</td>
<td>38.0† (13.3)</td>
<td>110 (28.7)</td>
<td>4.02† (0.341)</td>
</tr>
<tr>
<td>9 mg</td>
<td>6</td>
<td>3.0 (3.0–3.0)</td>
<td>34.8 (14.2)</td>
<td>3.86 (1.58)</td>
<td>370 (89.7)</td>
<td>41.0 (9.97)</td>
<td>359 (93.2)</td>
<td>4.38 (1.2)</td>
</tr>
<tr>
<td>75 mg</td>
<td>5</td>
<td>3.0 (1.0–12.0)</td>
<td>242 (121.0)</td>
<td>3.22 (1.62)</td>
<td>3550 (592.0)</td>
<td>47.4 (7.9)</td>
<td>3550 (592.0)</td>
<td>4.81 (0.959)</td>
</tr>
<tr>
<td>225 mg</td>
<td>4</td>
<td>9.0 (6.0–12.0)</td>
<td>548 (222.0)</td>
<td>2.43 (0.987)</td>
<td>14400 (3780.0)</td>
<td>64.2 (16.8)</td>
<td>14400 (3780.0)</td>
<td>6.88 (1.55)</td>
</tr>
<tr>
<td>Non-Japanese subjects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 mg</td>
<td>6</td>
<td>3.5 (1.0–12.0)</td>
<td>144 (71.3)</td>
<td>1.91 (0.951)</td>
<td>2620 (917.0)</td>
<td>34.9 (12.2)</td>
<td>2610 (919.0)</td>
<td>6.43 (1.35)</td>
</tr>
</tbody>
</table>

* Half-life ($t_{1/2}$) values for the 75 and 225 mg dose groups represent the β phase in the PK profile, whereas values in the 3 and 9 mg groups represent the terminal phase. Similarly, AUCinf values for the 75 and 225 mg group are based on the β phase, whereas values in the 3 and 9 mg groups are based on the terminal phase.

† $n = 3$. DN_AUCinf = dose-normalized AUCinf; DN_Cmax = dose-normalized Cmax; PK = pharmacokinetic.

Figure 3. Mean (SE) percentage changes from baseline in lipoprotein (Lp)-a over time, by olpasiran dose level.

had at least one AE. Overall, a single participant reported each AE, except for upper respiratory tract infection (1 participant each in the 9 and 225 mg cohorts) and rash (1 participant each in the 3 and 9 mg cohorts). None of the participants in the 75 mg cohorts (Japanese or non-Japanese) experienced any AEs. No notable differences in laboratory parameters were observed between cohorts. There were no clinically significant changes from baseline in creatine kinase, alanine aminotransferase, aspartate aminotransferase,
Clinical Therapeutics

Table III. Subject prevalence of treatment-emergent adverse events, by dose.

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Olpasiran 3 mg (n = 6)</th>
<th>Olpasiran 9 mg (n = 6)</th>
<th>Olpasiran 75 mg (n = 5)</th>
<th>Olpasiran 225 mg (n = 4)</th>
<th>Non-Japanese Cohort: Olpasiran 75 mg (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TEAEs</td>
<td>2 (33.3)</td>
<td>4 (66.7)</td>
<td>0</td>
<td>3 (75.0)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs by preferred term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcer</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral swelling</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Upper-airway cough syndrome</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event; TEAE = treatment-emergent adverse event.

other laboratory measures, vital signs, or ECG. Given that there were no unexpected PK or PD findings or any safety signals that warranted further investigation of drug immunogenicity, bioanalytical testing for anti-olpasiran antibodies was not conducted.

**DISCUSSION**

Olpasiran is a GalNAc-conjugated siRNA developed to specifically knock down hepatic Lp(a) production. This Phase I, open-label, parallel-group, single-dose study characterized the PK, PD, and tolerability profile of olpasiran at four dose levels (3, 9, 75, and 225 mg) in healthy Japanese participants and at one dose level (75 mg) in healthy non-Japanese participants. The results demonstrated that olpasiran was rapidly absorbed, well tolerated without any clinically important safety issues, and elicited robust and durable Lp(a) reduction.

When olpasiran was administered at a single SC dose of 0.1, 1, 3, and 10 mg/kg in cynomolgus monkeys, its PK was linear over the dose range. The dose-normalized AUClast and Cmax values were within 3-fold. Mean terminal t1/2 values ranged from 3.1 to 5.1 hours (data on file, Brooke Rock, PhD; Study 124309; Amgen, Inc.). In a Phase I FIH study, olpasiran was rapidly absorbed, with a mean tmax of within 7.5 hours after the administration of single SC doses of 3, 9, 30, 75, or 225 mg. Mean serum t1/2 ranged from 3.0 to 8.0 hours, with most of olpasiran cleared from the serum within 2 to 3 days. At doses up to 225 mg olpasiran, systemic exposures were increased nearly dose proportionally. Similarly, the present study...
in Japanese participants showed approximately dose-proportional increases of olpasiran C_{max} and AUC from 3 to 225 mg dose levels. Median t_{max} values ranged from 3.0 to 9.0 hours and mean t_{1/2} values ranged from 4.0 to 6.9 hours across all cohorts. At the 75 mg dose level, mean AUC_{inf} and C_{max} values were 1.35- and 1.68-fold higher, respectively, in the Japanese cohort than in the non-Japanese cohort. This modest trend of higher exposures in Japanese participants may be explained by lower body weights and smaller volumes of distribution in Japanese participants compared with non-Japanese participants. Specifically, a trend of lower exposure with higher body weight was observed. It should be noted, however, that there was significant overlap between individual C_{max} and AUC values among the Japanese cohorts. The small number of participants in each dose cohort should also be taken into consideration.

In the FIH study,\textsuperscript{20} Lp(a) reduction occurred in a dose-responsive manner. The maximal mean Lp(a) percentage changes from baseline ranged from −71\% to −97\% in patients whose screening Lp(a) level was between 70 and 199 nmol/L and from −76\% to −91\% in patients whose screening Lp(a) level was ≥200 nmol/L. The maximal Lp(a) suppression was observed between days 43 and 71 postdose and was sustained for longer durations at higher dose levels. At day 225, the Lp(a) level gradually returned toward baseline. The present study also demonstrated a dose-dependent Lp(a) reduction with a single dose of olpasiran ranging from 3 to 225 mg. Mean percentage changes from baseline in Lp(a) ranged from −56\% to −99\%, with maximal suppression occurring at day 57. By day 225, the mean Lp(a) percentage reductions returned to within 50\% of baseline in the 3 and 9 mg dose cohorts. Interestingly, the overall mean reductions in Lp(a) were similar between the Japanese and non-Japanese cohorts that received 75 mg olpasiran, despite the small differences in exposure observed between the Japanese and non-Japanese participants. Given the difference in the study entry criteria regarding baseline Lp(a) level between this study and the FIH study, direct empiric PK and PD comparisons were not performed. Although epidemiologic studies of Lp(a) level in Japanese patients are limited, there are no anticipated ethnicity-related differences in olpasiran efficacy based on reports of similar plasma Lp(a) concentrations and distributions between Japanese and white populations,\textsuperscript{22} as well as similarities in the increased prevalence of major adverse cardiovascular events due to an elevated Lp(a) level in patients with ASCVD.\textsuperscript{23–25} The results from this single-dose study may also be extrapolated to support the development of olpasiran in other East Asian populations, such as Chinese and Korean patients.

The potential safety risks, based on the siRNA/oligotherapeutics platform or previously approved siRNAs, include effects on platelets and coagulation, immune-inflammatory response, development of anti-drug antibodies, and peripheral neuropathy. However, several chemical modifications were incorporated into the structure of olpasiran to mitigate these potential risks. The FIH study showed no apparent relationship between olpasiran dose and the frequency of AEs.\textsuperscript{20} No clinically relevant changes in liver or kidney function, platelets, coagulation parameters, or other tolerability-related laboratory analytes were observed. This Phase I study also indicated that olpasiran was well tolerated in both healthy Japanese and non-Japanese participants. There were no serious or fatal AEs, nor were there any abnormalities found in vital signs or on ECG.

Despite scientific advances leading to an armamentarium of evidence-based guidelines and risk-reducing drugs, ASCVD still represents a major cause of death and morbidity, and an enormous financial burden.\textsuperscript{26} Recently, an elevated plasma Lp(a) level was identified as a strong independent risk factor for the development and progression of ASCVD.\textsuperscript{27,28} A high plasma Lp(a) concentration is genetically determined; it is not influenced by lifestyle modifications, and it is not effectively controlled by any of the currently available lipid-reducing medication. Therefore, a novel agent to lower high levels of Lp(a) is needed to provide additional protection against ASCVD. Although definitive evidence that a reduction in plasma Lp(a) will lower cardiovascular risk is not yet available, epidemiologic studies with mendelian randomization analyses, plasma apheresis cohort results, and laboratory experimental data suggest a causal role for elevated Lp(a) in cardiovascular risk.\textsuperscript{12,29} The results from the present Phase I study in healthy Japanese and non-Japanese participants evaluating a single dose of olpasiran ranging from 3 to 225 mg provided valuable insight into further investigation of the efficacy and tolerability of olpasiran in Japanese and East Asian participants. While small differences in olpasiran PK exposure were observed between Japanese and non-
Japanese participants, this did not translate into differences in the magnitude or durability of Lp(a) reduction and subsequently supported the evaluation of the same doses and regimens in Japanese and East Asian participants during Phase II and III development. A Phase II study of efficacy and tolerability of multiple doses of olpasiran in patients with elevated Lp(a) is currently ongoing (NCT04270760).

CONCLUSIONS
Following a single SC administration of olpasiran at dose levels ranging from 3 to 225 mg, Cmax and AUC values were increased approximately dose proportionally across all Japanese cohorts. Median tmax values ranged from 3.0 to 9.0 hours and mean t1/2 values ranged from 4.0 to 6.9 hours across all cohorts. While a trend of higher olpasiran PK exposures (Cmax and AUCinf) were observed in the Japanese participants in the 75 mg dose cohort, the magnitude and durability of Lp(a) reductions were similar between the Japanese and the non-Japanese cohorts. Olpasiran was well tolerated; no patterns indicative of clinically important AEs, laboratory abnormalities, or vital sign abnormalities were observed, and no serious or fatal AEs were reported.

ACKNOWLEDGMENTS
The authors thank Robina Smith (Providence St Jude Medical Center) for patient enrollment support, Kristina Torok (Amgen) for clinical study management support, Shauna Hutton (Amgen) for PK analysis support, Makoto Aoki (Amgen) for protocol and clinical study report review, and Shannon Rao (Amgen) for writing support.

FUNDING SOURCES
Amgen Inc sponsored this study and was involved in the study design; the collection, analysis, and interpretation of data; preparation of the manuscript; and approval of the manuscript for submission.

AUTHOR CONTRIBUTIONS
Study concept and design: Winnie Sohn, You Wu, Tracy Varrieur, and Jingying Wang. Data acquisition: Peter Winkle, and Joel Neutel. Data analysis and interpretation: Winnie Sohn, You Wu, Caitlin Terrio, Tracy Varrieur, Jingying Wang, and Jennifer Hellawell. Drafting and critically reviewing the manuscript: Winnie Sohn, Peter Winkle, Joel Neutel, You Wu, Freeman Jabari, Caitlin Terrio, Tracy Varrieur, Jingying Wang, and Jennifer Hellawell.

DECLARATION OF INTEREST
Winnie Sohn, You Wu, Freeman Jabari, Caitlin Terrio, Tracy Varrieur, Jingying Wang, and Jennifer Hellawell are employees and stockholders of Amgen Inc. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

DATA AVAILABILITY

REFERENCES


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