

RESEARCH MONOGRAPH . COMPOUND PROFILE

Olpasiran

A synthetic, chemically modified, GalNAc-conjugated siRNA developed by Arrowhead Pharmaceuticals and licensed to Amgen that silences hepatic LPA gene expression through RNA interference, producing sustained and near-complete reduction of circulating lipoprotein(a) concentrations in patients with established atherosclerotic cardiovascular disease.

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ABSTRACT

Olpasiran (AMG 890; formerly ARO-LPA) is an investigational, first-in-class, synthetic double-stranded small interfering RNA (siRNA) conjugated to a trivalent N-acetylgalactosamine (GalNAc) ligand for selective hepatocyte delivery via the asialoglycoprotein receptor (ASGPR). The compound targets the messenger RNA transcribed from the LPA gene, which encodes apolipoprotein(a), the defining protein component of lipoprotein(a) [Lp(a)]. Elevated Lp(a) is a genetically determined, independent, and causal risk factor for atherosclerotic cardiovascular disease (ASCVD), aortic valve stenosis, and thrombotic events, affecting an estimated 20 to 30 percent of the global population at concentrations associated with increased cardiovascular risk. Prior to the development of RNA-targeted therapies, no pharmacologic intervention produced clinically meaningful reduction in Lp(a) concentration; niacin and PCSK9 inhibitors achieve modest decreases of 20 to 30 percent, insufficient to test the causal hypothesis relating Lp(a) lowering to cardiovascular event reduction.

Following uptake into hepatocytes through ASGPR-mediated endocytosis, the antisense strand of olpasiran incorporates into the RNA-induced silencing complex (RISC), which catalytically cleaves LPA mRNA and suppresses de novo synthesis of apolipoprotein(a). The resulting reduction in hepatic apolipoprotein(a) secretion produces a dose-dependent, sustained, and near-complete lowering of circulating Lp(a) particles. In the Phase 1 single ascending-dose trial (NCT03626662), olpasiran produced dose-dependent Lp(a) reductions of 71 to 97 percent that persisted for several months

after a single subcutaneous injection, with effects lasting up to six months at higher doses [1]. In the pivotal Phase 2 OCEAN(a)-DOSE trial (NCT04270760), a randomized, double-blind, placebo-controlled study in 281 patients with established ASCVD and Lp(a) greater than 150 nmol/L, olpasiran at doses of 75 mg or higher administered every 12 weeks produced placebo-adjusted Lp(a) reductions exceeding 95 percent at 36 weeks, with the 225 mg every-12-week regimen achieving a placebo-adjusted reduction of 101.1 percent [2]. The off-treatment extension analysis demonstrated that participants who received doses of 75 mg or higher every 12 weeks sustained approximately 40 to 50 percent Lp(a) reduction close to one year after the last dose, reflecting the durability of RISC-mediated mRNA silencing in hepatocytes [3].

The serum pharmacokinetics of olpasiran are characterized by rapid absorption after subcutaneous injection (time to maximum concentration approximately 3 to 9 hours) and rapid clearance from the systemic circulation (serum half-life approximately 3 to 8 hours), consistent with efficient hepatocyte uptake via the GalNAc-ASGPR pathway. The pharmacodynamic effect is dissociated from serum drug concentrations: the prolonged Lp(a) lowering reflects the intracellular persistence of the active RISC complex in hepatocytes rather than circulating drug exposure. The compound is well tolerated. In the OCEAN(a)-DOSE trial, the overall incidence of adverse events was similar in the olpasiran and placebo arms; the most frequently reported treatment-related adverse event was mild injection-site pain, which resolved without intervention [2]. No clinically significant changes in hepatic, renal, hematologic, or glycemic laboratory parameters were observed.

Olpasiran is currently under evaluation in the Phase 3 OCEAN(a)-Outcomes trial (NCT05581303), a large cardiovascular outcomes

study assessing the effect of olpasiran versus placebo on the composite endpoint of coronary heart disease death, myocardial infarction, or urgent coronary revascularization in participants with ASCVD and elevated Lp(a). An additional Phase 3 primary prevention trial, OCEAN(a)-PreEvent (NCT07136012), is evaluating olpasiran for prevention of first major cardiovascular events. The compound is not approved by any regulatory authority as of the date of this monograph. This document reviews the chemistry and structural class of olpasiran; the biology of lipoprotein(a) and the LPA gene target; the GalNAc-siRNA delivery mechanism; the preclinical pharmacology in transgenic mice and cynomolgus monkeys; the comprehensive human pharmacokinetic and pharmacodynamic record; the clinical evidence base from Phase 1 through Phase 3; sourcing and handling considerations for research applications; stack interactions; adverse events and safety signal; and a structured comparative assessment of five Lp(a)-lowering candidates against olpasiran on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Olpasiran (proposed).

Development codes: AMG 890 (Amgen); ARO-LPA (Arrowhead Pharmaceuticals, original designation prior to licensing).

Chemical Abstracts Service registry number: 2225856-03-9.

UNII (Unique Ingredient Identifier): 8M4GC1EOB4.

Drug class designation: Small interfering RNA (siRNA), N-acetylgalactosamine-conjugated.

ClinicalTrials.gov identifiers: NCT03626662 (Phase 1), NCT04270760 (Phase 2, OCEAN(a)-DOSE), NCT05581303 (Phase 3, OCEAN(a)-Outcomes), NCT07136012 (Phase 3, OCEAN(a)-PreEvent), NCT04987320 (Chinese PK study), NCT07293260 (coronary CT angiography substudy).

1.2 Structural class and chemistry

Olpasiran is a synthetic, chemically modified, double-stranded RNA molecule conjugated to a trivalent N-acetylgalactosamine (GalNAc) targeting ligand. The compound belongs to the GalNAc-siRNA therapeutic class, a platform technology in which short (approximately 21 to 23 nucleotide) RNA duplexes are covalently attached to a GalNAc moiety that mediates highly efficient and selective uptake into hepatocytes through the asialoglycoprotein receptor (ASGPR) [4, 5].

Molecular formula: C₄₉₀H₆₅₂F₁₁N₁₆₄O₃₀₆P₄₁S₇.

Molecular weight: Approximately 15,438.70 g/mol (as the sodium salt form).

Physical properties: Supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous injection.

Chemical modifications: The RNA backbone incorporates 2'-O-methyl and 2'-fluoro ribose modifications at specific positions on both the sense and antisense strands to confer resistance to endonuclease and exonuclease degradation, enhance thermal stability of the duplex, reduce innate immune stimulation through Toll-like receptor pathways, and improve pharmacokinetic and pharmacodynamic properties [4]. Phosphorothioate linkages are incorporated at the terminal positions of both strands to provide additional nuclease resistance and to modulate plasma protein binding during the brief systemic exposure phase. The sense strand carries the trivalent GalNAc ligand at its 3' terminus through a tetraethylene glycol linker.

Structural class: Olpasiran is classified within the broader category of RNA interference (RNAi) therapeutics and specifically within the GalNAc-siRNA platform that has produced multiple approved or late-stage clinical compounds, including patisiran (Onpattro), givosiran (Givlaari), lumasiran (Oxlumo), inclisiran (Leqvio), and vutrisiran (Amvuttra). The GalNAc conjugation strategy exploits the high expression density (approximately 500,000 receptors per hepatocyte) and rapid recycling kinetics (approximately 15-minute cycle time) of ASGPR on hepatocyte surfaces to achieve efficient and selective liver targeting [5].

1.3 Target gene and rationale

Olpasiran targets the LPA gene, located on chromosome 6q25-26, which encodes apolipoprotein(a) [apo(a)]. The LPA gene evolved through duplication of the plasminogen (PLG) gene and encodes a protein containing 10 subtypes of kringle IV domains (KIV1 through KIV10), with a variable number of copies of the KIV2 domain (ranging from 2 to more than 40 copies across individuals), followed by a single kringle V-like domain and an inactive protease-like domain [6]. The number of KIV2 repeats is the principal genetic determinant of circulating Lp(a) concentration: smaller apo(a) isoforms are secreted more efficiently from hepatocytes and are associated with higher plasma Lp(a) levels. Apo(a) is synthesized exclusively in the liver and assembles with low-density lipoprotein (LDL) particles through a disulfide bond between apo(a) KIV9 and apolipoprotein B-100 on the LDL surface, forming the mature Lp(a) particle [6, 7].

The rationale for targeting LPA mRNA is the convergence of genetic, epidemiologic, and Mendelian randomization evidence establishing elevated Lp(a) as a causal, independent, and genetically determined risk factor for ASCVD, aortic valve

calcification, and venous thromboembolism. Genome-wide association studies and Mendelian randomization analyses have demonstrated that genetic variants in the LPA locus that predict higher Lp(a) concentrations are associated with proportionally increased cardiovascular event rates, satisfying the criteria for causal inference [7, 8]. Circulating Lp(a) concentrations are approximately 80 to 90 percent genetically determined, are minimally influenced by diet, exercise, or most pharmacologic interventions, and exhibit a right-skewed distribution with approximately 20 to 30 percent of individuals exceeding the 50 mg/dL (approximately 125 nmol/L) threshold associated with increased cardiovascular risk [7].

2. Abstract

Olpasiran is a GalNAc-conjugated siRNA that catalytically silences hepatic LPA messenger RNA through the RNA-induced silencing complex (RISC), producing sustained, dose-dependent, and near-complete reduction of circulating lipoprotein(a) [Lp(a)] concentrations in individuals with elevated Lp(a) and established atherosclerotic cardiovascular disease [1, 2]. The compound was originally developed by Arrowhead Pharmaceuticals as ARO-LPA and was licensed globally to Amgen in 2016, receiving the designation AMG 890 and subsequently the proposed International Nonproprietary Name olpasiran.

Lipoprotein(a) is a genetically determined, independent, and causal risk factor for atherosclerotic cardiovascular disease, with elevated concentrations affecting approximately one in five individuals worldwide [7, 8]. The Lp(a) particle consists of an LDL-like core covalently linked to apolipoprotein(a), a highly polymorphic glycoprotein encoded by the LPA gene and synthesized exclusively in the liver. The pathophysiological mechanisms linking Lp(a) to cardiovascular risk include proatherogenic effects through cholesterol deposition and oxidized phospholipid carriage, prothrombotic effects through structural homology between apo(a) and plasminogen (which interferes with fibrinolysis), and proinflammatory effects through the transport and presentation of oxidized phospholipids to vascular endothelium and immune cells [6, 7]. Prior to the emergence of RNA-targeted therapies, no pharmacologic agent produced Lp(a) reductions of sufficient magnitude to permit a definitive test of the Lp(a) causal hypothesis in cardiovascular outcomes.

In the Phase 1 single ascending-dose trial, olpasiran produced dose-dependent Lp(a) reductions of 71 to 97 percent persisting for months after a single subcutaneous injection [1]. The Phase 2 OCEAN(a)-DOSE trial in 281 patients demonstrated that olpasiran at 75 mg or higher every 12 weeks produced placebo-adjusted Lp(a) reductions exceeding 95 percent at 36 weeks, with effects persisting 40 to 50 percent below baseline close to one year after the last dose [2, 3]. The Phase 3 OCEAN(a)-Outcomes trial is currently evaluating whether these Lp(a) reductions translate to reduction in cardiovascular events [9].

The compound is well tolerated, with an adverse-event profile similar to placebo apart from mild injection-site reactions. Olpasiran is not approved by any regulatory authority. It is administered as a subcutaneous injection every 12 weeks (or every 24 weeks at higher doses) and is currently available only through clinical trial participation or as a research-grade preparation from specialty chemical suppliers.

3. Discovery and Development History

3.1 Origin and licensing

Olpasiran originated at Arrowhead Pharmaceuticals (formerly Arrowhead Research Corporation, Pasadena, California) as part of the company's Targeted RNAi Molecule (TRiM) platform for liver-directed gene silencing. The compound was designated ARO-LPA and was designed to target the LPA gene encoding apolipoprotein(a) in hepatocytes using the GalNAc-siRNA conjugation approach [4]. In 2016, Amgen licensed global rights to ARO-LPA from Arrowhead in a deal that included an upfront payment and milestone-based royalties. Amgen redesignated the compound AMG 890 and advanced it into clinical development under the proposed International Nonproprietary Name olpasiran.

3.2 Preclinical development

Preclinical pharmacology studies were conducted in transgenic mice expressing human apo(a) and in cynomolgus monkeys, as reported in the Koren et al. (2022) Nature Medicine publication [1]. In transgenic mice, single doses of olpasiran produced reductions in circulating apo(a) exceeding 80 percent from baseline, with effects persisting 5 to 8 weeks after a single administration. In cynomolgus monkeys, olpasiran demonstrated dose-dependent suppression of hepatic LPA mRNA expression and corresponding reduction in circulating Lp(a)-like particles, with a pharmacodynamic duration consistent with the expected intracellular persistence of the RISC complex in hepatocytes. Toxicology studies in rodents and non-human primates at multiples of the anticipated clinical dose did not identify dose-limiting toxicities or target-organ findings beyond those expected for the GalNAc-siRNA class (transient, reversible hepatocyte vacuolation at supratherapeutic exposures, consistent with class-related siRNA accumulation in hepatocyte endosomes and lysosomes).

3.3 Phase 1 clinical development

The Phase 1 trial (NCT03626662) was a randomized, double-blind, placebo-controlled single ascending-dose study in healthy volunteers and participants with elevated Lp(a) concentrations [1]. Participants received single subcutaneous doses of olpasiran ranging from 3 mg to 225 mg or placebo. The study demonstrated dose-dependent reductions in Lp(a) of 71 to 97 percent at doses of 9 mg and above, with effects persisting for several months after a single injection. At the highest doses studied, Lp(a) reduction was sustained for up to six months. No serious, fatal, or life-threatening adverse events were reported. The compound was well tolerated across all dose levels, and no clinically relevant changes in hepatic function, renal function, platelet counts, or coagulation parameters were observed. The Phase 1 results were published in *Nature Medicine* in January 2022 [1].

3.4 Phase 2 OCEAN(a)-DOSE trial

The OCEAN(a)-DOSE trial (Olpasiran trials of Cardiovascular Events And Lipoprotein(a) reduction, Dose-finding study; NCT04270760; TIMI 67) was a multi-center, randomized, double-blind, placebo-controlled Phase 2 trial conducted by the TIMI Study Group in collaboration with Amgen [2, 10]. The trial enrolled 281 patients with established ASCVD and Lp(a) concentrations greater than 150 nmol/L. Participants were randomized to one of four olpasiran dosing regimens (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) or placebo for 48 weeks, administered as subcutaneous injections. The primary endpoint was the placebo-adjusted percentage change in Lp(a) from baseline to week 36. Results were presented by Michelle O'Donoghue at the American Heart Association Scientific Sessions 2022 and published simultaneously in the *New England Journal of Medicine* [2].

The primary endpoint results demonstrated striking, dose-dependent Lp(a) reductions: placebo-adjusted mean percentage changes at week 36 were -70.5 percent (10 mg Q12W), -97.4 percent (75 mg Q12W), -101.1 percent (225 mg Q12W), and -100.5 percent (225 mg Q24W) [2]. The reductions exceeding 100 percent in the higher-dose groups reflect the statistical artifact of placebo adjustment in a setting where the active treatment produced near-complete elimination of circulating Lp(a). Olpasiran also produced dose-dependent, significant reductions in oxidized

phospholipids on apolipoprotein B (OxPL-apoB), with placebo-adjusted reductions ranging from 51.6 percent (10 mg Q12W) to 93.7 percent (225 mg Q24W) at week 36 [11].

3.5 Off-treatment extension and durability

An open-label extension period of the OCEAN(a)-DOSE trial evaluated the off-treatment durability of Lp(a) lowering [3]. Participants who had received olpasiran doses of 75 mg or higher every 12 weeks sustained approximately 40 to 50 percent placebo-adjusted mean reduction in Lp(a) levels close to one year (approximately 36 to 48 weeks) after the last dose of olpasiran. This prolonged pharmacodynamic effect reflects the intracellular persistence of the active RISC complex, which continues to catalytically degrade newly synthesized LPA mRNA transcripts long after olpasiran has been cleared from the systemic circulation. The results were published in the Journal of the American College of Cardiology in 2024 [3].

3.6 Phase 3 cardiovascular outcomes program

The Phase 3 OCEAN(a)-Outcomes trial (NCT05581303) is a randomized, double-blind, placebo-controlled cardiovascular outcomes study enrolling approximately 6,000 participants with established ASCVD and Lp(a) concentrations of 200 nmol/L (approximately 90 mg/dL) or greater [9]. The primary endpoint is the composite of coronary heart disease death, myocardial infarction, or urgent coronary revascularization. The trial initiated enrollment in 2022, with an estimated primary completion date in 2026 to 2027. A second Phase 3 primary prevention trial, OCEAN(a)-PreEvent (NCT07136012), is evaluating olpasiran for prevention of first major cardiovascular events in participants with elevated Lp(a) who have not yet experienced a cardiovascular event. An additional coronary CT angiography substudy (NCT07293260) is assessing the effect of olpasiran on coronary plaque burden.

3.7 Additional regional pharmacokinetic studies

Amgen has conducted additional regional pharmacokinetic and pharmacodynamic studies to characterize olpasiran in diverse populations. A Phase 1 open-label, single-dose study in healthy Japanese and non-Japanese participants confirmed that olpasiran pharmacokinetics and Lp(a) responses are generally consistent across East Asian and non-East Asian populations [12]. A similar study in Chinese partici-

pants with elevated Lp(a) (NCT04987320) demonstrated that olpasiran at 75 mg and 225 mg was safe and well tolerated, with pharmacokinetics and Lp(a) reductions consistent with those observed in the global Phase 2 trial [13].

4. Mechanism of Action

4.1 RNA interference and the RISC pathway

Olpasiran functions through the endogenous RNA interference (RNAi) pathway, a highly conserved post-transcriptional gene silencing mechanism present in all mammalian cells [4, 5]. The mechanism proceeds in defined steps. First, the GalNAc moiety of olpasiran binds with high affinity to ASGPR on hepatocyte surfaces. ASGPR is a calcium-dependent lectin receptor expressed almost exclusively on hepatocytes at a density of approximately 500,000 copies per cell, with rapid constitutive recycling between the cell surface and endosomal compartments (cycle time approximately 15 minutes). The receptor preferentially recognizes terminal galactose and N-acetylgalactosamine residues, and the trivalent GalNAc conjugation on olpasiran exploits the avidity effect of multivalent binding to achieve highly efficient receptor-mediated endocytosis [5].

Second, following ASGPR-mediated endocytosis into clathrin-coated vesicles and trafficking through early and late endosomes, a fraction of the internalized siRNA duplex escapes from the endosomal compartment into the cytoplasm. The mechanism of endosomal escape, while not fully elucidated, involves protonation of the siRNA and local disruption of the endosomal membrane at acidic pH.

Third, in the cytoplasm, the double-stranded siRNA is loaded into the Argonaute 2 (AGO2) protein, the catalytic component of the RNA-induced silencing complex (RISC). The sense (passenger) strand is cleaved and discarded, leaving the antisense (guide) strand stably incorporated into RISC. The guide strand directs RISC to complementary sequences on the LPA mRNA transcript through Watson-Crick base pairing.

Fourth, AGO2 catalytically cleaves the target mRNA at the phosphodiester bond opposite nucleotides 10 and 11 of the guide strand, rendering the mRNA unable to serve as a template for translation. The cleaved mRNA fragments are degraded by cellular exonucleases. Critically, the RISC complex is not consumed in this reaction: a single loaded RISC can catalytically cleave multiple mRNA transcripts, which accounts for the prolonged pharmacodynamic duration and the dissociation between serum drug clearance and biological effect [4, 14].

4.2 Target specificity

The antisense strand of olpasiran is designed with complementarity to a specific sequence within the LPA mRNA transcript. The LPA gene is expressed exclusively in hepatocytes, and the combination of GalNAc-mediated hepatocyte targeting with LPA mRNA sequence specificity provides a dual selectivity mechanism that limits off-target gene silencing in non-hepatic tissues and reduces the potential for suppression of non-target hepatic mRNAs. The chemical modifications (2'-O-methyl, 2'-fluoro) also reduce the potential for innate immune activation through Toll-like receptor 3 (TLR3), TLR7, and TLR8, which recognize unmodified double-stranded and single-stranded RNA as pathogen-associated molecular patterns [4].

4.3 Downstream effects on lipoprotein(a) metabolism

Suppression of LPA mRNA translation in hepatocytes reduces the de novo synthesis and secretion of apolipoprotein(a) into the circulation. Because Lp(a) particle assembly requires apo(a) to associate with an LDL particle (through a specific disulfide bond between apo(a) KIV9 and apolipoprotein B-100), reduction in apo(a) secretion produces a proportional reduction in circulating Lp(a) particle concentration [6, 7]. The effect is specific to Lp(a); olpasiran does not directly affect LDL particle number, apolipoprotein B-100 synthesis, or LDL receptor expression. In the OCEAN(a)-DOSE trial, olpasiran reduced Lp(a) by greater than 95 percent without producing clinically meaningful changes in LDL cholesterol, HDL cholesterol, triglycerides, or apolipoprotein B concentrations [2].

The reduction in Lp(a) also reduces the circulating pool of oxidized phospholipids (OxPL), which are preferentially carried on Lp(a) particles. OxPL on apolipoprotein B (OxPL-apoB) was reduced by 51.6 to 93.7 percent in a dose-dependent manner in the OCEAN(a)-DOSE trial [11]. Oxidized phospholipids are biologically active mediators of vascular inflammation, endothelial activation, and macrophage foam cell formation; their reduction may contribute to the anticipated cardiovascular benefit of Lp(a) lowering beyond the reduction in cholesterol-carrying particle number alone [11, 15].

4.4 Inflammatory biomarker effects

A prespecified analysis of the OCEAN(a)-DOSE trial evaluated the effect of olpasiran on systemic inflammatory biomarkers [11]. Despite the marked reduction in OxPL-apoB, olpasiran did not significantly alter high-sensitivity C-reactive protein (hs-CRP) or interleukin-6 (IL-6) concentrations compared with placebo over 48 weeks of treatment. This finding suggests that the inflammatory consequences of Lp(a) and OxPL may be primarily localized to the vascular wall (through direct interaction with endothelial and immune cells in atherosclerotic plaques) rather than reflected in systemic inflammatory biomarkers. Alternatively, the duration of treatment may have been insufficient to detect changes in systemic inflammatory markers, or the inflammatory signal carried by Lp(a) may be quantitatively small relative to the total systemic inflammatory burden in patients with established ASCVD.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Olpasiran is administered by subcutaneous injection. Following subcutaneous administration, the compound is absorbed from the injection site into the systemic circulation with a time to maximum observed serum concentration (t_{max}) of approximately 3 to 9 hours [1, 12, 13]. Serum exposure (area under the concentration-time curve and maximum concentration) increases in an approximately dose-proportional manner across the studied dose range of 3 mg to 225 mg.

5.2 Distribution

After reaching maximum serum concentration, olpasiran is rapidly distributed from the vascular compartment to hepatocytes. The GalNAc moiety mediates highly efficient first-pass hepatic extraction through ASGPR-mediated endocytosis, resulting in rapid clearance from the systemic circulation. Serum concentrations decline rapidly after C_{max} and are predominantly cleared from systemic circulation within approximately 3 days after dosing [12, 13]. The apparent volume of distribution is large relative to plasma volume, consistent with extensive hepatic uptake and intracellular accumulation. The fraction of the administered dose that reaches hepatocytes and is productively loaded into RISC determines the magnitude and duration of the pharmacodynamic effect.

5.3 Metabolism and intracellular persistence

Olpasiran is not metabolized by cytochrome P450 enzymes or other classical drug-metabolizing enzyme systems. Instead, the compound is processed intracellularly through the endogenous nuclease degradation pathways that handle RNA molecules. The chemical modifications (2'-O-methyl, 2'-fluoro, phosphorothioate) substantially retard nuclease-mediated degradation, extending the intracellular half-life of the active guide strand within the RISC complex [4, 14].

The pharmacodynamic duration of olpasiran is determined by the intracellular persistence of the loaded RISC complex in hepatocytes rather than by systemic drug exposure. The RISC complex containing the olpasiran guide strand continues to catalytically cleave newly transcribed LPA mRNA for weeks to months after a single dose, producing the characteristic dissociation between rapid serum clearance (half-life 3 to 8 hours) and prolonged pharmacodynamic effect (Lp(a) reduction persisting for months) [1, 3]. This property is shared by other GalNAc-siRNA therapeutics and is a defining feature of the RISC-mediated mechanism.

5.4 Elimination

Elimination of olpasiran occurs through a combination of hepatic metabolism (nuclease-mediated degradation of the RNA strands to inactive nucleotide fragments) and renal excretion of the degradation products. The parent compound is not excreted intact in urine in meaningful quantities. The GalNAc ligand is cleaved from the siRNA after endosomal processing and is metabolized through standard carbohydrate degradation pathways.

5.5 Pharmacokinetic-pharmacodynamic dissociation

The most pharmacologically important feature of olpasiran pharmacokinetics is the profound dissociation between serum drug exposure and pharmacodynamic effect. The serum half-life of approximately 3 to 8 hours reflects the rapid hepatic uptake and clearance of the GalNAc-siRNA conjugate from the blood compartment, while the pharmacodynamic effect (Lp(a) suppression) persists for 12 to 24 weeks or longer after a single dose [1, 2, 3]. This dissociation has important implications for dosing intervals (every 12 weeks or every 24 weeks rather than daily), for drug-drug interaction potential (minimal, because of the absence of CYP-mediated metabolism and the brief systemic exposure), and for the interpretation of adverse events (most toxicity risk is related to the hepatic intracellular accumulation rather than to systemic exposure).

5.6 Routes of administration

Olpasiran is administered exclusively by subcutaneous injection. Clinical trials have used prefilled syringes or vials with manual injection into the abdomen, thigh, or upper arm. The injection volume is small (approximately 1 mL or less depending on dose and concentration). No intravenous, oral, or other routes of ad-

ministration have been evaluated in human studies. The subcutaneous route is standard for the GalNAc-siRNA class and provides adequate bioavailability for hepatocyte delivery through the lymphatic and systemic circulation.

5.7 Special populations

Pharmacokinetic studies in Japanese participants demonstrated olpasiran exposure and Lp(a) responses consistent with those in non-Japanese participants at the same doses [12]. A study in Chinese participants with elevated Lp(a) confirmed similar pharmacokinetics and tolerability at 75 mg and 225 mg doses [13]. Formal studies in hepatic impairment, renal impairment, and pediatric populations have not been published as of the date of this monograph.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

The siRNA sequence of olpasiran was selected through systematic screening of candidate sequences targeting the LPA mRNA transcript for potent and specific gene silencing activity in hepatocyte-derived cell lines [1]. In vitro transfection of the siRNA duplex into human hepatocyte cell lines (HepG2 and primary human hepatocytes) produced dose-dependent suppression of LPA mRNA as measured by quantitative reverse-transcription polymerase chain reaction, with IC₅₀ values in the picomolar to low-nanomolar range. The GalNAc-conjugated formulation demonstrated efficient uptake into hepatocytes expressing ASGPR without the requirement for lipid transfection reagents, confirming the functionality of the GalNAc targeting ligand.

6.2 In vivo pharmacology in transgenic mice

Olpasiran was evaluated in transgenic mice expressing human apo(a) from the LPA gene [1]. Single subcutaneous doses produced dose-dependent reductions in circulating human apo(a) concentrations exceeding 80 percent from baseline, with the pharmacodynamic effect persisting for 5 to 8 weeks after a single administration. The dose-response relationship and the duration of effect in mice were consistent with the expected intracellular persistence of the RISC complex and with the pharmacodynamic profiles of other GalNAc-siRNA compounds in rodent models.

6.3 In vivo pharmacology in non-human primates

In cynomolgus monkeys, olpasiran produced dose-dependent suppression of hepatic LPA mRNA expression and corresponding reductions in circulating Lp(a)-like particles [1]. The non-human primate model provided critical pharmacokinetic and pharmacodynamic data for human dose prediction, as cynomolgus monkeys express ASGPR with similar density and binding characteristics to humans and metabolize GalNAc-siRNA conjugates through comparable intracellular pathways.

6.4 Toxicology

Repeat-dose toxicology studies in rodents and cynomolgus monkeys at multiples of the anticipated human clinical dose did not identify dose-limiting toxicities. Findings consistent with the GalNAc-siRNA class included transient, reversible hepatocyte vacuolation at supratherapeutic exposures, representing siRNA accumulation in hepatocyte endosomal and lysosomal compartments [1, 4]. This finding is a pharmacologic consequence of the delivery mechanism (ASGPR-mediated endocytosis delivers large quantities of siRNA to the endolysosomal pathway, a fraction of which is not productively loaded into RISC and accumulates intracellularly) and has been observed with other clinically approved GalNAc-siRNA compounds at supratherapeutic exposures without progressing to clinically significant hepatotoxicity at therapeutic doses.

7. Clinical Evidence Base

7.1 Phase 1 single ascending-dose trial

The Phase 1 trial (NCT03626662) was a randomized, double-blind, placebo-controlled single ascending-dose study enrolling participants with elevated Lp(a) concentrations (greater than 70 nmol/L) [1]. Cohorts received single subcutaneous doses of olpasiran at 3 mg, 9 mg, 30 mg, 75 mg, or 225 mg or placebo. The primary endpoints were safety and tolerability; secondary endpoints included change in Lp(a) concentration and pharmacokinetics.

Single doses of olpasiran at 9 mg and above produced dose-dependent Lp(a) reductions of 71 to 97 percent. At the 225 mg dose, the maximal Lp(a) reduction approached 97 percent and the effect persisted for up to six months after a single injection. Olpasiran was well tolerated at all dose levels; no serious, fatal, or life-threatening adverse events were reported. No clinically relevant changes in hepatic function tests, platelet counts, coagulation parameters, or renal function markers were observed [1]. The results, published in *Nature Medicine* in January 2022, provided the first human proof-of-concept for potent and sustained Lp(a) lowering with a GalNAc-conjugated siRNA.

7.2 Phase 2 OCEAN(a)-DOSE trial: primary results

The OCEAN(a)-DOSE trial (NCT04270760) was the pivotal Phase 2 dose-finding study [2, 10]. A total of 281 patients with established ASCVD (prior myocardial infarction, prior stroke, or symptomatic peripheral arterial disease) and Lp(a) greater than 150 nmol/L were randomized to one of four olpasiran dosing regimens or placebo. Baseline median Lp(a) concentration was approximately 260 nmol/L.

The primary endpoint, placebo-adjusted percentage change in Lp(a) from baseline to week 36, was met across all dose groups: -70.5 percent (10 mg Q12W), -97.4 percent (75 mg Q12W), -101.1 percent (225 mg Q12W), and -100.5 percent (225 mg Q24W) [2]. All comparisons versus placebo were statistically significant ($P < 0.001$). Maximal Lp(a) reductions were observed as early as week 12, with near-complete suppression maintained through week 48 in the higher-dose groups.

Secondary lipid endpoints demonstrated no clinically meaningful changes in LDL cholesterol, HDL cholesterol, triglycerides, or apolipoprotein B concentrations, confirming the specificity of olpasiran for Lp(a) reduction [2].

7.3 OCEAN(a)-DOSE: oxidized phospholipid and inflammatory biomarker substudy

A prespecified substudy of the OCEAN(a)-DOSE trial evaluated the effect of olpasiran on OxPL-apoB and systemic inflammatory biomarkers [11]. Among 272 evaluable participants, olpasiran produced dose-dependent, significant reductions in OxPL-apoB, with placebo-adjusted mean percentage reductions of -51.6 percent (10 mg Q12W), -88.3 percent (75 mg Q12W), -91.2 percent (225 mg Q12W), and -93.7 percent (225 mg Q24W) at week 36. These reductions were maintained through week 48.

Despite the substantial reduction in OxPL, olpasiran did not significantly alter hs-CRP or IL-6 compared with placebo [11]. The dissociation between OxPL reduction and systemic inflammatory markers suggests that Lp(a)-associated inflammation may operate primarily at the vascular wall rather than through systemic inflammatory cascades.

7.4 Off-treatment extension period

The open-label extension of the OCEAN(a)-DOSE trial followed participants after the cessation of olpasiran dosing to characterize the off-treatment pharmacodynamic trajectory [3]. Participants who had received olpasiran at doses of 75 mg or higher every 12 weeks sustained approximately 40 to 50 percent placebo-adjusted mean reduction in Lp(a) levels close to one year (approximately 36 to 48 weeks) after the last olpasiran dose. Lp(a) concentrations gradually returned toward baseline values over the off-treatment period, reflecting the eventual depletion of the intracellular RISC complex through normal hepatocyte turnover and gradual nuclease-mediated degradation of the guide strand [3]. The prolonged off-treatment effect is consistent with the known intracellular pharmacology of GalNAc-siRNA therapeutics.

7.5 Phase 3 OCEAN(a)-Outcomes trial

The OCEAN(a)-Outcomes trial (NCT05581303) is a randomized, double-blind, placebo-controlled, event-driven cardiovascular outcomes study enrolling approximately 6,000 participants with established ASCVD and Lp(a) of 200 nmol/L or greater [9]. Participants are randomized to olpasiran (dose selected based on Phase 2 results) or placebo, administered subcutaneously every 12 weeks. The primary endpoint is the composite of coronary heart disease death, myocardial infarction, or urgent coronary revascularization. The trial is designed to determine whether the Lp(a) reduction produced by olpasiran translates to a reduction in cardiovascular events, thereby testing the causal hypothesis that pharmacologic Lp(a) lowering reduces cardiovascular risk. Enrollment began in 2022, with an estimated primary completion date of 2026 to 2027.

7.6 Phase 3 OCEAN(a)-PreEvent trial

The OCEAN(a)-PreEvent trial (NCT07136012) extends the evaluation of olpasiran to primary prevention, enrolling participants with elevated Lp(a) who have not yet experienced a major cardiovascular event [9]. This trial addresses the question of whether Lp(a) lowering can prevent first cardiovascular events in high-risk individuals identified on the basis of elevated Lp(a) alone.

7.7 Regional pharmacokinetic studies

A Phase 1 study in Japanese and non-Japanese participants confirmed that olpasiran pharmacokinetics and Lp(a) pharmacodynamic responses are consistent across ethnic groups [12]. A study in Chinese participants (NCT04987320) at 75 mg and 225 mg doses demonstrated comparable pharmacokinetics, Lp(a) reduction (maximal reductions of -94.8 percent at 75 mg and -99.2 percent at 225 mg on day 57), and tolerability to the global Phase 2 cohort [13].

8. Sourcing and Quality Verification

Olpasiran is not commercially available as an approved pharmaceutical product in any jurisdiction. The compound is accessible through two pathways: clinical trial enrollment and research-grade procurement from specialty chemical suppliers.

Clinical trial access: Olpasiran is administered as an investigational agent in the ongoing OCEAN(a)-Outcomes, OCEAN(a)-PreEvent, and associated clinical trials. Clinical-grade olpasiran is manufactured by Amgen as a sterile, preservative-free solution for subcutaneous injection, supplied in prefilled syringes or vials. Access is limited to enrolled trial participants at designated clinical sites.

Research-grade access: Research-grade olpasiran (as the sodium salt) is available from specialty biochemical suppliers including MedChemExpress (catalog number HY-139184), BOC Sciences (CAS 2225856-03-9), and selected other oligonucleotide suppliers. Research-grade material is supplied in milligram quantities as a lyophilized powder or solution. Purity specifications from commercial suppliers are typically greater than 95 percent by high-performance liquid chromatography.

Investigators obtaining research-grade olpasiran should confirm compound identity and purity through:

- Polyacrylamide gel electrophoresis or capillary electrophoresis to verify duplex integrity and strand length
- High-performance liquid chromatography or ultra-performance liquid chromatography to confirm purity (area-percent greater than 95 percent)
- Electrospray ionization mass spectrometry to confirm molecular weight of both sense and antisense strands
- Endotoxin testing (limulus amebocyte lysate assay) for any material intended for cell culture or in vivo research applications
- Functional verification of gene silencing activity in a hepatocyte-derived cell line expressing ASGPR (such as primary human hepatocytes or differentiated HepaRG cells) where the experimental design requires confirmation of biological activity

The research-grade siRNA market for novel therapeutic targets is less mature than markets for small-molecule research compounds. Lot-to-lot variability in oligonucleotide synthesis can affect strand integrity, chemical modification fidelity, and GalNAc conjugation efficiency. On-receipt analytical verification is appropriate for any investigation where pharmacodynamic precision is important.

9. Reconstitution and Handling

Olpasiran is a nucleic acid therapeutic and requires handling procedures appropriate for RNA-based compounds. The principal considerations are protection from RNase contamination, temperature control, and appropriate storage conditions.

Storage of lyophilized material: Research-grade olpasiran in lyophilized form should be stored at -20 degrees Celsius or lower (preferably -80 degrees Celsius for long-term storage) in a desiccated environment. The lyophilized material is stable for at least 12 months at -20 degrees Celsius when stored according to supplier specifications.

Reconstitution: The lyophilized compound should be reconstituted in RNase-free water, phosphate-buffered saline, or the appropriate vehicle for the intended experimental application. Stock solutions are typically prepared at concentrations of 1 to 100 micromolar. All reconstitution should be performed using RNase-free consumables (pipette tips, tubes, water) to prevent degradation. Brief centrifugation before opening the vial is recommended to collect the lyophilized material at the bottom.

Storage of reconstituted solutions: Aqueous stock solutions of olpasiran should be stored at -20 degrees Celsius or lower in single-use aliquots to avoid repeated freeze-thaw cycles. The chemical modifications on olpasiran (2'-O-methyl, 2'-fluoro, phosphorothioate) confer substantially greater stability than unmodified RNA, and the compound tolerates limited freeze-thaw cycles (typically 3 to 5 cycles) without significant loss of duplex integrity or biological activity. Working dilutions should be prepared fresh from frozen stock solutions.

Light protection: RNA compounds are generally susceptible to photodegradation. Storage and handling should minimize exposure to direct sunlight and ultraviolet radiation; amber tubes or foil-wrapped containers are appropriate precautions.

Clinical-grade material: The Amgen clinical formulation of olpasiran is supplied as a sterile solution for subcutaneous injection and is stored refrigerated (2 to 8 degrees Celsius) according to the investigational product labeling. Clinical-grade material is not available for non-clinical research applications.

10. Stack Interaction Considerations

Olpasiran has a fundamentally different pharmacologic profile from small-molecule therapeutics, and the drug-drug interaction considerations reflect this difference.

Cytochrome P450 interactions: Olpasiran is not metabolized by cytochrome P450 enzymes and is not expected to inhibit or induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations [1, 2]. The brief systemic exposure (serum half-life 3 to 8 hours, with the majority of the compound sequestered in hepatocytes within hours of dosing) further minimizes the potential for CYP-mediated drug-drug interactions. No formal drug-drug interaction studies have been published, but the mechanistic expectation is that olpasiran has negligible CYP interaction potential.

Transporter interactions: Olpasiran is a substrate of ASGPR for hepatocyte uptake but is not expected to interact meaningfully with classical drug transporters (P-glycoprotein, OATP1B1, OATP1B3, BCRP, OCT2, OAT1, OAT3, MATE1, MATE2-K) at clinically relevant concentrations.

Concomitant lipid-lowering therapies: In the OCEAN(a)-DOSE trial, participants were permitted to continue background lipid-lowering therapies including statins, ezetimibe, and PCSK9 inhibitors [2]. Olpasiran efficacy and safety were preserved in the context of background statin therapy (used by the majority of enrolled participants), and no pharmacokinetic or pharmacodynamic interactions with statins were observed. The combination of olpasiran with PCSK9 inhibitors is pharmacologically rational, as the two mechanisms target distinct aspects of lipoprotein metabolism (PCSK9 inhibitors reduce LDL through upregulation of LDL receptor recycling, while olpasiran specifically reduces Lp(a) through suppression of apo(a) synthesis).

Concomitant anticoagulant and antiplatelet therapies: Because Lp(a) has prothrombotic properties through its structural homology with plasminogen, the reduction in Lp(a) by olpasiran might theoretically modulate the thrombotic-fibrinolytic balance. The clinical significance of this interaction has not been characterized. In the OCEAN(a)-DOSE trial, participants on standard antiplatelet therapy (aspirin, P2Y₁₂ inhibitors) showed no increased bleeding or thrombotic signal with ol-

pasiran treatment [2]. Investigators should consider monitoring for changes in fibrinolytic parameters in research settings where Lp(a) reduction is combined with anticoagulant therapy.

Other Lp(a)-lowering agents: Concurrent use of olpasiran with other investigational Lp(a)-lowering agents (pelacarsen, lepodisiran, zerlasiran, muvalaplin) has not been studied and is not recommended outside of formal research protocols. The combination would produce additive or redundant suppression of Lp(a) production or assembly, with uncertain safety implications related to the consequences of very prolonged, near-complete Lp(a) elimination.

Niacin: Niacin (nicotinic acid) reduces Lp(a) by approximately 20 to 30 percent through a mechanism that is incompletely characterized. The combination with olpasiran has not been studied. The clinical relevance is limited because niacin monotherapy does not achieve sufficient Lp(a) reduction to substantially contribute to cardiovascular risk reduction in the context of olpasiran treatment.

11. Adverse Events and Safety

11.1 Common adverse events

In the OCEAN(a)-DOSE trial, the overall incidence of adverse events was similar in the olpasiran and placebo groups [2]. The most frequently reported adverse events associated with olpasiran were:

- Injection-site reactions (pain, erythema, bruising at the injection site): more common with olpasiran (particularly at doses of 75 mg and above) than with placebo, but the majority were mild in severity, occurred as isolated events, and resolved within 48 hours without treatment. A total of 3 participants discontinued olpasiran due to injection-site reactions.
- Upper respiratory tract infections: similar incidence in olpasiran and placebo groups.
- Headache: similar incidence across groups.
- Nasopharyngitis: similar incidence across groups.

The incidence of adverse events leading to discontinuation was approximately 2 percent in both the olpasiran and placebo groups, with no dose-dependent pattern [2].

11.2 Laboratory safety

No clinically significant changes in hepatic transaminases (alanine aminotransferase, aspartate aminotransferase), bilirubin, alkaline phosphatase, platelet counts, coagulation parameters (prothrombin time, activated partial thromboplastin time), renal function (serum creatinine, estimated glomerular filtration rate), or glycemic parameters (fasting glucose, hemoglobin A1c) were observed with olpasiran treatment compared with placebo in either the Phase 1 or Phase 2 trials [1, 2]. Hyperglycemia and new-onset or worsening diabetes were similar across treatment arms and placebo.

11.3 Cardiovascular safety

No cardiovascular safety signal has been identified in the Phase 1 or Phase 2 clinical trials. The OCEAN(a)-Outcomes Phase 3 trial will provide the definitive assessment of cardiovascular safety and efficacy in a large population followed for cardiovascular events over several years [9].

11.4 Immunogenicity

Anti-drug antibodies against olpasiran have not been reported as a significant finding in published clinical trial results. The chemical modifications on the siRNA (2'-O-methyl, 2'-fluoro) are designed to minimize innate immune stimulation, and the GalNAc conjugate is composed of endogenous carbohydrate moieties with low immunogenic potential.

11.5 Theoretical safety considerations

The LPA gene is not known to be essential for viability or for any critical physiologic function. Individuals with genetically undetectable Lp(a) (homozygous for loss-of-function LPA variants) have been identified in population-based genetic studies and do not exhibit any recognized clinical phenotype [7, 8]. This genetic evidence provides reassurance that near-complete suppression of Lp(a) is unlikely to produce serious adverse consequences. However, the long-term safety of sustained, near-complete Lp(a) elimination (over years to decades) has not been established, and the OCEAN(a)-Outcomes trial will provide data on cardiovascular events and safety over a multi-year treatment period.

The GalNAc-siRNA class has produced approved therapeutics (patisiran, givosiran, lumasiran, inclisiran, vutrisiran) with generally favorable safety profiles in their respective disease populations. Class-related hepatocyte vacuolation observed at supratherapeutic doses in preclinical studies has not translated to clinically significant hepatotoxicity at approved doses of other GalNAc-siRNA compounds. Thrombocytopenia has been reported rarely with other GalNAc-siRNA compounds but has not been a significant finding with olpasiran.

11.6 Pregnancy and lactation

No human data are available regarding olpasiran use in pregnancy or lactation. Given the investigational status of the compound, pregnant and breastfeeding individuals are excluded from clinical trials. The intracellular mechanism of action (RNA interference in hepatocytes) and the rapid systemic clearance suggest limited fetal exposure, but formal reproductive toxicology data in the public domain are limited.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five Lp(a)-lowering candidates against olpasiran, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal investigational agents with substantive clinical programs targeting Lp(a) reduction, with priority on those that have produced Phase 2 or Phase 3 clinical evidence.

12.1 Pelacarsen (TQJ230, AKCEA-APO(a)-LRx)

Mechanism: GalNAc-conjugated antisense oligonucleotide (ASO) targeting LPA mRNA in hepatocytes. Unlike siRNA (which operates through RISC-mediated catalytic mRNA degradation), ASO compounds function through RNase H-mediated single-strand RNA cleavage after DNA-RNA heteroduplex formation [16, 17].

Development trajectory: Developed by Ionis Pharmaceuticals in collaboration with Novartis (which acquired rights from Akcea Therapeutics). Pelacarsen is the most clinically advanced Lp(a)-lowering agent, with an ongoing Phase 3 cardiovascular outcomes trial (Lp(a) HORIZON, NCT04023552) enrolling approximately 8,323 participants with established cardiovascular disease and Lp(a) of 70 mg/dL or greater. The trial primary completion was estimated for mid-2025 [16, 17].

Dosing: 80 mg subcutaneously once monthly. The dosing frequency is higher than olpasiran (every 4 weeks versus every 12 weeks), reflecting the shorter pharmacodynamic duration of the ASO mechanism compared with RISC-mediated siRNA activity.

Novelty: Moderate. The GalNAc-ASO mechanism is established but represents a different pharmacologic approach (RNase H versus RISC) from the siRNA class.

Effect size: Phase 2 studies demonstrated mean Lp(a) reductions of approximately 80 percent at the highest tested dose (20 mg weekly), with the Phase 3 dose of 80 mg monthly achieving somewhat lower reductions [16, 17]. Pelacarsen

achieves approximately 80 percent Lp(a) reduction at the Phase 3 dose compared with greater than 95 percent for olpasiran at the 75 mg Q12W dose.

Promising potential: High. Pelacarsen is the furthest advanced Lp(a)-lowering agent in clinical development, with Phase 3 cardiovascular outcomes data expected to read out before olpasiran. A positive result would validate the Lp(a) hypothesis and establish the therapeutic class.

Side-effect profile: The most common adverse events in Phase 2 were injection-site reactions (27 percent of treatment group versus 6 percent of placebo), which were predominantly mild [16]. No significant hepatotoxicity, thrombocytopenia, or other serious adverse events have been reported.

Overall validation: High. Pelacarsen has the largest clinical development program and the nearest-term cardiovascular outcomes readout.

Comparison to olpasiran: Pelacarsen achieves somewhat lower Lp(a) reductions (approximately 80 percent versus greater than 95 percent for olpasiran), requires more frequent dosing (monthly versus every 12 weeks), and uses a different molecular mechanism (ASO versus siRNA). Olpasiran produces more complete Lp(a) suppression with less frequent dosing. The relative cardiovascular benefit will depend on the Phase 3 outcomes results for both compounds.

12.2 Lepodisiran (LY3819469)

Mechanism: GalNAc-conjugated siRNA targeting LPA mRNA, with the same general mechanism as olpasiran (RISC-mediated catalytic mRNA degradation in hepatocytes) but with different sequence, chemical modification pattern, and pharmacokinetic-pharmacodynamic characteristics [18].

Development trajectory: Developed by Eli Lilly. Phase 1 (NCT04914546) in 48 participants demonstrated dose-dependent Lp(a) reductions exceeding 90 percent at doses of 96 mg and above, with the 608 mg dose producing a median Lp(a) reduction of 94 percent that was sustained through day 337 (approximately 48 weeks) after a single dose [18]. Phase 2 (NCT05565742) is ongoing with approximately 216 participants. The Phase 3 ACCLAIM-Lp(a) trial (NCT06292013) is enrolling approximately 12,500 participants for a cardiovascular outcomes study with approximately 4.5 years of follow-up.

Dosing: Potential for dosing once or twice per year (every 24 to 52 weeks), reflecting potentially longer pharmacodynamic duration than olpasiran [18].

Novelty: Low. The mechanism is the same as olpasiran (GalNAc-siRNA targeting LPA mRNA). The differentiation is in the dosing interval and the chemical modification pattern.

Effect size: Phase 1 maximal Lp(a) reductions exceed 90 percent, comparable to olpasiran. The 608 mg dose maintained 94 percent reduction through nearly one year after a single dose.

Promising potential: Moderate to high. Lepodisiran has a large Phase 3 outcomes program, though the trial timeline (4.5 years of follow-up) means results will be available later than those of pelacarsen or olpasiran.

Side-effect profile: Phase 1 data demonstrated favorable tolerability. Only one serious adverse event was reported (a bicycle fall, unrelated to the drug). Transient elevations in liver enzymes were observed in some participants but normalized at follow-up [18].

Overall validation: Moderate. Phase 1 pharmacodynamic data are strong, but Phase 2 and Phase 3 results are pending.

Comparison to olpasiran: Lepodisiran shares the same fundamental mechanism as olpasiran and achieves comparable Lp(a) reduction. The potential differentiator is the dosing interval (potentially twice yearly versus every 12 weeks for olpasiran), which could improve patient adherence. Head-to-head comparative data are not available.

12.3 Zerlasiran (SLN360)

Mechanism: GalNAc-conjugated siRNA targeting LPA mRNA in hepatocytes, with the same general mechanism as olpasiran and lepodisiran [19].

Development trajectory: Developed by Silence Therapeutics. Phase 1 (NCT04606602) single ascending-dose study demonstrated dose-dependent Lp(a) reductions of up to 98 percent at the 600 mg dose [19]. Phase 2 (NCT05537571) has been completed, with all treatment groups achieving greater than 80 percent time-averaged Lp(a) reduction.

Dosing: 300 mg or 450 mg subcutaneously every 16 to 24 weeks.

Novelty: Low. Same mechanism class as olpasiran and lepodisiran.

Effect size: Phase 1 maximal reductions of 96 to 98 percent at the 300 to 600 mg doses, comparable to olpasiran. Phase 2 time-averaged reductions greater than 80 percent.

Promising potential: Low to moderate. Zerlasiran is behind olpasiran and pelacarsen in clinical development, with no Phase 3 outcomes trial initiated as of the date of this monograph.

Side-effect profile: Well tolerated in Phase 1 and Phase 2, with mild injection-site reactions as the most common adverse events [19]. No serious adverse events attributed to the drug.

Overall validation: Low to moderate. Phase 2 data are encouraging but a Phase 3 outcomes program has not been initiated.

Comparison to olpasiran: Zerlasiran produces comparable Lp(a) reduction by the same mechanism. Olpasiran is substantially further advanced in clinical development, with a Phase 3 outcomes trial in progress.

12.4 Muvalaplin (LY3473329)

Mechanism: Small-molecule inhibitor of the interaction between apolipoprotein(a) and apolipoprotein B-100, preventing the assembly of the Lp(a) particle [20]. This mechanism is fundamentally different from the RNA-targeting approach of olpasiran, pelacarsen, lepodisiran, and zerlasiran: muvalaplin blocks Lp(a) particle formation at the protein-protein interaction level rather than suppressing apo(a) synthesis.

Development trajectory: Developed by Eli Lilly. Phase 1 (NCT04472676) demonstrated dose-dependent Lp(a) reductions of 63 to 65 percent at doses of 100 mg and above [20]. Phase 2 (NCT05563246) demonstrated placebo-adjusted reductions of 47.6 percent (10 mg daily), 81.7 percent (60 mg daily), and 85.8 percent (240 mg daily) using an intact Lp(a) assay.

Dosing: Oral, once daily. The oral route of administration is a significant practical differentiator from the injectable RNA-based therapies.

Novelty: High. The protein-protein interaction inhibitor mechanism is distinct from all other Lp(a)-lowering approaches and represents a novel therapeutic concept.

Effect size: Phase 2 maximal Lp(a) reduction of approximately 86 percent (240 mg daily), which is substantial but lower than the greater than 95 percent achieved by olpasiran at the 75 mg Q12W dose.

Promising potential: Moderate. The oral administration route is a significant practical advantage for patient adherence. Phase 3 development plans have not been publicly disclosed as of the date of this monograph.

Side-effect profile: No clinically significant adverse events in Phase 1 or Phase 2 [20]. Most common events (headache, diarrhea) were mild and transient.

Overall validation: Moderate. Phase 2 data demonstrate a novel mechanism with meaningful Lp(a) reduction, but the compound is behind olpasiran in clinical development.

Comparison to olpasiran: Muvalaplin offers the significant practical advantage of oral daily dosing versus subcutaneous injection every 12 weeks. Olpasiran achieves more complete Lp(a) reduction (greater than 95 percent versus approximately 86 percent) with less frequent dosing. The oral route and the distinct mechanism make muvalaplin a complementary rather than directly competing approach.

12.5 Inclisiran (Leqvio)

Mechanism: GalNAc-conjugated siRNA targeting PCSK9 mRNA in hepatocytes [21]. While inclisiran uses the same GalNAc-siRNA platform and RISC-mediated mechanism as olpasiran, its target is proprotein convertase subtilisin/kexin type 9 (PCSK9) rather than LPA. PCSK9 inhibition increases LDL receptor recycling and reduces LDL cholesterol. Inclisiran produces a secondary, modest reduction in Lp(a) of approximately 15 to 25 percent, which is an off-target benefit rather than the primary pharmacologic effect [21].

Development trajectory: Developed by Alnylam Pharmaceuticals and licensed to Novartis. Inclisiran is approved by the FDA (2021), EMA (2020), and other regulatory authorities for the treatment of primary hypercholesterolemia and mixed dys-

lipidemia as an adjunct to diet and maximally tolerated statin therapy. The compound is dosed at 284 mg subcutaneously every 6 months after initial and 3-month loading doses.

Novelty: Moderate as an Lp(a)-lowering agent, because Lp(a) reduction is a secondary rather than primary effect. High as a validated example of the GalNAc-siRNA platform.

Effect size: Lp(a) reduction of approximately 15 to 25 percent, substantially less than the greater than 95 percent achieved by olpasiran [21]. The primary effect is LDL cholesterol reduction of approximately 50 percent.

Promising potential: Not applicable as a primary Lp(a)-lowering agent. However, inclisiran provides proof-of-platform validation for the GalNAc-siRNA approach in a cardiovascular indication, supporting the development rationale for olpasiran.

Side-effect profile: Injection-site reactions (mild, 5 to 8 percent), otherwise comparable to placebo in Phase 3 trials [21]. The safety profile of the GalNAc-siRNA platform in a large, approved cardiovascular indication provides reassurance for the olpasiran safety expectations.

Overall validation: High as a GalNAc-siRNA platform compound in cardiovascular medicine. Low as a primary Lp(a)-lowering agent.

Comparison to olpasiran: Inclisiran is not a direct competitor for Lp(a) lowering but validates the platform technology. Olpasiran targets the specific biology of Lp(a) through LPA gene silencing, while inclisiran targets LDL metabolism through PCSK9 silencing. The two could be used concurrently to address both LDL cholesterol and Lp(a) in patients with dual lipid abnormalities.

12.6 Comparator summary

The five comparators occupy distinct positions in the Lp(a) therapeutic landscape. **Pelacarsen** is the most clinically advanced Lp(a)-lowering agent, with the nearest-term cardiovascular outcomes readout, but achieves lower Lp(a) reduction (approximately 80 percent) than olpasiran (greater than 95 percent) and requires more frequent dosing. **Lepodisiran** shares the siRNA mechanism with olpasiran and achieves comparable Lp(a) reduction with potentially less frequent dosing (once or twice yearly), but is earlier in clinical development. **Zerlasiran** is mechanistically

similar to olpasiran and lepodisiran but is the least clinically advanced of the siRNA candidates. **Muvalaplin** offers a mechanistically novel oral approach with meaningful but somewhat lower Lp(a) reduction than olpasiran. **Inclisiran** validates the GalNAc-siRNA platform in cardiovascular medicine but is not a primary Lp(a)-lowering agent.

Olpasiran occupies a central position in this landscape: it produces the most complete Lp(a) reduction of any agent with Phase 2 data (greater than 95 percent at doses of 75 mg or higher every 12 weeks), has a well-characterized safety profile with no signal beyond mild injection-site reactions, has demonstrated durable off-treatment effects lasting approximately one year, and has an active Phase 3 cardiovascular outcomes program. The principal practical limitation is the requirement for subcutaneous injection (shared with all RNA-based comparators except muvalaplin) and the injectable dosing interval of every 12 weeks (longer than pelacarsen's monthly dosing but shorter than lepodisiran's potential twice-yearly dosing).

The central unanswered question for olpasiran and the entire Lp(a) therapeutic class is whether the pharmacologic reduction in Lp(a) produces a proportional reduction in cardiovascular events. The genetic and epidemiologic evidence is strongly supportive; the pharmacologic outcomes evidence awaits the readouts of the Phase 3 cardiovascular outcomes trials for pelacarsen (Lp(a) HORIZON), olpasiran (OCEAN(a)-Outcomes), and lepodisiran (ACCLAIM-Lp(a)). These trials collectively will determine whether Lp(a) lowering becomes an established pillar of cardiovascular risk management alongside LDL cholesterol lowering, blood pressure reduction, and antiplatelet therapy.

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