Review



# The Genetic Revolution in Cardiometabolic Disease: A Review of Novel RNA and Gene-Editing Therapies Targeting APOC3, ANGPTL3, and Lp(a)

Masab Mansoor *, Andrew Ibrahim, Affan Rizwan

Posted Date: 13 November 2025

doi: 10.20944/preprints202511.0942.v1

Keywords: genetic therapies; cardiovascular disease; pathophysiology; apolipoprotein C-III (APOC3); angiopoietin-like protein 3 (ANGPTL3); lipoprotein(a); CRISPR; antisense oligonucleotide (ASO); siRNA; 2025 clinical trials

*Review*

# The Genetic Revolution in Cardiometabolic Disease: A Review of Novel RNA and Gene-Editing Therapies Targeting APOC3, ANGPTL3, and Lp(a)

**Masab Mansoor [1,*], Andrew Ibrahim [2] and Affan Rizwan [3]**

[1] Edward Via College of Osteopathic Medicine—Louisiana Campus
[2] Texas Technical University Health Science Center School of Medicine; Lubbock, Texas
[3] Baylor University School of Medicine; Houston, Texas
* Correspondence: mmansoor@vcom.edu

## Abstract

**Background/Objectives**: Despite the success of statin and PCSK9 inhibitor therapies, significant residual cardiovascular risk persists, driven by atherogenic triglyceride-rich lipoproteins (TRLs) and the independent, causal risk factor, lipoprotein(a) [Lp(a)]. This review aims to elucidate the pathophysiology of three key genetic drivers of this risk—Apolipoprotein C-III (APOC3), Angiopoietin-like protein 3 (ANGPTL3), and Lp(a)—and to comprehensively analyze the groundbreaking efficacy and safety data from 2025 clinical trials for novel RNA-silencing and gene-editing therapies targeting them. **Methods**: This narrative review synthesizes foundational genetic validation studies with a focused analysis of late-breaking Phase 1, 2, and 3 clinical trial data presented at major 2025 cardiometabolic conferences (AHA 2025, ACC 2025) and simultaneously published in high-impact journals. **Results**: Landmark 2025 trials demonstrated profound efficacy. (1) For APOC3, the Phase 3 CORE-TIMI 72a/b trials showed the antisense oligonucleotide (ASO) olezarsen not only reduced severe hypertriglyceridemia (sHTG) (up to -72.2%) but also achieved a pivotal 85% reduction in acute pancreatitis events. (2) For ANGPTL3, the first-in-human Phase 1 trial of CTX310 (CRISPR-Cas9) validated in vivo gene editing as a clinical tool, achieving deep, dose-dependent reductions from a single infusion in ANGPTL3 (-73%), triglycerides (-55%), and LDL-C (-49%). (3) For Lp(a), the Phase 2 ALPACA trial of the siRNA lepodisiran demonstrated >94% Lp(a) reduction with unprecedented durability, sustained at >90% at day 540.15 (4) Concurrently, the 2024-2025 pause of the VERVE-101 base-editing trial due to LNP-related toxicity (thrombocytopenia, ALT elevation) and successful 2025 pivot to the reformulated VERVE-102 20 highlighted delivery, not just payload, as a critical safety hurdle. **Conclusions**: The year 2025 marks a paradigm shift from chronic oral therapy toward long-acting injectable (ASO/siRNA) or permanent "one-and-done" (CRISPR/base editing) treatments for cardiovascular disease. These genetic therapies show immense promise for targeting previously "undruggable" risk factors. Future success now hinges on demonstrating MACE reduction in large cardiovascular outcome trials (CVOTs) and navigating the critical translational hurdles of delivery vehicle (LNP) safety and the long-term, off-target monitoring of in vivo gene editing.

**Keywords:** genetic therapies; cardiovascular disease; pathophysiology; apolipoprotein C-III (APOC3); angiopoietin-like protein 3 (ANGPTL3); lipoprotein(a); CRISPR; antisense oligonucleotide (ASO); siRNA; 2025 clinical trials

 doi:10.20944/preprints202511.0942.v1



# 1. Introduction: The Residual Risk Landscape in Cardiovascular Pathophysiology

## *1.1. The Unmet Need Beyond LDL-C: Re-evaluating the Pathophysiological Role of Triglycerides and Lp(a)*

The advent of statin therapy revolutionized cardiovascular medicine, establishing low-density lipoprotein cholesterol (LDL-C) as the primary target for the prevention of atherosclerotic cardiovascular disease (ASCVD).[1] The subsequent development of PCSK9 inhibitors further reinforced the "lower is better" paradigm for LDL-C. However, despite achieving guideline-directed LDL-C levels, many patients remain at a high "residual risk" of major adverse cardiovascular events (MACE).[1]

This residual risk is increasingly attributed to pathophysiological pathways distinct from the LDL-C receptor axis. Two factors, in particular, have been validated as independent and causal drivers of ASCVD.

- **Triglyceride-Rich Lipoproteins (TRLs):** For decades, elevated triglycerides (TGs) were often dismissed as a bystander. However, extensive epidemiological and Mendelian randomization studies have confirmed a causal relationship between TGs, remnant cholesterol, and ASCVD.[2]
- **Lipoprotein(a) [Lp(a)]:** Lp(a) is now recognized as an independent, causal, and highly prevalent genetic risk factor for ASCVD, myocardial infarction, stroke, and calcific aortic valve stenosis.[1]

A significant unmet clinical need arises from the fact that these risk factors are poorly addressed by current standard-of-care therapies.[3] Statins and PCSK9 inhibitors, while potent for LDL-C, have minimal or modest effects on Lp(a) and are often insufficient for managing severe hypertriglyceridemia (sHTG).[4] This therapeutic gap has driven a search for novel mechanisms to target these pathways directly.

## *1.2. From Chemical Inhibition to Genetic Silencing: A New Therapeutic Modality*

Traditional cardiovascular pharmacotherapy, such as statins or ezetimibe, relies on the chronic, daily administration of small molecules that inhibit protein function. A fundamental weakness of this model is patient adherence. Data presented at the American Heart Association (AHA) 2025 Scientific Sessions highlighted profound "care gaps," demonstrating that even among high-risk young adults, statin initiation and follow-up testing are dismally low.[24]

Genetic therapies offer a revolutionary solution to this problem by moving the point of intervention "upstream"—targeting the messenger RNA (mRNA) or the genomic DNA itself, rather than the final protein product.[25] This approach enables the development of long-acting (months to years) or even permanent, "one-and-done" single-course treatments.[26] Such a paradigm, by minimizing or eliminating the burden of adherence, could fundamentally transform cardiovascular prevention.[26]

## *1.3. Overview of Genetic Platforms: ASO, siRNA, CRISPR-Cas9, and Base Editing*

The 2025 clinical trial landscape is dominated by four distinct genetic platforms, each with a unique mechanism of action.[25]

### 1.3.1. Antisense Oligonucleotides (ASOs)

These are single-stranded, chemically modified nucleic acids designed to be complementary to a target mRNA. Upon binding, the ASO-mRNA duplex is recognized and degraded by the enzyme RNase H, preventing protein translation.[29] Modern hepatic ASOs are typically conjugated to N-acetylgalactosamine (GalNAc), which facilitates specific uptake by hepatocytes via the asialoglycoprotein receptor.[30]

 doi:10.20944/preprints202511.0942.v1



1.3.2. Small Interfering RNA (siRNA)

These are double-stranded RNA molecules that utilize the endogenous RNA interference (RNAi) pathway. The siRNA is incorporated into the RNA-induced silencing complex (RISC), which is then guided to the target mRNA. The RISC complex subsequently cleaves the mRNA, silencing gene expression.[25] Like modern ASOs, hepatocyte-targeted siRNAs also employ GalNAc conjugation for delivery.[25]

1.3.3. CRISPR-Cas9 (Nuclease Editing)

This is a true gene-editing system. It is delivered in vivo, typically via a lipid nanoparticle (LNP), as an mRNA encoding the Cas9 nuclease and a single-guide RNA (sgRNA).[32] The sgRNA guides Cas9 to a specific 20-base-pair sequence in the genomic DNA. Cas9 then induces a double-strand break (DSB).[21] The cell's default, error-prone repair mechanism (non-homologous end joining) attempts to fix the break, often creating small insertions or deletions (indels) that result in a frameshift mutation, permanently inactivating the gene.[25]

1.3.3. Base Editing

A "second-generation" gene editor that avoids the potential dangers of DSBs. It uses a modified Cas9 (a "nicker" that only cuts one strand) fused to a deaminase enzyme. Guided by an sgRNA, the base editor binds to the target DNA, and the deaminase directly converts one nucleotide base to another (e.g., converting an adenine to a guanine) at a specific location, which can create a "stop" codon that permanently inactivates the gene.[25] This system is also delivered via LNPs.[19]

The current therapeutic landscape is thus defined by a fundamental conflict between two distinct philosophies. The field is bifurcating into (1) transient, titratable, and reversible RNA-level silencing (ASOs and siRNAs) and (2) permanent, irreversible, and potentially curative DNA-level editing (CRISPR and Base Editing). This strategic choice is further complicated by the divergent safety profiles of their respective delivery systems: the well-established GalNAc platform versus the novel, and still challenging, LNP platform, which has recently been associated with significant off-target toxicities.[18]

**Table 1.** Comparison of Novel Genetic Therapy Platforms in Cardiovascular Medicine.

| Modality | Target Molecule | Mechanism of Action | Common Delivery Vehicle | Typical Durability | Key Class-Specific Safety Concerns |
|---|---|---|---|---|---|
| **Antisense Oligonucleotide (ASO)** | mRNA | RNase H-mediated degradation [29] | GalNAc conjugation [30] | Weeks to Months [30] | Thrombocytopenia, hepatotoxicity (historical) [25], injection site reactions [35] |
| **Small Interfering RNA (siRNA)** | mRNA | RISC-mediated cleavage [25] | GalNAc conjugation [25] | Months to Year+ [16] | Generally well-tolerated, injection site reactions, transient LFT elevations [15] |
| **CRISPR-Cas9 (Nuclease)** | Genomic DNA | sgRNA-guided Double-Strand Break (DSB) & NHEJ-mediated indel [21] | Lipid Nanoparticle (LNP) [12] | Permanent (Lifelong) [26] | LNP-related toxicity [13], off-target DSBs, genomic rearrangements [33] |

 doi:10.20944/preprints202511.0942.v1



| | | | | | |
|---|---|---|---|---|---|
| **Base Editing** | Genomic DNA | sgRNA-guided base conversion (no DSB) [25] | Lipid Nanoparticle (LNP) [19] | Permanent (Lifelong) [28] | LNP-related toxicity [18], off-target base conversions [37] |

## 2. Targeting Apolipoprotein C-III (APOC3) for Severe Hypertriglyceridemia

### *2.1. Pathophysiology of APOC3: The Linchpin of Triglyceride-Rich Lipoprotein Metabolism*

Apolipoprotein C-III (APOC3) is a glycoprotein that plays a central, inhibitory role in TRL metabolism.[38] Its primary pathophysiological function is mediated through two distinct mechanisms: (1) it is a potent inhibitor of lipoprotein lipase (LPL), the primary enzyme responsible for hydrolyzing TGs in plasma, and (2) it interferes with apolipoprotein E (apoE)-mediated hepatic uptake and clearance of TRLs and their remnants.[38] The net effect of high APOC3 levels is a profound reduction in TRL clearance, leading to hypertriglyceridemia.

The causal role of APOC3 in cardiovascular disease is unequivocally supported by human genetics. Individuals with heterozygous, loss-of-function (LOF) mutations in the *APOC3* gene exhibit 36-41% lower risk of ischemic vascular disease and ischemic heart disease, associated with significantly lower plasma TG levels.[7] Beyond its effects on lipids, APOC3-containing lipoproteins are considered more atherogenic, and APOC3 itself has been shown to have pro-inflammatory properties, stimulating vascular inflammation.[40] In genetic disorders like Familial Chylomicronemia Syndrome (FCS), the overexpression of APOC3 contributes to severe, refractory hypertriglyceridemia and the subsequent, life-threatening complication of recurrent acute pancreatitis.[3]

### *2.2. ASO-Mediated Silencing: Mechanism of Olezarsen*

Olezarsen (brand name TRYNGOLZA®) is a second-generation, GalNAc-conjugated ASO.[30] It is designed to specifically target *APOC3* mRNA in hepatocytes.[30] Upon binding to the *APOC3* mRNA, it facilitates its degradation, thereby preventing the synthesis of APOC3 protein. This inhibition of the inhibitor "releases the brake" on LPL, markedly increasing LPL activity and accelerating the clearance of TGs from the plasma.[38]

Based on strong efficacy data, olezarsen was approved by the U.S. FDA in December 2024 for the treatment of the rare genetic disorder FCS.[35] The landmark data presented in 2025 sought to validate its use in the much larger patient population with non-FCS severe hypertriglyceridemia (sHTG).

### *2.3. 2025 Landmark Trial Focus: Olezarsen in the CORE-TIMI 72a & 72b Trials*

The most significant data for APOC3 inhibition in 2025 came from the CORE-TIMI 72a and CORE2-TIMI 72b trials. These results were presented as a late-breaking clinical trial at the AHA Scientific Sessions 2025 on November 8, 2025, and were simultaneously published in *The New England Journal of Medicine*.[9]

These were two pivotal Phase 3, international, double-blind, placebo-controlled trials that randomized a combined 1,061 patients with sHTG (defined as TGs between 500 and 2,000 mg/dL) at high risk for pancreatitis.[9] Patients received monthly subcutaneous injections of olezarsen (50 mg or 80 mg) or placebo for 12 months.[9]

The primary efficacy endpoint was the percent change in fasting TG levels at 6 months.[9] The results were statistically significant and clinically profound:

- CORE-TIMI 72a: Placebo-adjusted TG reduction was -62.9% for the 50-mg dose and -72.2% for the 80-mg dose.[9]
- CORE2-TIMI 72b: Placebo-adjusted TG reduction was -49.2% for the 50-mg dose and -54.5% for the 80-mg dose.[9]

 doi:10.20944/preprints202511.0942.v1



All comparisons were highly significant (p<0.001).[9] This potent TG lowering was accompanied by significant reductions in apoC-III, remnant cholesterol, and non-HDL-C.[9] Critically, more than 85% of patients treated with olezarsen achieved TG levels below 500 mg/dL, the recognized threshold for pancreatitis risk.[10]

However, the most transformative finding of the trials was the effect on the hard clinical endpoint of acute pancreatitis. In a prespecified pooled analysis, olezarsen demonstrated an 85% reduction in the incidence of acute pancreatitis compared to placebo (p=0.0002).[9] The event rates were 1.1 per 100 patient-years in the pooled olezarsen groups versus 6.2 per 100 patient-years in the placebo group.[10]

The safety profile was favorable and consistent with its FCS trial data.[35] Adverse events were balanced, with serious adverse events (SAEs) occurring *less* frequently in the olezarsen groups than in the placebo group.[35] The most common adverse event was mild injection site reactions.[35] Importantly, there were no clinically meaningful hepatic, renal, or platelet abnormalities, distinguishing it from first-generation ASOs.[44]

### *2.4. Comparative Analysis: Plozasiran (siRNA) and the Legacy of Volanesorsen*

The success of olezarsen must be viewed in context. Volanesorsen, a first-generation ASO targeting APOC3, was effective but its clinical utility was severely limited by high rates of thrombocytopenia.[3] The GalNAc-conjugation of olezarsen, a second-generation design, appears to have successfully mitigated this risk, as evidenced by the clean safety data from the CORE trials.[44]

Olezarsen's primary competitor is now plozasiran, an *siRNA* that also targets *APOC3* mRNA.[38] Data from 2024 and 2025, including the SHASTA-2 trial, demonstrated that plozasiran also achieves substantial TG lowering and an 83% reduction in pancreatitis risk.[38] The combined success of olezarsen and plozasiran provides robust, cross-platform validation that APOC3 is a highly effective target. The CORE trial data, however, represents a pivotal moment, as it is not merely another lipid-lowering study but a large-scale *pancreatitis prevention trial*. As noted by the trial investigators, previous therapies for sHTG had modest effects and had not been shown to reduce pancreatitis in this population.[9] The 85% reduction in this debilitating, life-threatening, organ-damaging event [9] provides the first-ever prospective, large-scale evidence for a non-ASCVD hard clinical endpoint in this field. This fundamentally changes the clinical justification for treating sHTG, moving the goal from simply correcting a lab value to actively preventing end-organ disease.

## 3. Targeting Angiopoietin-Like Protein 3 (ANGPTL3) for Mixed Hyperlipidemia

### *3.1. Pathophysiology of ANGPTL3: A Dual Regulator of LDL-C and Triglyceride Pathways*

Angiopoietin-like protein 3 (ANGPTL3) is another key hepatokine (a protein secreted by the liver) that regulates lipid metabolism.[8] Its unique pathophysiological importance stems from its role as a dual inhibitor of two critical lipases: **Lipoprotein Lipase (LPL)** and **Endothelial Lipase (EL)**.[39] By inhibiting LPL, ANGPTL3 raises TGs; by inhibiting EL, it raises LDL-C.

This dual mechanism makes ANGPTL3 an exceptionally attractive therapeutic target. Human genetic studies show that individuals with LOF mutations in ANGPTL3 are a "double-positive": they exhibit simultaneously low levels of both TGs and LDL-C, which translates to a significantly reduced risk of ASCVD.[5] This profile makes ANGPTL3 the ideal target for treating patients with mixed hyperlipidemia. Furthermore, emerging evidence suggests ANGPTL3 may also exert direct pro-atherosclerotic effects, independent of lipid levels, by promoting endothelial cell adhesion and vascular inflammation.[46] While a monoclonal antibody (evinacumab) targeting ANGPTL3 is approved for homozygous familial hypercholesterolemia (HoFH), the focus of 2025 has been on permanent genetic inactivation.[3]

 doi:10.20944/preprints202511.0942.v1



*3.2.2025. Landmark Trial Focus: First-in-Human In Vivo CRISPR-Cas9 Editing with CTX310*

The most anticipated dataset presented at AHA 2025 was the first-in-human data for CTX310. The results of this Phase 1 trial were presented as a late-breaking session on November 8, 2025, and simultaneously published in The New England Journal of Medicine.[32]

CTX310 is an investigational in vivo CRISPR-Cas9 gene-editing therapy.[13] It is administered as a single intravenous (IV) infusion, using an LNP to deliver the Cas9 mRNA and an sgRNA to hepatocytes, where it is designed to permanently inactivate the ANGPTL3 gene.[12]

The Phase 1, dose-escalation trial enrolled 15 participants with refractory dyslipidemias (uncontrolled hypercholesterolemia, sHTG, or mixed dyslipidemia).[13] The efficacy results were profound, durable, and clearly dose-dependent [12]. At the highest dose (0.8 mg/kg), participants achieved:

- Mean ANGPTL3 reduction: -73% (maximum reduction -89%).[12]
- Mean TG reduction: -55% (maximum reduction -84%).[12]
- Mean LDL-C reduction: -49% (maximum reduction -87%).[12]
- Mean Non-HDL-C reduction: -49.8%.[13]

These reductions were observed within two weeks of the single infusion and were sustained through at least 60 days of follow-up.[13]

Safety was the most scrutinized aspect of the trial. Overall, the therapy was tolerated, with no dose-limiting toxicities (DLTs) reported.[13] Three participants at the higher 0.6 mg/kg and 0.8 mg/kg doses experienced infusion-related reactions (fever, nausea, back pain). In all cases, the infusion was paused, supportive medications were administered, and the full dose was successfully infused.[13] One participant (at the highest dose, with pre-existing elevated liver enzymes) experienced a transient increase in aminotransferases (ALT/AST) to 3–5 times the upper limit of normal (ULN). This peaked at day 4 and returned to baseline by day 14, with no associated rise in bilirubin.[13] Notably, the trial data did not report any clinically significant changes in platelet counts.[32] Two SAEs were reported and deemed unrelated to CTX310 by investigators: a spinal disk herniation 7 months post-infusion, and a sudden death 179 days post-infusion in a patient with an extensive history of advanced cardiovascular disease who had received the lowest trial dose.[13]

*3.3.2025. Trial Focus: The Advent of Base Editing: The VERVE-201 Pulse-1 Trial*

A direct competitor to CTX310's nuclease approach is VERVE-201, an in vivo **base editor**.[25] This therapy targets the same ANGPTL3 gene for permanent inactivation [51] but uses the "no DSB" mechanism, which is theoretically safer by avoiding the risk of large-scale genomic rearrangements.[25]

The first-in-human, Phase 1b (Pulse-1) trial for VERVE-201 is actively recruiting, with the first patient dosed in late 2024.[51] A program update, including initial safety and efficacy data, is highly anticipated in the second half of 2025.[20]

The concurrent 2025 trials of CTX310 (CRISPR-nuclease) [13] and VERVE-201 (base editor) [51] targeting the same ANGPTL3 gene have created a high-stakes, head-to-head race. This race will be pivotal in defining the future of permanent gene editing. The key differentiator will likely not be efficacy—as both platforms are expected to be highly potent—but safety. This includes both long-term genotoxicity (the risk of DSBs from CTX310 vs. off-target base conversions from VERVE-201) and, more immediately, the acute toxicity of their respective LNP delivery systems. Given that Verve Therapeutics recently experienced a major LNP-driven toxicity issue with a different asset [18], the entire field is hypersensitive to any signal of LNP-related hepatotoxicity or thrombocytopenia. The transient liver enzyme spike seen in the CTX310 trial [13] and the pending VERVE-201 data [55] will be scrutinized heavily for these exact signals.

 doi:10.20944/preprints202511.0942.v1



## 4. Targeting Lipoprotein(a): Silencing a Causal Cardiovascular Risk Factor

### *4.1. Pathophysiology of Lp(a): The "Unstickable" Genetic Risk*

Lipoprotein(a) is a unique, highly atherogenic particle. It consists of an LDL-like core, with its apolipoprotein B (apoB) molecule, covalently bonded to a large, distinct glycoprotein called apolipoprotein(a) [apo(a)].[4] An individual's plasma Lp(a) concentration is 80–90% genetically determined, primarily by the LPA gene, and remains relatively stable throughout life.[4]

It is now established as a strong, independent, and causal risk factor for ASCVD and calcific aortic valve stenosis.[1] This particle represents one of the largest remaining unmet needs in cardiovascular prevention. An estimated 20% of the global population has elevated Lp(a) levels (>50 mg/dL).[50] Crucially, its levels are not meaningfully reduced by diet, lifestyle changes, statins, or even PCSK9 inhibitors.[4] It requires a dedicated, targeted therapy.

### *4.2.2025. Landmark Trial Focus: The ALPACA Trial: Lepodisiran (siRNA)*

The most exciting Lp(a)-lowering data in 2025 emerged from the Phase 2 ALPACA study. The results were presented at the American College of Cardiology (ACC) 2025 Scientific Session on March 30, 2025, and simultaneously published in The New England Journal of Medicine.[15] Lepodisiran is an investigational, long-duration siRNA.[31] It uses the RNAi pathway to specifically silence the LPA gene in the liver, thereby inhibiting the synthesis of the apo(a) protein.[4]

The Phase 2, randomized, placebo-controlled trial enrolled 320 participants with a median baseline Lp(a) concentration of 253.9 nmol/L.[16] The trial tested various dosing regimens. The key arms received a 400 mg subcutaneous injection at baseline, with some receiving a second 400 mg dose at day 180.[17] The efficacy of lepodisiran was profound. In the pooled 400 mg dose groups, the therapy achieved a -94% placebo-adjusted time-averaged reduction in Lp(a) concentration from day 60 to day 180.[16]

The most groundbreaking finding, however, was its unprecedented durability. In participants who received a second 400 mg dose at day 180, the near-total Lp(a) reduction was maintained, with a -91% reduction still observed at day 540 (nearly 1.5 years after the first dose).[16] In terms of safety, lepodisiran was generally well-tolerated.[15] The most common adverse events were mild-to-moderate injection site reactions (occurring in up to 11.6% of patients).[15] There were some reports of transient, clinically meaningful elevations of ALT and AST in up to 5.8% of patients, which resolved.[15]

### *4.3. The Evolving CVOT Landscape: Pelacarsen and Olpasiran*

While the lepodisiran data demonstrates best-in-class efficacy and durability [16], the entire field is awaiting definitive cardiovascular outcome trial (CVOT) data. Several large-scale Phase 3 CVOTs are underway to determine if lowering Lp(a) translates to a reduction in MACE. These include the Lp(a)-HORIZON trial for the ASO pelacarsen [4] and the CVOT for the siRNA olpasiran.[23] The olpasiran program, OCEAN(a)-PreEvent, was notable for initiating enrollment in August 2025 for an 11,000-patient trial aimed at primary prevention of a first cardiovascular event.[59]

The durability data from the ALPACA trial [16] is transformative, as it fundamentally blurs the line between "transient" RNAi therapies and "permanent" gene editing. A >90% reduction in a major causal risk factor, sustained at 1.5 years from just two injections [16], is functionally equivalent to a "one-and-done" therapy for the duration of a patient's 5-year MACE risk window. This approach may represent the "best of both worlds": it provides the adherence-solving efficacy of a permanent therapy [26] while avoiding the irreversible risks [21] and complex bioethical questions [60] of altering the human genome. This positions long-duration siRNA as a powerful competitor to DNA-editing platforms.

 doi:10.20944/preprints202511.0942.v1



**Table 2.** Summary of Key 2025 Clinical Trial Data for Novel Cardiovascular Genetic Therapies.

| Therapy (Trial Name) | Target (Gene) | Modality | Phase | Key Efficacy Endpoints (2025 Data) | Key Reported Adverse Events (2025 Data) |
|---|---|---|---|---|---|
| **Olezarsen** (CORE-TIMI 72a/b) [9] | APOC3 [30] | ASO [30] | 3 [9] | ~55-72% TG reduction in sHTG; **85% reduction in acute pancreatitis** [9] | Favorable; mild injection site reactions [35] |
| **CTX310** (Phase 1) [13] | ANGPTL3 [12] | CRISPR-Cas9 [12] | 1 [13] | (Single dose) -73% ANGPTL3, -55% TGs, -49% LDL-C [12] | Infusion reactions (fever, nausea); transient (3-5x ULN) ALT elevation in 1 pt [13] |
| **Lepodisiran** (ALPACA) [16] | Lp(a) / *LPA* [57] | siRNA [57] | 2 [16] | >94% Lp(a) reduction; **durable effect (>90%) at Day 540** [16] | Injection site reactions; transient ALT/AST elevations (up to 5.8%) [15] |
| **VERVE-102** (Heart-2) [20] | PCSK9 [28] | Base Editing [28] | 1b [20] | (Initial data) -53% LDL-C (max -69%) [20] | **Well-tolerated, no clinically significant lab abnormalities** [54] |
| **VERVE-201** (Pulse-1) [51] | ANGPTL3 [51] | Base Editing [51] | 1b [51] | First patient dosed late 2024; update expected 2H 2025 [54] | Data pending (2H 2025) |

## 5. Translational Hurdles: Safety, Durability, and Ethics

### *5.1. Distinguishing the Safety Profiles of Genetic Therapies*

The rapid progress of these therapies has been accompanied by a steep learning curve regarding their distinct safety profiles. ASOs have been shadowed by historical risks of thrombocytopenia (seen with volanesorsen) [3] and hepatotoxicity (seen with mipomersen).[25] However, the second-generation GalNAc-conjugated ASOs, such as olezarsen, appear to have a vastly improved safety profile, with injection site reactions being the primary reported issue.[35] The siRNA platform is generally considered to have a very favorable safety profile. The most common adverse events are mild injection site reactions and, as seen in the ALPACA trial, occasional transient and asymptomatic liver function test (LFT) elevations.[15] With CRISPR/Base Editing, the risks are two-fold and substantially more complex, involving both the delivery vehicle (LNP toxicity) and the payload (genotoxicity).[21]

### *5.2. Case Study in LNP Toxicity: The 2024 Pause of VERVE-101 and 2025 Pivot to VERVE-102*

The most important translational lesson of the past year for the entire in vivo gene-editing field came from Verve Therapeutics' PCSK9 program. In April 2024, Verve announced it was pausing enrollment in the Heart-1 trial of VERVE-101, its first-generation base editor for PCSK9.18 This pause was triggered after the sixth patient in the 0.45 mg/kg dose cohort experienced asymptomatic but severe laboratory abnormalities: a Grade 3 transient elevation in ALT and Grade 3 thrombocytopenia (low platelets).[18] Verve concluded that this toxicity was not caused by the base editor "payload" but by the LNP delivery system itself.[19] The company immediately pivoted to its backup candidate, VERVE-102. This asset uses the exact same base editor to target PCSK9, but packages it in a different, next-generation LNP that incorporates a novel ionizable lipid and a GalNAc ligand for more precise liver targeting.[19]

This pivot was validated throughout 2025. By February 2025, Verve reported that VERVE-102 (in its Heart-2 trial) was "well-tolerated," with "no clinically significant laboratory abnormalities

 doi:10.20944/preprints202511.0942.v1



observed".[54] This clean safety profile was confirmed again in initial efficacy data reported in May 2025.[20]

This VERVE-101/102 saga represents a clear, clinical-level "A/B test." It provides definitive evidence that for LNP-delivered in vivo gene therapies, the delivery vehicle is an independent and primary source of dose-limiting toxicity. The payload (the editor) was constant, but the LNP "A" (VERVE-101) caused severe toxicity [18] while LNP "B" (VERVE-102) did not.[55] This proves that the future success of the entire DNA-editing field, including competitors like CTX310 (which also showed a transient LFT spike [13]), is critically dependent on LNP engineering and optimization.

### *5.3. The Long-Term Horizon: Quantifying Off-Target Risks of In Vivo CRISPR*

Beyond the acute toxicity of the delivery vehicle lies the long-term risk of the payload: genotoxicity.

- **Nuclease Editors (e.g., CTX310):** The DSB induced by Cas9 is a violent event for the cell. While effective for gene knockout, these breaks can lead to unintended, large-scale genomic rearrangements, translocations, or large deletions, which are notoriously difficult to detect with standard sequencing.[21]
- **Base Editors (e.g., VERVE-102, VERVE-201):** These were designed to avoid DSBs.[27] However, they have their own off-target risks, including inadvertent single-base conversions at other genomic locations (DNA off-targets) or nonspecific deamination of RNA (RNA off-targets).[37]

The short-term data from the 2025 trials is promising, but it cannot answer these long-term safety questions. There is a critical need for standardized regulatory guidelines for detecting, quantifying, and reporting in vivo genotoxicity.[22] This requires a comprehensive workflow, combining in silico prediction with deep experimental validation (e.g., CIRCLE-seq, GUIDE-seq) and long-term functional assays to ensure no oncogenic or other adverse events emerge years or decades after the single-course treatment.[37]

### *5.4. Bioethical Considerations for Somatic Gene Editing as a Public Health Tool*

It is essential to differentiate the therapies discussed from germline editing. All ongoing cardiovascular trials, including those for CTX310 and the VERVE programs, involve somatic cell gene therapy.[64] These modifications affect only the patient and cannot be inherited by their descendants. This avoids the profound ethical quandaries of germline editing, such as permanent alteration of the human gene pool or eugenics.[60]

However, the use of somatic gene editing for a common, non-monogenic disease like ASCVD—as opposed to a severe, life-threatening monogenic disease like sickle cell—opens a new ethical frontier.[64] This raises two critical questions for society:

- Risk/Benefit Ratio: Is a permanent, irreversible treatment [26] justified for a condition that is, in many cases, manageable with chronic (albeit poorly adhered to) medication? The "one-and-done" appeal must be carefully weighed against the unknown long-term risks of permanent genomic modification.[21]
- Social Equity: These therapies will inevitably be extraordinarily expensive, at least initially.[25] This creates a significant risk of a two-tiered system of cardiovascular care: a "cure for the wealthy" while the majority of the population relies on low-cost, low-adherence pills. This could paradoxically widen, rather than narrow, societal health inequalities.[60]

## 6. Conclusions and Future Directions

The year 2025 was a watershed moment in cardiovascular medicine. It marked the simultaneous clinical validation of three distinct genetic platforms (ASO, siRNA, and CRISPR-Cas9) against the most recalcitrant and high-value targets in lipidology. The conceptual shift from a chronic, daily-dose model—with its well-documented adherence gap [24]—to a long-acting or permanent, single-course therapeutic model is no longer a future aspiration but a clinical reality.[26]

 doi:10.20944/preprints202511.0942.v1



The 2025 data provided key proof-of-concept victories for each platform:

- ASO: Olezarsen's Phase 3 CORE trial data provided the first-ever demonstration of acute pancreatitis prevention with a lipid-lowering therapy, validating the platform for a hard, non-ASCVD clinical outcome.[9]
- siRNA: Lepodisiran's Phase 2 ALPACA data demonstrated "gene-editing-like" durability, sustaining >90% Lp(a) reduction at 1.5 years and setting a new bar for long-acting, reversible therapy.[16]
- Gene Editing: The CTX310 and VERVE-102 data provided the first human proof-of-concept that in vivo DNA editing for ASCVD risk factors is not only possible but highly effective.[13]

The path forward now depends on clearing three major hurdles. Cardiovascular Outcome Trials (CVOTs are the final and most important frontier. Demonstrating potent biomarker reduction is insufficient. These therapies must prove they reduce MACE (myocardial infarction, stroke, and cardiovascular death). The ongoing Lp(a) CVOTs, such as OCEAN(a) [59], are the vanguard of this effort, and their results will determine the ultimate clinical utility of these agents.

Safety and delivery are the second major hurdle. The VERVE-101/102 saga [18] has definitively identified LNP optimization as the single greatest priority for all in vivo DNA-editing platforms. Concurrently, robust, long-term (10–15 year) follow-up studies are now essential to monitor for any delayed genotoxicity from off-target edits.[21]

Finally, the field must proactively move from the scientific question of "can we do this?" to the societal question of "how, and for whom, should we do this?".[61] We must establish a robust bioethical framework for the use of somatic editing in common diseases and simultaneously develop health policy and access models to prevent the creation of a new, profound class of health disparity.[25]

**Author Contributions:** Conceptualization, M.M.; methodology, M.M.; software, M.M.; validation, M.M and A.R.; formal analysis, M.M..; investigation, M.M..; resources, M.M. and A.I.; data curation, M.M.; writing—original draft preparation, M.M.; writing—review and editing, M.M.; visualization, M.M.; supervision, M.M.; project administration, M.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study due to this narrative review only synthesizing existing information and literature.

**Informed Consent Statement:** Patient consent was waived due to this narrative review synthesizing existing literature.

**Data Availability Statement:** Data available at reasonable request to the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| **ACC** | American College of Cardiology |
| **AHA** | American Heart Association |
| **ALT** | Alanine Aminotransferase |
| **ANGPTL3** | Angiopoietin-like protein 3 |
| **apo(a)** | Apolipoprotein(a) |
| **apoB** | Apolipoprotein B |
| **APOC3** | Apolipoprotein C-III |

 doi:10.20944/preprints202511.0942.v1



| | |
|---|---|
| **apoE** | Apolipoprotein E |
| **ASCVD** | Atherosclerotic Cardiovascular Disease |
| **ASO** | Antisense Oligonucleotide |
| **AST** | Aspartate Aminotransferase |
| **Cas9** | CRISPR-associated protein 9 |
| **CRISPR** | Clustered Regularly Interspaced Short Palindromic Repeats |
| **CVD** | Cardiovascular Disease |
| **CVOT** | Cardiovascular Outcome Trial |
| **DLT** | Dose-Limiting Toxicity |
| **DNA** | Deoxyribonucleic Acid |
| **DSB** | Double-Strand Break |
| **EL** | Endothelial Lipase |
| **FCS** | Familial Chylomicronemia Syndrome |
| **GalNAc** | N-acetylgalactosamine |
| **HoFH** | Homozygous Familial Hypercholesterolemia |
| **Indel** | Insertion or Deletion |
| **IV** | Intravenous |
| **LDL** | Low-Density Lipoprotein |
| **LDL-C** | Low-Density Lipoprotein Cholesterol |
| **LFT** | Liver Function Test |
| **LNP** | Lipid Nanoparticle |
| **LOF** | Loss-of-Function |
| **Lp(a)** | Lipoprotein(a) |
| **LPL** | Lipoprotein Lipase |
| **MACE** | Major Adverse Cardiovascular Events |
| **mRNA** | Messenger Ribonucleic Acid |
| **NHEJ** | Non-Homologous End Joining |
| **RISC** | RNA-Induced Silencing Complex |
| **RNA** | Ribonucleic Acid |
| **RNAi** | RNA Interference |
| **SAE** | Serious Adverse Event |
| **sgRNA** | Single-Guide RNA |
| **sHTG** | Severe Hypertriglyceridemia |
| **siRNA** | Small Interfering RNA |
| **TG** | Triglyceride |
| **TRL** | Triglyceride-Rich Lipoprotein |
| **ULN** | Upper Limit of Normal |

## References

1. Luo, F.; Das, A.; Khetarpal, S.A.; Fang, Z.; Zelniker, T.A.; Rosenson, R.S.; Qamar, A. ANGPTL3 inhibition, dyslipidemia, and cardiovascular diseases. *Trends Cardiovasc. Med.* **2024**, *34*, 215–222.
2. Sandesara, P.B.; Virani, S.S.; Fazio, S.; Shapiro, M.D. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr. Rev.* **2019**, *40*, 537–557.
3. Laufs, U.; Parhofer, K.G.; Kastelein, J.J.; Toth, P.P. Novel approaches to the management of hypertriglyceridemia. *Eur. Heart J.* **2020**, *41*, 99–109c.

 doi:10.20944/preprints202511.0942.v1




4. Koschinsky, M.L. Novel Therapeutic Approaches for Targeted Reduction of Lp(a) in Patients with ASCVD. *J. Clin. Lipidol.* **2025**.
5. Wang, F.; Wang, Z.; Liu, Z.; et al. Genetic variants of apoC-III and ANGPTL3 and the risk of cardiovascular diseases. *Eur. Heart J. Open* **2022**, *2*, oeac040.
6. Arteriosclerosis, Thrombosis, and Vascular Biology. APOC3 and ANGPTL3 Inhibition and Cardiovascular Risk. *Arterioscler. Thromb. Vasc. Biol.* **2022**, *42*, 1329–1339.
7. Jorgensen, A.B.; Frikke-Schmidt, R.; Nordestgaard, B.G.; Tybjaerg-Hansen, A. Loss-of-Function Mutations in *APOC3*and Risk of Ischemic Vascular Disease. *N. Engl. J. Med.* **2014**, *371*, 32–41.
8. Luo, F.; Das, A.; Khetarpal, S.A.; et al. ANGPTL3 inhibition, dyslipidemia, and cardiovascular diseases. *Trends Cardiovasc. Med.* **2024**, *34*, 215–222.
9. Mass General Brigham. Olezarsen Significantly Reduces Rate of Acute Pancreatitis Events in People with Severe Hypertriglyceridemia. Press Release, November 8, 2025.
10. American College of Cardiology. Late-Breaking Science Highlights New Treatments For Severe Hypertriglyceridemia. ACC News Story, November 8, 2025.
11. Marston, N.A.; Alexander, V.J.; Prohaska, T.A.; et al. Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk. *N. Engl. J. Med.* **2025**, DOI: 10.1056/NEJMoa2512761.
12. TCTMD. CRISPR-Cas9 Gene-Editing Therapy Shows Early Promise for Dyslipidemia. November 08, 2025.
13. CRISPR Therapeutics. CRISPR Therapeutics Announces Positive Phase 1 Clinical Data for CTX310® Demonstrating Deep and Durable ANGPTL3 Editing, Triglyceride and Lipid Lowering. Press Release, November 8, 2025.
14. CRISPR Therapeutics. CRISPR/Cas9 in vivo gene editing therapy, CTX310®, targeting angiopoietin-related protein 3 (ANGPTL3). Press Release, November 8, 2025.
15. American College of Cardiology. A Study of Lepodisiran in Participants With Elevated Lipoprotein(a). ACC News Story, March 30, 2025.
16. Nissen, S.E.; Ni, W.; Shen, X.; et al. Lepodisiran — A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N. Engl. J. Med.* **2025**, *392*, 1673–1683.
17. Nissen, S.E.; Ni, W.; Shen, X.; et al. Lepodisiran — A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N. Engl. J. Med.* **2025**, *392*, 1673–1683. DOI: 10.1056/NEJMoa2415818.
18. Verve Therapeutics. Verve Therapeutics Announces Updates on its PCSK9 Program. Press Release, April 2, 2024.
19. FierceBiotech. Verve halts enrollment in lead trial after grade 3 side effects, prioritizing next PCSK9 editor. April 2, 2024.
20. Chen, H.; et al. Current Challenges in the Management of Off-Target Effects for CRISPR/Cas9 Gene Therapy. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1339189.
21. Paixão, S.; et al. Ensuring the Genomic Safety of CRISPR-Based Genome Editing Therapies: A Workflow for Off-Target Assessment. *Mol. Ther. Nucleic Acids* **2025**, *39*, 102636.
22. Koschinsky, M.L. Novel Therapeutic Approaches for Targeted Reduction of Lp(a) in Patients with ASCVD. *J. Clin. Lipidol.* **2025**. (Presented at National Lipid Association 2025 Scientific Sessions).
23. Harrison, T.N. Care Gaps in Lipid Management Among Young Adults With Severe Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2025**. (Presented at AHA 2025).
24. Ugoala, O.; et al. Emerging Gene Therapies for Familial Hypercholesterolemia. American College of Cardiology. May 27, 2025.
25. American College of Cardiology. First-in-Human Trial Suggests CRISPR-Cas9 Therapy Targeting ANGPTL3 is Safe and Reduces LDL and Triglycerides. ACC News Story, November 8, 2025.
26. Brandts, J.; Ray, K.K. From Genes to Therapy: The Evolving Landscape of Lipid-Lowering in Familial Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2021**, *78*, 2167–2170.
27. BioPharma Dive. Verve is expanding a gene editing trial for a cholesterol and heart disease treatment into the U.S. March 24, 2025.
28. Cancers. Advancements in RNA Therapeutics: The Promise of Antisense Oligonucleotides in Cancer Therapy. *Cancers***2024**, *16*, 2940.

 doi:10.20944/preprints202511.0942.v1




29. American College of Cardiology. Efficacy and Safety of Olezarsen in Managing Hypertriglyceridemia. October 21, 2024.
30. New England Journal of Medicine. Lepodisiran — A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N. Engl. J. Med.* **2025**, *392*, 1673–1683.
31. CRISPR Therapeutics. CRISPR Therapeutics to Present Late-Breaking Data at the American Heart Association (AHA) Scientific Sessions 2025. Press Release, September 9, 2025.
32. Gouni-Berthold, I.; et al. Safety of antisense oligonucleotide and siRNA-based therapeutics. *Curr. Med. Chem.* **2017**.
33. Ionis Pharmaceuticals, Inc. Olezarsen significantly reduces triglycerides and acute pancreatitis events in landmark pivotal studies. Press Release, November 8, 2025.
34. Chen, H.; et al. Current Challenges in the Management of Off-Target Effects for CRISPR/Cas9 Gene Therapy. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1339189.
35. Paixão, S.; et al. Ensuring the Genomic Safety of CRISPR-Based Genome Editing Therapies: A Workflow for Off-Target Assessment. *Mol. Ther. Nucleic Acids* **2025**, *39*, 102636.
36. Karwatowska-Prokopczuk, E.; et al. Apolipoprotein C-III (apo C-III) as a Regulator of Triglyceride-Rich Lipoprotein Metabolism and Cardiovascular Risk. *Int. J. Clin. Ther. Med.* **2024**.
37. Dron, J.S.; Hegele, R.A. Novel agents for lowering triglycerides. *Expert Rev. Cardiovasc. Ther.* **2020**, *18*, 461–471.
38. Wyler von Ballmoos, M.C.; Haring, B.; Sacks, F.M. The Risk of Cardiovascular Events with Increased Apolipoprotein CIII: A Systematic Review and Meta-Analysis. *J. Clin. Lipidol.* **2015**, *9*, 498–510.
39. Packard, C.J.; Pirillo, A.; Tsimikas, S.; Ference, B.A.; Catapano, A.L. Exploring apolipoprotein C-III: Pathophysiological and pharmacological relevance. *Cardiovasc. Res.* **2024**, *119*, 2843–2857.
40. Stroes, E.S.G.; Alexander, V.J.; Karwatowska-Prokopczuk, E.; et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *N. Engl. J. Med.* **2024**, *390*, 1781–1792.
41. Ionis Pharmaceuticals, Inc. Detailed data from the landmark CORE and CORE2 pivotal studies of olezarsen for sHTG to be presented as a late breaker at AHA Scientific Sessions. Press Release, October 27, 2025.
42. Wolters Kluwer Health, Inc. Olezarsen: A Review of its Mechanism, Efficacy, and Safety. *Lippincott*® **2025**.
43. Watts, G.F.; Rosenson, R.S.; Hegele, R.A.; et al. Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N. Engl. J. Med.* **2025**, *392*, 127–137.
44. CRISPR Therapeutics. First-in-Human Phase 1 Clinical Trial of a CRISPR-Cas9 Gene Editing Therapy Targeting ANGPTL3. *N. Engl. J. Med.* **2025**. (Simultaneous publication with ).
45. TCTMD. CRISPR-Cas9 Gene-Editing Therapy Shows Early Promise for Dyslipidemia. November 8, 2025.
46. American Heart Association. First-in-human trial of CRISPR gene-editing therapy safely lowered cholesterol, triglycerides. News Release, November 8, 2025.
47. Gao, H.; Dan, Z.; et al. ANGPTL3: A Breakthrough Target in Treatment for Dyslipidemia and Atherosclerosis. *Cardiol. Discov.* **2024**.
48. Verve Therapeutics. VERVE-201. ClinicalTrials.gov ID: NCT06451770. (Accessed 2025).
49. Verve Therapeutics. Verve Therapeutics Announces Pipeline Progress and Reports Fourth Quarter and Year-End 2024 Financial Results. Press Release, February 27, 2025.
50. Nissen, S.E.; Ni, W.; Shen, X.; et al. Lepodisiran — A long-duration small interfering RNA targeting lipoprotein(a). *N. Engl. J. Med.* **2025**, *392*, 1673–1683. (Presented at ACC.25, March 30, 2025).
51. New England Journal of Medicine (YouTube). Lepodisiran for Elevated Lipoprotein(a). Quick Take Video Summary. March 30, 2025.
52. Lepodisiran - A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N. Engl. J. Med.* **2025**.
53. Amgen. OCEAN(a)-PreEvent - Olpasiran Trials of Cardiovascular Events And LipoproteiN(a) Reduction to Prevent First Major Cardiovascular Events. ClinicalTrials.gov ID: NCT07136012. (Accessed 2025).
54. National Human Genome Research Institute. Ethical Concerns of Genome Editing. (Accessed 2025).
55. Häberle, J.; et al. Somatic vs. Germline Genome Editing: Risks and Benefits. *Bioethics* **2020**, *34*, 826–833.
56. Verve Therapeutics. Verve Therapeutics Announces Updates on its PCSK9 Program. Press Release, April 2, 2024.
57. BioSpace. Verve Halts Trial for Lead Gene-Editing Program Due to Safety Concerns. April 2, 2024.

 doi:10.20944/preprints202511.0942.v1



58. Liscovitch, N.; et al. Bioethical debate on somatic gene therapy: a systematic review of reasons. *Humanit. Soc. Sci. Commun.* **2024**, *11*, 141.
59. National Institutes of Health. Ethical, Legal, and Social Implications (ELSI) of Human Genome Editing. (Accessed 2025).
60. Bonow, R. O. JAMA Cardiology - The Year in Review 2024. *JAMA Cardiol.* **2025**, *10*, 409–411.
61. European Heart Journal. Year in Cardiovascular Medicine 2024. *Eur. Heart J.* **2025**, *46*.
62. JACC. Angiopoietin-like 3 (ANGPTL3): A New Target for Lipid Lowering. *J. Am. Coll. Cardiol.* **2021**, *77*, 190–200.
63. Schmitz, N.; Abdelmageed, M.M.; Monine, M.; Xu, Y. Trends in First-in-Human Studies for Intrathecal Antisense Oligonucleotides: Insights From 2010 to 2024. *J. Clin. Pharmacol.* **2025**, *65*, 1065–1075.