IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ARROWHEAD PHARMACEUTICALS, INC., Plaintiff, v. IONIS PHARMACEUTICALS, INC., Defendant.	C.A. No. 1:25-cv-01130-UNA **JURY TRIAL DEMANDED**

PLAINTIFF'S COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Arrowhead Pharmaceuticals, Inc. ("Arrowhead"), by and through its undersigned counsel, brings this action for declaratory judgment against Defendant Ionis Pharmaceuticals, Inc. ("Ionis") and alleges as follows:

NATURE OF THE ACTION

1. This is an action for a declaratory judgment of patent invalidity and noninfringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq*. and the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq*.

2. Arrowhead seeks a declaratory judgment that U.S. Patent No. 9,593,333 (the "'333 patent"), attached hereto as Exhibit A, is either invalid, not infringed, or both. Specifically, Arrowhead seeks a declaration that no valid claim of the '333 patent will be infringed by Arrowhead's investigational therapeutic, plozasiran, within the meaning of 35 U.S.C. § 271.

PARTIES

3. Plaintiff Arrowhead Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its headquarters at 177 East Colorado Boulevard, Suite 700, Pasadena, California 91105.

4. Arrowhead is an innovator in the field of RNAi (RNA interference) technology, creating therapeutics for the treatment of a variety of diseases, including orphan diseases for which few or no treatment options are available. Arrowhead's therapies are focused on treating diseases by targeting the underlying disease using Arrowhead's targeted RNAi molecule (TRiM™) platform.

5. On information and belief, Defendant Ionis Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010.

JURISDICTION AND VENUE

6. This action arises under the patent laws of the United States of America, 35 U.S.C. §§ 100, *et seq*., and the Federal Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

7. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

8. This Court has personal jurisdiction over Ionis because, *inter alia*, Ionis is a corporation organized and existing under the laws of Delaware.

9. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b) and (c) at least because Ionis is incorporated in and resides in Delaware. Venue is also proper in this judicial district pursuant to 28 U.S.C. § 1400(b).

THE PATENT-IN-SUIT

10. U.S. Patent No. 9,593,333 (the "'333 patent"), titled "Modulation of apolipoprotein C-III (ApoCIII) expression in lipoprotein lipase deficient (LPLD) populations," was issued by the U.S. Patent and Trademark Office on March 14, 2017 from U.S. Application No. 14/768,180.

11. On its face, the '333 patent names Veronica J. Alexander, Nicholas J. Viney, and Joseph L. Witztum as inventors.

12. On information and belief, Ionis Pharmaceuticals, Inc. is the current assignee of the '333 patent.

13. The '333 patent purports to disclose "methods, compounds, and compositions for reducing expression of ApoCIII mRNA and protein for treating, preventing, delaying, or ameliorating Frederickson Type I dyslipidemia/FCS/LPLD, in a patient." '333 patent at Abstract. The '333 patent has one independent claim, claim 1, which is illustrative:

> 1. A method of treating or ameliorating lipoprotein lipase deficiency (LPLD) in an animal comprising administering a therapeutically effective amount of a compound comprising an ApoCIII specific inhibitor to the animal, where:
>
> administering the compound reduces a triglyceride level by at least 10%, thereby treating or ameliorating LPLD.

Id. at 83:48–53. As evidenced by independent claim 1, the breadth of claims of the '333 patent is so broad as to cover at least any form of an "ApoCIII specific inhibitor," any "animal," and any "therapeutically effective amount." The specification discloses a single example, describing a clinical trial for ISIS 304801. *See id*. at 68:51–76:20.

FACTUAL BACKGROUND

A. Arrowhead Was Founded to Harness RNAi to Deliver Breakthrough Medicines for Patients with Unmet Needs

14. Arrowhead's mission is closely tied to the patients it serves. It is committed to what it calls "20 in 25": a pledge to have twenty investigational drugs in clinical trials or on the market by the end of 2025. That ambition reflects the urgency of the serious and often rare diseases Arrowhead targets, including cardiometabolic, pulmonary, and liver disorders that have resisted other, more traditional approaches. For Arrowhead, advancing its pipeline means addressing conditions that impose a heavy burden on patients and lack adequate treatments.

15. Arrowhead is a biopharmaceutical company built around a simple but ambitious idea: silence the genes that cause disease. Arrowhead has become a leader in RNA interference, or "RNAi," a mechanism that cells use to regulate the translation of messenger RNA into protein. In scientific terms, Arrowhead develops double-stranded or duplexed small interfering RNA molecules that enter a cell and cause the cleavage and destruction of messenger RNA, the "instructions" the cell uses to build proteins. By destroying messenger RNA, the drug prevents production of the target protein.

16. Over the past decade, Arrowhead has developed and refined a platform it calls "TRiM™", short for Targeted RNAi Molecule. TRiM™ is designed to deliver RNAi drugs precisely where they are needed. In practice, this means attaching a targeting ligand—a kind of molecular homing device—that directs the RNAi molecule into specific tissues, such as the cells that make up liver tissue. Once inside a cell in the target tissue, the duplexed RNAi molecule is taken up by a natural cellular structure called "the RNA-induced silencing complex," or "RISC," which allows the RNAi molecule to block the production of the target protein in that cell. Importantly, Arrowhead's TRiM™ molecules work catalytically: the guide strand of the RNAi

molecule can remain in the RISC complex to do its work of preventing protein production, and thus each TRiM™ RNAi molecule can destroy hundreds of messenger RNAs, resulting in deep and long-lasting gene silencing.

17. Arrowhead's commitment to this technology has been reinforced by strategic growth. In 2011, Arrowhead acquired the RNAi therapeutics business of Hoffman-LaRoche, Inc. and F. Hoffmann-La Roche Ltd., cementing its foundation with more than a decade of prior work in the field. Then in 2015, Arrowhead acquired Novartis's RNAi research portfolio. Arrowhead has also entered major partnerships, including with Amgen in 2016 for a cardiovascular RNAi therapy that is currently the subject of a large, Phase 3 clinical trial, and Janssen in 2018 for other liver-targeted programs. Today, multiple biopharmaceutical companies, including for example Amgen, GSK, and Takeda, are all conducting clinical trials of innovative new drugs that Arrowhead has discovered. These moves position Arrowhead not as a niche player, but as a central force in developing a new class of medicines.

B. FCS Is a Rare Genetic Disease That Causes Life-Threatening Pancreatitis and Has Limited Therapies

18. FCS (familial chylomicronemia syndrome) is a severe, ultrarare disorder in which patients are unable to clear fat particles called triglycerides from their blood. FCS affects only a few thousand people worldwide, making it among the rarest diseases. Patients with FCS often have triglyceride levels exceeding 880 mg/dL, and even up to ten times the normal range. For adults, a normal triglyceride level is below 150 mg/dL.

19. These extreme triglyceride levels can cause a cascade of serious health problems. The key clinical outcome of concern in FCS is acute pancreatitis, a sudden and painful inflammation of the pancreas that can be fatal. Patients with FCS frequently suffer from chronic abdominal pain, diabetes, liver fat accumulation, and cognitive issues.

C. Plozasiran Is Arrowhead's First-in-Class Therapy That Dramatically Reduces Triglycerides and Pancreatitis Risk in FCS Patients

20. Arrowhead's most advanced drug candidate is plozasiran, formerly known as ARO-APOC3. Plozasiran is designed to treat FCS by silencing the gene that produces apolipoprotein C-III ("ApoC3"). ApoC3 is a protein that prevents the body from clearing triglycerides from the blood.

21. To test plozasiran in FCS patients, Arrowhead conducted the PALISADE study—a pivotal Phase 3 clinical trial. The study enrolled 75 adults with genetically confirmed (n=44, 59%) or clinically diagnosed (n=31, 41%) FCS. Enrollment took place across 39 sites in 18 countries. Participants were randomized to receive either placebo or a 25 mg or 50 mg dose of plozasiran once every three months.

22. The results of the PALISADE clinical study were selected for publication in the New England Journal of Medicine, one of the most prestigious medical journals in the world. During the study, plozasiran reduced triglycerides by up to 80% and ApoC3 levels by up to 94%, while also reducing the incidence of acute pancreatitis in a statistically significant manner. *See* Exhibit B (Watts et al., *Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk*, 392 NEJM 127, 130–31 (2025)). Patients on plozasiran achieved these results with only one 25 mg subcutaneous injection just once every three months, and the therapeutic effect was generally seen starting in the first month of therapy.

23. The FDA has recognized plozasiran's promise. In March 2023, the agency granted Arrowhead's request for Fast Track designation for plozasiran. In September 2024, the agency again recognized the potential benefit of Arrowhead's plozasiran for patients with FCS when it designated plozasiran as a Breakthrough Therapy. FDA designed these specific programs to expedite development and review of therapies for serious diseases with unmet needs. *See* Exhibit

C (Mar. 20, 2023 Press Release: Arrowhead Receives FDA Fast Track Designation); Exhibit D (Sep. 10 2024 Press Release: Arrowhead Receives FDA Breakthrough Therapy Designation).

24. Arrowhead submitted a New Drug Application for approval of plozasiran in November 2024, and FDA has set a Prescription Drug User Fee Act ("PDUFA") action date of November 18, 2025—the target deadline by which FDA may make a decision on whether to approve plozasiran. *See* Exhibit E (Nov. 18, 2024 Press Release: Arrowhead Submits Plozasiran NDA). Arrowhead expects to receive a decision on its New Drug Application on or before the PDUFA date of November 18, 2025.

D. Ionis's FCS Treatment: Tryngolza®

25. Ionis is a biotechnology company that develops antisense oligonucleotide ("ASO") medicines. Its approach relies on single strands of synthetic nucleic acid molecules that incorporate DNA nucleotides and bind messenger RNA to interfere with protein production.

26. In December 2024, FDA approved Ionis's drug Tryngolza® (olezarsen) for adults with FCS. Tryngolza® requires patients to inject themselves once a month using an autoinjector into the abdomen or thigh. The Tryngolza® label notes that patients may experience side effects such as hypersensitivity reactions, injection-site reactions, low platelet counts, elevated liver enzymes, increased glucose, and higher LDL cholesterol.

27. The active ingredient in Tryngolza®—olezarsen—targets ApoC3. Unlike Arrowhead's RNAi mechanism, which harnesses RISC to catalytically degrade messenger RNA, Ionis's ASO technology works differently by blocking the translation of messenger RNA into protein through a different enzyme called RNase H. Because the mechanism for ASO therapies such as Tryngolza® is not catalytic, the ASO is typically consumed as it does its work within the body. As a result, the effect tends to wane over the dosing interval.

28. While Tryngolza® is FDA-approved for the treatment of FCS, there remains a clear need for additional therapies with improved properties for patients with this rare and debilitating disease.

E. Ionis Tries to Block Plozasiran Through Threats of Litigation

29. After Arrowhead announced strong Phase 3 results for plozasiran, Ionis began an early campaign to obstruct Arrowhead's ability to bring plozasiran to FCS patients if approved by FDA.

30. On April 23, 2025, Ionis's outside counsel sent Arrowhead a letter accusing it of unlawfully "promoting" plozasiran and making "false and misleading statements" that compared plozasiran to Ionis's FDA-approved drug, Tryngolza®. Exhibit F at 1, 2 (Apr. 23, 2025 Ionis correspondence to Arrowhead). Ionis's central complaint was that Arrowhead was presenting its Phase 3 efficacy findings for plozasiran in too close proximity to presentations of Tryngolza® efficacy findings and that viewers of such presentations might reach a conclusion that plozasiran has superior efficacy. In a May 22, 2025 response, Arrowhead addressed Ionis's categorically false accusations, and raised concerns with Ionis's own marketing and promotion practices surrounding Tryngolza®, to which Ionis did not further respond. *See* Exhibit G (May 22, 2025 Arrowhead correspondence to Ionis).

31. Ionis escalated yet another manufactured dispute with Arrowhead on September 3, 2025. This time, Ionis's correspondence baselessly alleged that Arrowhead's plan to bring plozasiran to market—pending FDA approval—showed a "blatant disregard of Ionis's patent rights" under U.S. Patent No. 9,593,333 and accused Arrowhead of infringement. Exhibit H at 2 (Sept. 3, 2025 Ionis correspondence to Arrowhead).

32. The September letter claimed that if Arrowhead launched plozasiran, it would cause Ionis "serious and irreparable harm." *Id.* Ionis warned that unless the matter was resolved, it would

"seek relief . . . on September 11, 2025" by filing suit—timed just two months before FDA's expected decision on plozasiran. *Id.* at 1–2.

33. Given Ionis's repeated threats of litigation, Arrowhead must act affirmatively to dispel any cloud of uncertainty surrounding the imminent approval of plozasiran.

COUNT I

DECLARATORY JUDGMENT OF INVALIDITY OF THE '333 PATENT

34. Arrowhead realleges the foregoing paragraphs as if fully set forth herein.

35. On information and belief, Ionis is the owner of the '333 patent and contends that the claims of the '333 patent are valid.

36. The claims of the '333 patent are invalid for failing to meet the requirements of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, and 112, improper inventorship, the doctrine of obviousness-type double patenting, and/or pursuant to other judicially created or non-statutory requirements for patentability and/or equitable doctrines.

37. As one example, the claims of the '333 patent are invalid for anticipation under 35 U.S.C. § 102 and/or obviousness under 35 U.S.C. § 103 in light of prior art that published or was otherwise available to the public before the earliest possible priority date of the '333 patent.

38. For example, and without limiting the grounds of invalidity or invalidating prior art that will be asserted in this action, the following prior art references anticipate and/or render obvious each and every claim of the '333 patent: International Pat. App. Pub. No. WO2010/080953 (published July 15, 2010) ("Mullick"); International Pat. App. Pub. No. WO2012/149495 (published November 1, 2012) ("Mullick II"); International Pat. App. Pub. No. WO2012/177947 (published December 27, 2012) ("Bettencourt"); Ionis Pharma., Inc., *Safety, Tolerability, and Pharmacokinetic Study of ISIS ApoC-III Rx in Hypertriglyceridemia*, NIH,

https://clinicaltrials.gov/study/NCT01529424 (published February 7, 2012); Paavo K.J. Kinnunen & Christian Ehnholm, *Effect of Serum and C-apoproteins from Very Low Density Lipoproteins on Human Postheparin Plasma Hepatic Lipase*, 65 FEBS LETTERS 354, 354–57 (1976); Ephraim Sehayek & Shlomo Eisenberg, *Mechanisms of Inhibition by Apolipoprotein C of Apolipoprotein E-dependent Cellular Metabolism of Human Triglyceride-rich Lipoproteins Through the Low Density Lipoprotein Receptor Pathway*, 266 J. BIOLOGICAL CHEMISTRY 18259, 18259–67 (1991); K. Aalto-Setala et al., *Mechanism of Hypertriglyceridemia in Human Apolipoprotein (Apo) CIII Transgenic Mice*, 90 J. CLINICAL INVESTIGATION 1889, 1889–1900 (1992); Pat. Pub. No. US2011/0060030 (published on March 10, 2011) ("Crooke"); Miek C. Jong et al., *Role of ApoCs in Lipoprotein Metabolism: Functional Differences Between ApoC1, ApoC2, and ApoC3*, 19 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 472, 472–84 (1999); Christopher J. Mann et al., *Inhibitory Effects of Specific Apolipoprotein C-III Isoforms on the Binding of Triglyceride-rich Lipoproteins to the Lipolysis-stimulated Receptor*, 272 J. BIOLOGICAL CHEMISTRY 31348, 31348–54 (1997); Ronald M. Krauss, *Lipids and Lipoproteins in Patients with Type 2 Diabetes*, 27 DIABETES CARE 1496, 1496–1504 (2004); Esther M. M. Ooi et al., *Apolipoprotein C-III: Understanding an Emerging Cardiovascular Risk Factor*, 114 CLINICAL SCI. 611, 611–24 (2008); Chunyu Zheng et al., *Apolipoprotein C-III and the Metabolic Basis for Hypertriglyceridemia and the Dense Low-Density Lipoprotein Phenotype*, 121 CIRCULATION 1722, 1722–34 (2010).

39. As another example and without limiting the grounds of invalidity that will be asserted in this action, each claim of the '333 patent is invalid for failure to comply with the written description and enablement requirements of 35 U.S.C. § 112. The claims of the '333 patent are directed to treating or ameliorating lipoprotein lipase deficiency (LPLD) through administration

of an ApoC3 specific inhibitor. But the '333 patent fails to provide sufficient written description and/or enabling disclosure, such as a representative number of species falling within the broad genus of ApoC3 specific inhibitors that would treat or ameliorate LPLD or structural features common to the members of that broad genus so that one of skill in the art at the time of the purported invention could visualize or recognize all members of the purportedly claimed genus. Indeed, the breadth of the claims of the '333 patent is so broad as to cover at least any form of the claimed ApoC3 specific inhibitor, any animal, and any therapeutically effective amount, without the requisite disclosure in the specification, and similar claims have been repeatedly invalidated. Therefore, the '333 patent specification fails to demonstrate to a person of skill in the art that the named inventors of the '333 patent claims were in possession of the full scope of the claimed subject matter, and likewise does not allow a person of ordinary skill in the art to make or use the invention without undue experimentation.

40. As a result of Ionis's actions and the allegations it made against Arrowhead, an actual and justiciable controversy exists between Arrowhead and Ionis as to the validity of the '333 patent. Without a declaratory judgment of invalidity, Arrowhead has and will continue to suffer uncertainty and unquantifiable financial and business risks due to Ionis's infringement allegations with respect to Arrowhead's plozasiran product and the '333 patent.

41. Arrowhead is entitled to a judicial declaration that all claims of the '333 patent are invalid. Such a declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

COUNT II

DECLARATORY JUDGMENT OF NON-INFRINGEMENT OF THE '333 PATENT

42. Arrowhead realleges the foregoing paragraphs as if fully set forth herein.

43. On information and belief, Ionis is the owner of the ’333 patent and contends that one or more claims of the ’333 patent is or will be infringed by Arrowhead’s plozasiran product.

44. Arrowhead has not infringed and will not infringe, directly or indirectly, literally or under the doctrine of equivalents, any valid and enforceable claims of the ’333 patent for any activity related to FDA-approval of Arrowhead’s plozasiran product because plozasiran is currently under review by FDA, and all of Arrowhead’s plozasiran-related activities to-date fall within the scope of the safe harbor under 35 U.S.C. § 271(e)(1).

45. Arrowhead has not infringed and will not infringe, directly or indirectly, literally or under the doctrine of equivalents, any valid and enforceable claims of the ’333 patent under 35 U.S.C. § 271. For example and without limitation to other non-infringement defenses, Arrowhead may raise in this action, no valid claim of the ’333 patent encompasses a method of treating LPLD using RNAi drugs. Because Arrowhead’s plozasiran treats FCS using RNAi drugs that destroy messenger RNA, Arrowhead does not and will not infringe any valid and enforceable claim of the ’333 patent.

46. As a result of Ionis’s actions and the allegations it made against Arrowhead, an actual and justiciable controversy exists between Arrowhead and Ionis as to the infringement of the ’333 patent. Without a declaratory judgment of non-infringement, Arrowhead has and will continue to suffer uncertainty and unquantifiable financial and business risks due to Ionis’s competitive obstruction efforts, including its infringement allegations with respect to Arrowhead’s plozasiran product and the ’333 patent.

47. Arrowhead is entitled to a judicial declaration that the making, use, offer for sale, sale, or import into the United States of Arrowhead’s plozasiran therapeutic does not and will not infringe any valid and enforceable claim of the ’333 patent under 35 U.S.C. § 271. Such a

declaration is necessary and appropriate at this time to determine the rights and obligations of the parties.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests that the Court enter a Judgment and Order in its favor and against Ionis as follows:

A. Declaring that all claims of the ’333 patent are invalid;

B. Declaring that Arrowhead has not, does not, and will not infringe any valid and enforceable claim of the ’333 patent;

C. Enjoining and restraining Ionis and its officers, agents, servants, employees, attorneys, and those persons in active concert or participation with Ionis from pursuing further charges of infringement or acts of enforcement based on the ’333 patent against Arrowhead or its actual and prospective business partners, customers, suppliers, clinical investigators, and anyone in privity with Arrowhead;

D. Denying Ionis any request for injunctive relief and any other remedy available under Title 35 of the United States Code;

E. Declaring this an exceptional case in favor of Arrowhead and awarding Arrowhead its attorneys’ fees pursuant to 35 U.S.C. § 285;

F. Awarding Arrowhead taxable costs, disbursements, other expenses, and interest to the fullest extent permitted by law; and

G. Awarding any and all such relief as the Court determines to be just and proper, including pursuant to 28 U.S.C. § 2202.

DEMAND FOR TRIAL BY JURY

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiff demands trial by jury on all issues so triable.

Dated: September 10, 2025

By: */s/ Susan E. Morrison*

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