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IN THE UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

IONIS PHARMACEUTICALS, INC., a Delaware Corporation, Plaintiff, v. ARROWHEAD PHARMACEUTICALS, INC., a Delaware corporation, Defendant.	Case No. 2:25-cv-8609 **COMPLAINT FOR PATENT INFRINGEMENT** **DEMAND FOR JURY TRIAL**

COMPLAINT

Plaintiff Ionis Pharmaceuticals, Inc. ("Ionis") brings this Complaint against Defendant Arrowhead Pharmaceuticals, Inc. ("Arrowhead") to address Arrowhead's infringement of U.S. Patent No. 9,593,333 (the "'333 patent").

INTRODUCTION

1. Scientists at Ionis spent many years searching for a way to treat people with hypertriglyceridemia, a serious condition marked by elevated triglyceride levels in the blood. People with high triglyceride levels face a range of negative health outcomes, including cardiovascular problems and potentially life-threatening acute pancreatitis, a painful inflammation of the pancreas.

2. Over the course of many years, Ionis created and tested a series of candidate medicines designed to reduce the amount of a particular protein, called apolipoprotein C-III ("ApoCIII"). ApoCIII inhibits the function of a second protein, called lipoprotein lipase ("LPL"), which is responsible for breaking down triglycerides. Ionis hoped that by reducing the amount of ApoCIII available to interfere with LPL, the LPL would be free to break down triglycerides more effectively and thereby reduce triglyceride levels. But no one knew whether this idea would work in practice to help patients.

3. Instead of targeting the ApoCIII protein directly, Ionis took a different route. Ionis used specially designed molecules called antisense oligonucleotides to target ApoCIII messenger RNA ("mRNA"), which is the genetic material that encodes the ApoCIII protein. Doing so prevents the ApoCIII protein from being made in the first place. After years of research, Ionis created many different molecules that bind to ApoCIII mRNA and thereby inhibit the synthesis of the ApoCIII protein. Ionis ultimately selected one of these oligonucleotides to develop into a clinical drug candidate, called volanesorsen.

4. The Ionis team started by testing volanesorsen in the general hypertriglyceridemia population—*i.e.*, people with high triglyceride levels, but who were expected to have functional LPL protein. The hope was that for these people,

lowering ApoCIII would allow their LPL to break down harmful triglycerides. Ionis was the first company to demonstrate that an ApoCIII inhibitor would in fact work to treat people with hypertriglyceridemia. And it did work—unexpectedly well. Ionis received early, promising study readouts.

5. Meanwhile, the Ionis team had another extraordinary idea: what if inhibiting ApoCIII *also* could treat people who lacked functional LPL? At the time, this seemed far-fetched. Why would reducing the amount of a protein that inhibits LPL treat people who do not have meaningful levels of functional LPL in the first place? But Ionis decided to move forward with clinical testing on this patient population nonetheless and added three people with genetic mutations causing LPL deficiency to its clinical trial.

6. The results were nothing short of spectacular, defying both conventional thinking and the expectations of those in the field. Treatment with volanesorsen led to remarkable reductions of triglyceride levels—even in people without meaningful levels of functional LPL. In recognition of its invention of the very first treatment for LPL-deficient people, the U.S. Patent and Trademark Office granted Ionis the '333 patent at issue here.

7. Volanesorsen went on to be approved in Europe for the treatment of certain people with familial chylomicronemia syndrome ("FCS"). LPL deficiency is also known as FCS.

8. Meanwhile, Ionis developed a next-generation ApoCIII inhibitor, called olezarsen. In December 2024, the United States Food and Drug Administration ("FDA") approved Tryngolza® (olezarsen), Ionis's next-generation product, for the treatment of adults living with FCS. Ionis launched Tryngolza® in the United States in December 2024. The FCS community was "overjoyed" by this news, recognizing Tryngolza® as a "major milestone" in the treatment of FCS.[1,2]

[1] The FCS Foundation, LinkedIn, https://www.linkedin.com/posts/the-fcs-foundation_breaking-news-were-thrilled-to-share-we-activity-7276207907954720768-E1fM/

[2] First FDA Approved FCS Treatment, Mission-Cure, https://mission-cure.org/fcs-treatment-ionis/

9. When Ionis began to see success in its trials of ApoCIII inhibitors, Defendant Arrowhead Pharmaceuticals saw an opportunity. Instead of carving its own path, it simply copied Ionis's, wrongfully capitalizing on Ionis's many years of research and development by selecting an antisense ApoCIII inhibitor (plozasiran) and applying for FDA approval to use it to treat people with FCS. Arrowhead's application was filed with FDA in January 2025, and FDA is slated to act on that application by November of this year. If plozasiran receives approval, Arrowhead intends to market its copycat product for use in patients with FCS, in blatant disregard for Ionis's patent rights—years ahead of when it is lawfully permitted to do so.

10. Ionis brings this lawsuit to enforce its duly-issued patent rights in the '333 patent.

PLAINTIFF

11. Plaintiff Ionis is a corporation organized and existing under the laws of the State of Delaware with its principal place of business located at 2855 Gazelle Court, Carlsbad, California 92010.

DEFENDANT

12. Defendant Arrowhead is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 177 East Colorado Boulevard, Ste 700, Pasadena, CA 92205.

JURISDICTION AND VENUE

13. This action arises under the Patent Laws of the United States, Title 35 of the United States Code. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

14. The Court has jurisdiction over Arrowhead in this action.

15. Arrowhead is a corporate entity currently doing business in the State of California and having a regular established place of business within the forum. Arrowhead's office and principal place of business located at 177 East Colorado Boulevard, Ste 700, Pasadena, CA 92205 is a regular and established place of business

within the forum. Arrowhead is listed with the Office of the California Secretary of State as an entity that is currently doing business in the State of California, and the Office of the California Secretary of State has assigned Arrowhead the following business entity number: 2288610.

16. Arrowhead purposefully engaged in activities that are directed at the forum, this action arises out of or relates to those activities, and the assertion of personal jurisdiction in the forum comports with traditional notions of fair play and substantial justice.

17. Venue is proper in the Central District of California under 28 U.S.C. §§ 1391(b)(1) and 1400(b) because Arrowhead resides in the Central District of California and a substantial part of the events and injury giving rise to Plaintiff's claims has and continues to occur in the Central District of California.

FACTUAL ALLEGATIONS

Ionis's Novel Idea Led to a New Treatment Paradigm for FCS

18. About 30% of Americans suffer from hypertriglyceridemia—*i.e.*, high levels of triglyceride (fat) in their blood. Triglyceride levels over 150 mg/dL are considered abnormal, but for certain people with genetic defects in fat processing, triglyceride levels can exceed 1,000 mg/dL. The results can be dangerous. Severely elevated triglyceride levels are often associated with a build-up of "chylomicrons" (fatty particles) in the blood, and lead to a host of symptoms, including severe inflammation of the pancreas (called acute pancreatitis), which can lead to debilitating abdominal pain, hospitalization, and even death. Other symptoms of high triglyceride levels include xanthomas (a raised, waxy, yellowish skin condition caused by fats building up under the surface of the skin), loss of appetite, nausea and vomiting, and muscle and bone pain.

19. Ionis set out to change the lives of these people. Ionis specializes in oligonucleotide medicines that target and destroy molecules called mRNAs that the body uses to make proteins. Proteins are the workhorses of the body and are responsible for almost every bodily function. Sometimes, causing a person to make less of a protein

can be helpful—for example, because the protein does something the person needs to happen less, or because the protein inhibits a process that the person needs to happen more. Each protein corresponds to a specific mRNA. Ionis's RNA-targeting medicines can be used to target and destroy the precursor mRNA molecule specific to the harmful protein at issue, thereby causing the person's body to make less of that harmful protein.

20. To help people suffering from hypertriglyceridemia, Ionis focused its work on targeting mRNA for a protein called ApoCIII. ApoCIII was understood to inhibit the function of LPL, a protein with a critical role in breaking down triglycerides in the blood. Ionis hoped that by reducing the amount of ApoCIII in people with high triglycerides, those people's existing LPL would be available to break down the triglycerides more effectively. Neither Ionis nor anyone else in the field knew whether this approach would work—and if so, whether it would reduce triglyceride levels sufficiently to make a meaningful difference to patient health.

21. Ionis took a chance and put a medicine called volanesorsen into clinical trials. Volanesorsen is an oligonucleotide designed to trigger the degradation of mRNA that encodes the ApoCIII protein. By down-regulating the body's production of ApoCIII, Ionis was hoping to take the brakes off the body's natural LPL fat-metabolizing machinery.

22. But what about the sickest patients—those whose bodies do not make LPL at all, or whose bodies make only very small amounts or defective versions of LPL? For people who suffer from "LPL deficiency" or "LPLD," triglycerides can reach 100 times normal levels—*i.e.*, more than 15,000 mg/dL—and treatment options were virtually nonexistent. With no approved drugs available, doctors could recommend only that such patients severely restrict their diet, which was socially isolating and largely ineffective.

23. For people without meaningful levels of functioning LPL, the prevailing scientific consensus was that suppressing ApoCIII would be ineffective. But the Ionis team thought differently and charted their own path—one that would change the lives of people living with LPLD around the world. Ionis added three individuals with FCS to

an ongoing volanesorsen clinical trial; each had genetic mutations known to result in less than 5% of normal LPL activity. To the complete surprise of those in the field, the results were astounding. As the Ionis team explained in a paper published in the *New England Journal of Medicine*, "[a]fter 13 weeks of study-drug administration, plasma APOC3 levels were reduced by 71 to 90% and *triglyceride levels by 56 to 86%*."[3] The study reported that all three participants with FCS achieved triglyceride levels below 500 mg/dL at some point during the study.[4] Thanks to years of research and remarkable scientific insight from the Ionis team, hope for the hardest-to-treat patients had arrived at last. Since its publication, this research has been cited over 190 times and counting. Ultimately, Ionis brought volanesorsen to market in Europe.

24. In connection with publishing this groundbreaking article, Ionis disclosed that they had filed a patent application, PCT/US2014/016546, covering their invention.[5] The United States Patent and Trademark Office subsequently granted Ionis the '333 patent based upon this application.

25. In 2024, Ionis sought FDA approval for a new ApoCIII-inhibitor, called olezarsen, to treat people with FCS in the United States. In recognition of the importance of olezarsen to treat people with FCS, the FDA granted olezarsen both Fast Track designation and Breakthrough Therapy designation, and also expedited review of its New Drug Application. The FDA granted olezarsen approval in December 2024. As the FDA explained, "[t]his is a first-in-class approval, meaning [olezarsen] uses a new mechanism of action, or works differently in the body, than other therapies currently used to treat FCS."[6]

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[3] Daniel Gaudet et al., *Targeting APOC3 in the Familial Chylomicronemia Syndrome*, 371 New England Journal of Medicine 2200, 2200 (2014) ("NEJM 2014")

[4] *Id.*

[5] Supplemental Disclosure Form, NEJM 2014, *available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa1400284/suppl_file/nejmoa1400284_disclosures.pdf

[6] *FDA Approves Drug to Reduce Triglycerides in Adult Patients with Familial Chylomicronemia Syndrome*, FDA, https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-reduce-triglycerides-adult-patients-familial-chylomicronemia-syndrome

26. Olezarsen is now marketed as Tryngolza® and is changing the lives of people with FCS on a daily basis, including by relieving what was previously an ever-present worry of developing devastating pancreatitis attacks. As one doctor who treats FCS observed, "[t]he FDA approval of Tryngolza is an important moment for people living with FCS, their families and physicians who now, for the first time, have a treatment that significantly lowers triglycerides and decreases the risk of potentially life-threatening acute pancreatitis events, as an adjunct to a low-fat diet."[7] The FCS Foundation, a patient advocacy foundation, announced they were "overjoyed with the news that the FDA has approved the first treatment for patients with Familial Chylomicronemia Syndrome," emphasizing that they "are so happy that our patients will finally get the treatment they deserve."[8] A non-profit patient advocacy organization for individuals with pancreatitis described Tryngolza®'s approval as "a major milestone—not just for people with FCS, but for the entire pancreatitis community."[9]

27. A literature review published in the Annals of Pharmacotherapy also recently lauded the product as "represent[ing] a significant advancement in the treatment of FCS, offering a targeted and effective option for managing this rare genetic disorder," explaining that by "significantly reducing triglyceride levels, olezarsen addresses the limitations of traditional treatments and provides a much-needed therapeutic alternative" and that the medicine's "integration into clinical practice has the potential to transform the management of FCS."[10]

28. In addition to being the first-ever treatment for FCS approved in the United States, olezarsen's commercial launch also represented "a pivotal moment for Ionis,"

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[7] *Tryngolza Approved for Familial Chylomicronemia Syndrome*, Endocrinology Advisor, https://www.endocrinologyadvisor.com/news/tryngolza-approved-for-familial-chylomicronemia-syndrome/

[8] The FCS Foundation, LinkedIn, https://www.linkedin.com/posts/the-fcs-foundation_breaking-news-were-thrilled-to-share-we-activity-7276207907954720768-E1fM/

[9] *First FDA Approved FCS Treatment*, Mission-Cure, https://mission-cure.org/fcs-treatment-ionis/

[10] Bradley Phillips et al., *Olezarsen for the Treatment of Familial Chylomicronemia Syndrome*, https://journals.sagepub.com/doi/10.1177/10600280251332500 (April 15, 2025)

reflecting its "evolution into a fully integrated commercial-stage biotechnology company."[11] It is the first medicine Ionis has ever commercialized entirely on its own, without the help of a commercial partner.

Arrowhead Copies Ionis's Patented Technology

29. After Ionis began to realize extraordinary clinical results and disclosed its invention to the world in the *New England Journal of Medicine* ("NEJM"), Arrowhead saw an opportunity to ride Ionis's coattails. In December 2018, Arrowhead announced it was entering clinical trials for an ApoCIII inhibitor for use in people with FCS.

30. Arrowhead proceeded on this path, despite knowing that Ionis already patented the use of ApoCIII inhibitors to treat people with LPLD in the '333 patent. For example, Ionis's NEJM publication disclosure form discloses that Ionis's research is covered by a patent application that issued as the '333 patent.[12] Arrowhead cited Ionis's NEJM publication in their own paper on ApoCIII inhibition.[13] In reviewing Ionis's NEJM publication, Arrowhead would have learned of Ionis's patent application covering the use of ApoCIII inhibitors to treat people with LPLD and—given Arrowhead's decision to develop a drug for the same indication—would have monitored this application until it issued as the '333 patent. At a minimum, Arrowhead was willfully blind to the existence of the '333 patent.

31. Arrowhead also knew about, or was willfully blind to, the '333 patent because it was listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluation (known as the "Orange Book") in connection with Tryngolza®. The Orange Book identifies drugs that are approved by the FDA and lists the patents

[11] *TRYNGOLZA™ (olezarsen) approved in U.S. as first-ever treatment for adults living with familial chylomicronemia syndrome as an adjunct to diet*, https://ir.ionis.com/news-releases/news-release-details/tryngolzatm-olezarsen-approved-us-first-ever-treatment-adults

[12] Supplemental Disclosure Form, NEJM 2014, *available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa1400284/suppl_file/nejmoa1400284_disclosures.pdf

[13] Daniel Gaudet et al., *RNA Interference Therapy Targeting Apolipoprotein C-III in Hypertriglyceridemia*, NEJM Evidence (Nov. 17, 2023), *available at* https://evidence.nejm.org/doi/pdf/10.1056/EVIDoa2200325?download=true

that cover each drug. For any patents that claim a method of use, the FDA also publishes an associated "use code" that describes the patented method. For Tryngolza®, the Orange Book identifies the '333 patent and provides the use code: "U-4050: Use in Reducing Triglyceride Levels in Adults with Familial Chylomicronemia Syndrome (FCS)." As a pharmaceutical company, Arrowhead would have been familiar with the Orange Book listings, as Arrowhead acknowledged in its securities filings: "NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book."[14] Because Arrowhead was developing a drug to compete directly with Tryngolza®, Arrowhead would have known about the patents listed for Tryngolza® in the Orange Book and would have further known that the '333 patent covers a method of reducing triglyceride levels in adults with FCS.

32. Furthermore, in its November 26, 2024 securities filing, Arrowhead stated that "if granted marketing approval, we are currently aware of certain patent rights held by third parties that, if found to be valid and enforceable, could be alleged to render one or more of our drug candidates infringing."[15]

33. On information and belief, Arrowhead's reference to potentially infringing drug candidates in its November 26, 2024 securities filing included Plozasiran—its most advanced clinical candidate.

34. Moreover, on information and belief, Arrowhead's reference to "certain patent rights held by third parties" in its November 26, 2024 securities filing included the '333 patent.

35. Despite acknowledging "freedom to operate" issues in its securities filings,[16] Arrowhead chose to ignore Ionis's patent rights and flagrantly copy its path to success. The result is plozasiran, the ApoCIII inhibitor that Arrowhead submitted to

[14] Form 10-K, https://ir.arrowheadpharma.com/node/17611/html
[15] Form 10-K, https://ir.arrowheadpharma.com/node/19771/html
[16] *Id.*

FDA in January 2025. The FDA is set to act upon Arrowhead's submission by November—less than one year after Ionis's Tryngolza® reached the market.[17]

36. Arrowhead already is planning for the imminent launch of its product. In April 2025, it announced that "Arrowhead's first commercial launch of plozasiran in familial chylomicronemia [is] planned for Q4 2025 (PDUFA 11/18/25)."[18] Similarly, in its quarterly earnings call on August 7, 2025, Arrowhead reported no indications that plozasiran would face delays in regulatory approval, stating: "the cadence of our interactions with US and global regulators has not changed, nor have our expectations of adhering to established timelines."[19] Arrowhead told its investors that "U.S. launch preparations are now [in] full swing for plozasiran in FCS and we intend to be launch ready even before our PDUFA date."[20]

37. In light of the aforementioned NEJM publications, the listing in the Orange Book, and the warnings made in Arrowhead's securities filings, among other things, Ionis has every reason to believe that Arrowhead has been aware of the '333 patent for quite some time. Nonetheless, on September 3, 2025, to ensure that Arrowhead has had every opportunity to comply with the United States patent laws, Ionis sent Arrowhead's general counsel a letter emphasizing that "the manufacture, importation, offer for sale, sale, use, or promotion of use of plozasiran would contribute to and induce infringement of the '333 patent." (Exhibit 2). Ionis offered to engage in constructive dialogue regarding its intellectual property rights. Ionis also stated that if Arrowhead was not prepared to have a dialogue, Ionis would file suit on September 11, 2025, in Arrowhead's home forum, the Central District of California. On September 5th,

[17] *Arrowhead Pharmaceuticals Announces Acceptance of New Drug Application by U.S. FDA of Plozasiran for the Treatment of Familial Chylomicronemia Syndrome*, https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-announces-acceptance-new-drug (Jan. 17, 2025)

[18] *Corporate Overview*, Arrowhead Pharmaceuticals, https://ir.arrowheadpharma.com/static-files/25007351-232f-400a-bc0e-0fd4e2906fe8

[19] *Fiscal 2025 Third Quarter Conference Call – Prepared Remarks* at 9, Arrowhead Pharmaceuticals, https://ir.arrowheadpharma.com/static-files/30338961-1938-4e72-8120-41a85d47f80b

[20] *Id.* at 8.

Arrowhead responded that it was evaluating Ionis's letter. (Exhibit 3). Arrowhead did not further respond to Ionis. Instead, on September 10th, the day before Ionis had indicated it was planning to file this action in the Central District of California, Arrowhead filed an improper anticipatory Declaratory Judgment action against Ionis in the District of Delaware.

38. Arrowhead's shortcut to market will infringe Ionis's patent rights. As described in further detail below, the use of plozasiran to treat people with LPLD will infringe several claims of Ionis's '333 patent.

CLAIM FOR RELIEF

COUNT 1: INFRINGEMENT OF

U.S. PATENT NO. 9,593,333 UNDER 35 U.S.C. §§ 271 (b) and (c)

39. Ionis incorporates by reference the allegations set forth above as if fully set forth herein.

40. On March 14, 2017, the U.S. Patent and Trademark Office duly and legally issued the '333 patent, entitled "Modulation of apolipoprotein C-III (ApoCIII) expression in lipoprotein lipase deficient (LPLD) populations." The patent is attached as Exhibit 1.

41. Ionis is the owner of all right, title, and interest in the '333 patent.

42. The '333 patent has not yet expired.

43. On information and belief, Arrowhead filed a New Drug Application ("NDA") seeking to market plozasiran (25mg) for the treatment of FCS, and FDA accepted that application on January 17, 2025.[21]

44. On information and belief, Arrowhead submitted its NDA seeking FDA approval to market plozasiran with the intention to engage in the commercial

[21] *Arrowhead Pharmaceuticals Announces Acceptance of New Drug Application by U.S. FDA of Plozasiran for the Treatment of Familial Chylomicronemia Syndrome*, https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-announces-acceptance-new-drug (Jan. 17, 2025)

manufacture, use, offer for sale, and/or sale in the United States, or import into the United States, of plozasiran before the expiration of the '333 patent.

45. FDA expects to make a decision as to whether to approve Arrowhead's plozasiran NDA no later than November 18, 2025.[22]

46. On information and belief, following FDA approval, Arrowhead intends to and will immediately infringe the '333 patent under 35 U.S.C. § 271(b) and/or (c) as a result of its activities relating to the manufacture, importation, offer for sale, sale, use, or promotion of use of plozasiran.

47. On information and belief, such conduct will contribute to and induce infringement of multiple claims of the '333 patent. For example, such conduct will contribute to and induce infringement of at least claims 1-7, 9, 10, 14, 15, 18, 20-23 of the '333 patent, literally and/or under the doctrine of equivalents.

48. For example, claims 1-3 of the '333 Patent recite:

> 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, wherein:
>
> administering the compound reduces a triglyceride level by at least 10%, thereby treating or ameliorating LPLD.
>
> 2. The method of claim 1, wherein the ApoCIII specific inhibitor comprises a nucleic acid capable of inhibiting the expression or activity of ApoCIII.
>
> 3. The method of claim 1, wherein the ApoCIII specific inhibitor comprises an antisense compound targeting ApoCIII.

49. Arrowhead has stated that it intends to market plozasiran in a manner that will induce or contribute to infringement of the '333 patent.

[22] *Id.*

50. Arrowhead has stated that it intends to market plozasiran as a method of treating or ameliorating LPLD in patients. For example, on January 17, 2025, Arrowhead issued a press release stating that "Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced that the U.S. Food and Drug Administration (FDA) has accepted the New Drug Application (NDA) for investigational plozasiran for the treatment of familial chylomicronemia syndrome (FCS), a severe and rare genetic disease."[23] Arrowhead also has stated that "[t]he clinical basis of the NDA submission is comprised of the positive findings in the Phase 3 PALISADE study." Arrowhead further described "the PALISADE study (NCT05089084)" as "a Phase 3 placebo controlled study to evaluate the efficacy and safety of plozasiran in adults with genetically confirmed or clinically diagnosed FCS."[24] LPLD is also known as FCS.

51. On information and belief, the prescribing information for plozasiran, once approved, will instruct physicians to administer plozasiran for the treatment of patients who have LPLD.

52. Plozasiran is an ApoCIII specific inhibitor. Arrowhead has stated that plozasiran is an "investigational RNA interference (RNAi) therapeutic designed to reduce production of apolipoprotein C-III (APOC3)."[25]

53. On information and belief, Arrowhead intends to market plozasiran with labeling/prescribing information that directs administration of a therapeutically effective amount of plozasiran to patients. On information and belief, the prescribing information for plozasiran, once approved, will instruct physicians to administer a therapeutically effective amount of plozasiran to patients.

54. On information and belief, Arrowhead intends to market plozasiran as a method of reducing a triglyceride level by at least 10%, thereby treating or ameliorating

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[23] *Arrowhead Pharmaceuticals Announces Acceptance of New Drug Application by U.S. FDA of Plozasiran for the Treatment of Familial Chylomicronemia Syndrome*, https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-announces-acceptance-new-drug (Jan. 17, 2025)

[24] *Id.*

[25] *Id.*

FCS. For example, Arrowhead has stated that in its phase III PALISADE trial, "plozasiran achieved deep and durable reductions in triglycerides with a median change from baseline of 80% in the plozasiran 25 mg group."[26] On information and belief, administering plozasiran in accordance with Arrowhead's label will reduce triglyceride levels by at least 10%, thereby treating or ameliorating LPLD.

55. Plozasiran is an ApoCIII specific inhibitor that comprises a nucleic acid capable of inhibiting the expression or activity of ApoCIII. In particular, Plozasiran is a type of nucleic acid called small-interfering RNA ("siRNA") and Arrowhead has described plozasiran as an "investigational RNA interference (RNAi) therapeutic designed to reduce production of apolipoprotein C-III (APOC3)."[27]

56. Plozasiran is an ApoCIII specific inhibitor that comprises an antisense compound targeting ApoCIII.

57. On information and belief, Arrowhead has had knowledge of the '333 patent for years.

58. There is no question that Arrowhead presently has knowledge of the '333 patent which was identified in Ionis's letter of September 3, 2025. Arrowhead acknowledged receipt of that letter on September 5, 2025. Furthermore, Arrowhead has knowledge of the '333 patent by virtue of the filing of this Complaint.

59. Arrowhead knows (or at the very least is willfully blind to the fact) that use of plozasiran will infringe the '333 patent.

60. Arrowhead has an affirmative intent to actively induce infringement by others of one or more claims of the '333 patent. On information and belief, Arrowhead's proposed labeling for plozasiran will instruct medical practitioners and/or patients to administer and/or use plozasiran in a manner that infringes one or more claims of the '333 patent.

[26] *Id.*
[27] *Id.*

61. On information and belief, Arrowhead has not, in its current application to the FDA, sought approval of plozasiran for any use other than one that infringes the '333 patent, and plozasiran therefore has no substantial non-infringing use.

62. On information and belief, Arrowhead knows or should know that it will aid and abet another's direct infringement of at least one of the claims of the '333 patent at least by recommending such infringing acts in its labeling for plozasiran.

63. In view of Arrowhead's submission of its NDA and the FDA's response date of November 18, 2025, an actual controversy has arisen and now exists between the parties concerning whether Arrowhead will infringe by actively inducing and/or contributing to the infringement of one or more claims of the '333 patent.

64. Ionis is entitled to a declaration that commercial marketing of plozasiran before the expiration of the '333 patent would actively induce or contribute to the infringement of one or more claims of the '333 patent, making Arrowhead liable for infringement under 35 U.S.C. § 271(b) and/or (c).

65. Upon launch of plozasiran, as a consequence of Arrowhead's infringement of the '333 patent, Ionis will suffer monetary damages in an amount not yet determined, but that includes lost profits from foregone sales of Tryngolza®, and/or a reasonable royalty.

PRAYER FOR RELIEF

WHEREFORE, Ionis requests the following relief:

(a) A declaration that the commercial manufacture, use, offer for sale, and/or sale in the United States, or import into the United States, of plozasiran before the expiration of the '333 patent Arrowhead will induce and/or contribute to the infringement of the '333 patent;

(b) If Arrowhead markets plozasiran, that judgment be entered that Arrowhead has infringed one or more of claims of the '333 patent through the offer for sale and/or sale in the United States, or import into the United States of plozasiran before the expiration of the '333 patent.

(c) If Arrowhead markets plozasiran, that Ionis be awarded damages in an amount sufficient to compensate them for Arrowhead's infringement of the '333 patent, together with prejudgment and post-judgment interest and costs under 35 U.S.C. § 284.

(d) If Arrowhead markets plozasiran, that Ionis be awarded enhanced damages pursuant to 35 U.S.C. § 284 for Arrowhead's willful infringement of the '333 patent;

(e) A declaration that this is an exceptional case and an award of attorneys' fees, pursuant to 35 U.S.C. § 285;

(f) An award of Ionis's costs and expenses in this action; and

(g) Such further relief as this Court may deem just and proper.

JURY TRIAL DEMANDED

Plaintiff hereby demands a trial by jury.

Dated: September 11, 2025

Respectfully submitted,

/s/ *Matthew Donald Umhofer*

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