

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE BIOLOGICALS SA	)	
and GLAXOSMITHKLINE LLC,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 24-512 (GBW)
	)	
PFIZER INC., PHARMACIA & UPJOHN	)	JURY TRIAL DEMANDED
CO. LLC, BIONTECH SE, BIONTECH	)	
MANUFACTURING GMBH, and	)	
BIONTECH US INC.,	)	
	)	
Defendants.	)	

**ANSWER, AFFIRMATIVE DEFENSES, AND COUNTERCLAIMS IN RESPONSE
TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT**

Defendants Pfizer Inc. (“Pfizer”) and Pharmacia & Upjohn Co. LLC (“Pharmacia”) (collectively, “Pfizer”) and BioNTech SE, BioNTech Manufacturing GmbH (“BioNTech Manufacturing”), and BioNTech US Inc. (“BioNTech US”) (collectively, “BioNTech,” and together with Pfizer, “Defendants”) hereby answer the First Amended Complaint for Patent Infringement (“First Amended Complaint”) filed by Plaintiffs GlaxoSmithKline Biologicals SA (“GSK Biologicals”) and GlaxoSmithKline LLC (“GSK LLC”) (collectively, “GSK” or “Plaintiffs”). Any allegations not expressly admitted are denied. This answer follows the numbering provided in Plaintiffs’ First Amended Complaint. To the extent that the section headings of Plaintiffs’ First Amended Complaint contain allegations, those allegations are denied. To the extent Plaintiffs’ footnotes contain allegations, those allegations are denied.

INTRODUCTION

1. GSK Biologicals researches, develops, and manufactures innovative vaccines and specialty medicines to serve patients and healthcare professionals worldwide. GSK Biologicals is the sole owner and assignee of numerous United States patents directed to formulations comprising lipids and messenger ribonucleic acid (“mRNA”) molecules encoding an immunogen, and

methods of administering the same. See Exhibits 1–5, 83–85 (the “Patents-in-Suit,” as defined in paragraph 9, below).

RESPONSE: Defendants admit that GSK Biologicals is listed as the assignee on the face of the Patents-in-Suit. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 1 and therefore deny the same.

2. In 2008, more than a decade before the SARS-CoV-2 (2019) coronavirus disease (COVID-19) pandemic, a team of accomplished scientists, including the named inventors of the Patents-in-Suit, Andrew Geall and Ayush Verma, working under the leadership of vaccinologist Christian Mandl (the “Mandl team”), set their sights on developing mRNA vaccines. These talented individuals discovered formulations comprising lipids and mRNA molecules encoding a viral immunogen that provide protection from viral infection. The Mandl team described the inventions now claimed in the Patents-in-Suit, in patent applications filed in 2010.

RESPONSE: Defendants deny that “the Mandl team described the inventions now claimed in the Patents-at-Issue, in patent applications filed in 2010.” Defendants further deny that the Patents-at-Issue are valid, enforceable, or infringed by Defendants. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 2 and therefore deny the same.

3. The Mandl team’s innovation has been revolutionary for vaccine development. A significant advantage over other approaches to vaccine design is the ability to employ the technology as a platform to formulate and administer mRNA encoding a wide range of immunogens. The prestigious science journal *Nature* noted in 2021 that “[e]very mRNA company now uses some variation of [the Mandl team’s] delivery platform and manufacturing system[.]” Exhibit 6 (Dolgin, “The Tangled History of mRNA Vaccines,” *Nature* 597, 318 (2021) (“Dolgin (2021)”) at 323.

RESPONSE: To the extent the allegations of Paragraph 3 purport to rely on Exhibit 6, that exhibit speaks for itself. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 3 and therefore deny the same.

4. Another major advance of the Mandl team’s inventions over preexisting vaccine technologies is the speed with which a new vaccine candidate can be made and tested. Indeed, in response to the 2013 influenza outbreak in China, the Mandl team created a new mRNA vaccine candidate in just eight days—“in real time the moment that sequence was available.” Exhibit 7

(Dolgin, “Injection of Hope,” *Nature* 574, S10 (2019)) at S11. *Nature* recognized this achievement as “[t]he current speed record” of vaccine development. *Id.*

RESPONSE: To the extent the allegations of Paragraph 4 purport to rely on Exhibit 7, that exhibit speaks for itself. Defendants also note that before they began a collaborative effort focused on bringing a COVID-19 disease vaccine to market, no mRNA vaccines previously had been approved by FDA. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 4 and therefore deny the same.

5. The foundation of Defendants’ technical and financial success with COVID-19 vaccines is the technology of GSK’s patented inventions. Defendants have repeatedly touted the speed at which they produced their original COVID-19 vaccine and were later able to modify it to address new viral strains. But Defendants have consistently failed to acknowledge how they applied the Mandl team’s revolutionary platform to do so, while at the same time consistently relying on the Mandl team’s published work to contest the patent rights of competitors.

RESPONSE: Denied.

6. Defendants have reaped billions of dollars in revenue from infringing GSK’s Patents-in-Suit and continue to benefit, without ever obtaining a license. GSK brings this suit to recover a reasonable royalty for Defendants’ infringing sales of mRNA vaccines that apply the Mandl team’s inventions.

RESPONSE: Defendants deny infringement of any valid and enforceable claim of the Patents-in-Suit and that Plaintiffs are entitled to any relief.

NATURE OF THE ACTION

7. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

8. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*, seeking damages for Defendants’ infringing manufacture, use, sale, marketing, offer for sale, and/or importation of its following products (as defined in paragraphs 55–92, below): (1) the original “monovalent” (containing a single mRNA active ingredient) Comirnaty® COVID-19 vaccine; (2) the “bivalent” (containing two different mRNA active ingredients) Comirnaty® COVID-19 original plus BA.1 variant vaccine; (3) the bivalent Comirnaty® COVID-19 original plus BA.4/5 variant vaccine; and (4) the monovalent Comirnaty®

COVID-19 XBB.1.5 variant vaccine (collectively, the “Accused Products” or “Defendants’ COVID-19 vaccines”).

RESPONSE: Paragraph 8 states legal conclusions to which no response is required. To the extent a response is required, Defendants admit that the First Amended Complaint purports to state a claim for infringement arising under 35 U.S.C. § 100 *et seq.* but deny that they have infringed or will infringe, directly or indirectly, the Patents-in-Suit and that Plaintiffs are entitled to any relief. Defendants deny the remaining allegations of Paragraph 8.

9. As alleged herein, Defendants’ manufacture, use, sale, marketing, offer for sale, and/or importation of the Accused Products directly infringed and continues to directly infringe, actively induced and continues to actively induce infringement of, and/or contributed to and continues to contribute to the infringement of, one or more claims of the following GSK Biologicals patents directed to mRNA vaccine technology: U.S. Patent Nos. 11,638,693 (the “’693 patent”) (Exhibit 1), 11,638,694 (the “’694 patent”) (Exhibit 2), 11,666,534 (the “’534 patent”) (Exhibit 3), 11,766,401 (the “’401 patent”) (Exhibit 4), 11,786,467 (the “’467 patent”) (Exhibit 5), 11,759,422 (the “’422 patent”) (Exhibit 83), 11,655,475 (the “’475 patent”) (Exhibit 84), and 11,851,660 (the “’660 patent”) (Exhibit 85) (collectively, the “Asserted Patents” or “Patents-in-Suit”). At all relevant times, GSK Biologicals has lawfully owned, and continues to lawfully own, all rights, title, and interest in the Patents-in-Suit, including the right to sue and recover for past infringement.

RESPONSE: Defendants deny infringement of any valid and enforceable claim of the Patents-in-Suit and that Plaintiffs are entitled to any relief. To the extent the allegations of Paragraph 9 purport to rely on Exhibits 1–5 and 83–85, those exhibits speak for themselves. Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of the remainder of Paragraph 9 and therefore deny the same.

THE PARTIES

10. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

11. Plaintiff GSK Biologicals is a corporation organized and existing under the laws of Belgium, with its principal place of business at Avenue Fleming 20, 1300 Wavre, Belgium. GSK Biologicals is the owner of all patents asserted in this litigation.

RESPONSE: Defendants admit that GSK Biologicals purports to be a corporation organized and existing under the laws of Belgium, with its principal place of business at Avenue Fleming 20, 1300 Wavre, Belgium. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 11 and therefore deny the same.

12. Plaintiff GSK LLC is a limited liability corporation organized and existing under the laws of Delaware, with its principal place of business at 2929 Walnut Street, Suite 1700, Philadelphia, PA 19104. GSK LLC produces and distributes pharmaceutical products. GSK Biologicals has designated GSK LLC as the exclusive distributor of any products covered by the Patents-in-Suit in the United States.

RESPONSE: Defendants admit that GSK LLC purports to be a limited liability corporation organized and existing under the laws of Delaware, with its principal place of business at 2929 Walnut Street, Suite 1700, Philadelphia, PA 19104. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 12 and therefore deny the same.

13. Defendant Pfizer Inc. is a corporation organized and existing under the laws of Delaware, with its principal place of business at 66 Hudson Boulevard East, New York, New York 10001. Pfizer Inc., itself and through its subsidiaries and business partners, develops, manufactures, imports, markets, distributes, offers to sell, and/or sells the Accused Products and other medicines in the State of Delaware and throughout the United States, for use in the State of Delaware and throughout the United States.

RESPONSE: Defendants admit that Pfizer is incorporated in Delaware with a principal place of business at 66 Hudson Boulevard East, New York, New York 10001. Paragraph 13 otherwise states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for the purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest personal jurisdiction. Defendants otherwise deny the remaining allegations of this Paragraph.

14. Defendant Pharmacia & Upjohn Co. LLC is a wholly owned subsidiary of Pfizer Inc. Pharmacia & Upjohn Co. LLC is a company organized and existing under the laws of

Delaware with its principal place of business at 100 Route 206 N, Peapack, New Jersey 07977. On information and belief, Pharmacia & Upjohn Co. LLC manufactures, labels, and packages the Accused Products in facilities located at 7000 Portage Road, Kalamazoo, Michigan 49001. Exhibit 8 (August 23, 2021, FDA Comirnaty® (original monovalent) COVID-19 vaccine Approval Letter) at 1.

RESPONSE: Defendants admit that Pharmacia & Upjohn Co. LLC is a wholly owned subsidiary of Pfizer Inc. organized and existing under the laws of Delaware with its principal place of business at 100 Route 206 N. Peapack, New Jersey 07977. Paragraph 14 otherwise states legal conclusions to which no response is required. To the extent the allegations of Paragraph 14 purport to rely on Exhibit 8, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

15. Defendant BioNTech SE is a corporation organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, 55131 Mainz, Germany.

RESPONSE: Defendants admit that BioNTech SE is a corporation organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, 55131 Mainz, Germany.

16. Defendant BioNTech Manufacturing GmbH, a wholly owned subsidiary of BioNTech SE, is a limited liability company organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, 55131 Mainz, Germany, and is the Biologics License Application (“BLA”) holder for the Accused Products in the United States. Exhibit 8 (August 23, 2021, FDA Comirnaty® (original monovalent) vaccine Approval Letter); *ModernaTX, Inc. v. Pfizer Inc.*, No. 1:22-CV-11378, D.I. 45 at 20 (D. Mass. Dec. 5, 2022).

RESPONSE: Defendants admit that BioNTech Manufacturing GmbH is a wholly owned subsidiary of BioNTech SE organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, 55131 Mainz, Germany, and is holder of the BLA for Comirnaty® (original monovalent). Paragraph 16 otherwise states legal conclusions to which no response is required. To the extent the allegations of Paragraph 16 purport to rely on Exhibit 8, that exhibit speaks for itself.

17. Defendant BioNTech US Inc., a wholly owned subsidiary of BioNTech SE, is a corporation organized and existing under the laws of Delaware, has its principal place of business at 40 Erie St., Suite 110, Cambridge, MA 02139. On information and belief, BioNTech US Inc. serves as the North American Headquarters for BioNTech SE,¹ and is BioNTech SE's agent for service of process in the United States. Exhibit 9 (excerpts from March 30, 2022, BioNTech SE 2021FY Annual Report (Form 20-F)), at 81; *see also ModernaTX, Inc. v. Pfizer Inc.*, No. 1:22-CV-11378, D.I. 45 at 21 (D. Mass. Dec. 5, 2022).

RESPONSE: Defendants admit that BioNTech US Inc. is a wholly owned subsidiary of BioNTech SE organized and existing under the laws of Delaware, with its principal place of business at 40 Erie St., Suite 110, Cambridge, MA 02139. Defendants deny that BioNTech US Inc. is BioNTech SE's agent for service of process in the United States. Paragraph 17 otherwise states legal conclusions to which no response is required. To the extent the allegations of Paragraph 17 purport to rely on Exhibit 9, that exhibit speaks for itself.

18. On information and belief, Defendants are agents of one another or work in concert with each other regarding the development, regulatory approval, manufacturing, marketing, offering for sale, sale, or distribution of the Accused Products in the United States. *See ModernaTX, Inc. v. Pfizer Inc.*, No. 1:22-CV-11378, D.I. 45 at 21 (D. Mass. Dec. 5, 2022).

RESPONSE: Paragraph 18 states legal conclusions to which no response is required. To the extent the allegations of Paragraph 18 rely on a document filed in a proceeding before the U.S. District Court for the District of Massachusetts, captioned *ModernaTX, Inc. v. Pfizer Inc.*, No. 1:22-CV-11378 (D. Mass Dec. 5, 2022), that document speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

JURISDICTION AND VENUE

19. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

20. This action arises under the patent laws of the United States, including 35 U.S.C. § 100 *et seq.* generally, and 35 U.S.C. § 271 *et seq.* specifically.

¹ See www.biontech.com/int/en/home/about/biontech-us-website.html, last visited April 20, 2024.

RESPONSE: Paragraph 20 purports to characterize GSK’s First Amended Complaint, which speaks for itself, and states legal conclusions to which no response is required. To the extent a response is required, Defendants admit that the First Amended Complaint purports to state a claim for patent infringement arising under the patent laws of the United States, including 35 U.S.C. § 100 *et seq.* and 35 U.S.C. § 271 *et seq.* Defendants otherwise deny the remaining allegations of this Paragraph.

21. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

RESPONSE: Paragraph 21 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action only, they do not contest that this Court has subject matter jurisdiction over this action.

22. This Court has personal jurisdiction over Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, and BioNTech US, Inc. because each is organized under the laws of Delaware.

RESPONSE: Paragraph 22 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest personal jurisdiction.

23. This Court also has personal jurisdiction over Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, BioNTech SE, BioNTech Manufacturing GmbH, and BioNTech US Inc. On information and belief, each has conducted and continues to conduct business in Delaware at least by offering for sale or selling the Accused Products in Delaware, and because each has committed and continues to commit acts of infringement in Delaware. For example, as reported by the United States Center for Disease Control and Prevention (“CDC”), by May 10, 2023, Defendants had delivered to the State of Delaware over 1.65 million doses of Comirnaty® (original monovalent) COVID-19 vaccine and over 300 thousand doses of Comirnaty® (bivalent BA.4/5) (both products as defined in paragraphs 55–92, below). Exhibit 10 (printout of CDC Data on Comirnaty® (original monovalent and bivalent BA.4/5) doses distributed in Delaware, May 10, 2023).² On information and belief, Defendants continue to deliver doses of Comirnaty® COVID-19 vaccine

² Spreadsheet available at https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisd/unsk-b7fc/data_preview; Delaware specific data last accessed, April 10, 2024.

products to the State of Delaware. Therefore, Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, BioNTech SE, BioNTech Manufacturing GmbH, and BioNTech US, Inc. have transacted and continue to transact business within Delaware relating to GSK's claims and have engaged in and maintain systematic and continuous business contacts in Delaware.

RESPONSE: Paragraph 23 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest personal jurisdiction. To the extent the allegations of Paragraph 23 purport to rely on Exhibit 10, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

24. Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, BioNTech SE, and BioNTech Manufacturing GmbH have consented to this Court's exercise of personal jurisdiction in other litigations involving the Accused Products, including in *Alnylam Pharmaceuticals, Inc. v. Pfizer Inc., et al*, C.A. No. 22-cv-336-CFC and *Alnylam Pharmaceuticals, Inc. v. Pfizer Inc., et al*, C.A. No. 23-cv-578-CFC.

RESPONSE: Paragraph 24 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest personal jurisdiction. To the extent the allegations of Paragraph 24 rely on documents filed in other proceedings, those documents speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

25. Venue is proper in this judicial District with respect to Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, and BioNTech US Inc. pursuant to 28 U.S.C. § 1400(b) because Pfizer Inc., Pharmacia & Upjohn Co. LLC, and BioNTech US, Inc. are entities organized and existing under the laws of the State of Delaware and reside in Delaware for purposes of venue.

RESPONSE: Paragraph 25 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest venue. Defendants otherwise deny the remaining allegations of this Paragraph.

26. Venue is proper in this District with respect to BioNTech SE and BioNTech Manufacturing GmbH under 28 U.S.C. § 1391(c)(3) because BioNTech SE and BioNTech Manufacturing GmbH are not residents of the United States.

RESPONSE: Paragraph 26 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest venue. Defendants otherwise deny the remaining allegations of this Paragraph.

27. Defendants Pfizer Inc., Pharmacia & Upjohn Co. LLC, BioNTech SE, and BioNTech Manufacturing GmbH have consented to this Court as a proper venue in other litigations involving the Accused Products, including in *Alnylam Pharmaceuticals, Inc. v. Pfizer Inc., et al*, C.A. No. 22-cv-336-CFC and *Alnylam Pharmaceuticals, Inc. v. Pfizer Inc., et al*, C.A. No. 23-cv-578-CFC.

RESPONSE: Paragraph 27 states legal conclusions to which no response is required. To the extent a response is required, Defendants respond that, solely for purposes of this action and solely for the claims asserted in the First Amended Complaint, they do not contest venue. To the extent the allegations of Paragraph 27 rely on documents filed in other proceedings, those documents speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

BACKGROUND

28. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

A. The Claimed Inventions

29. In conventional vaccines, a protein (or “polypeptide”) is administered to a patient, is recognized as foreign by the body, and triggers the patient’s immune response (hence the protein is an “immunogen”). With mRNA vaccines, mRNA that encodes for an immunogenic protein is administered to a patient. If the mRNA can reach the inside of a patient’s cells, existing cellular machinery will read instructions encoded by the mRNA to make the protein—a process called “translation”—which then triggers the immune response. *See* Exhibit 1 (’693 Patent) at col. 9, ll. 29–38 (“RNA molecules used with the invention encode a polypeptide immunogen. After administration ... the RNA is translated in vivo and the immunogen can elicit an immune response in the recipient.”).

RESPONSE: To the extent the allegations of Paragraph 29 purport to rely on Exhibit 1, that exhibit speaks for itself. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 30 and therefore deny the remaining same.

30. By 2008, there were many well-understood and significant hurdles to employing mRNA in vaccines. Getting mRNA molecules, intact, from where they are made in the laboratory into a patient's cell had historically presented seemingly insurmountable challenges. For example, mRNA is chemically fragile—it can degrade quickly even in a controlled laboratory environment. It needs to be protected from the moment of preparation through formulation, storage, handling, administration, and even inside the body following administration. And even if the mRNA remains intact following administration to a patient, the mRNA still needs some way to get into the cell so it can be translated and the immunogenic protein can effectuate an immune response. See Exhibit 6 (Dolgin (2021)) at 320 (“In the 1990s and for most of the 2000s, nearly every vaccine company that considered working on mRNA opted to invest its resources elsewhere. The conventional wisdom held that mRNA was too prone to degradation[.]”).

RESPONSE: To the extent the allegations of Paragraph 30 purport to rely on Exhibit 6, that exhibit speaks for itself. At least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

31. Despite unsuccessful efforts by others dating back decades, in 2008, a talented team of researchers led by Christian Mandl set out to overcome these hurdles and develop vaccines using mRNA. Exhibit 6 (Dolgin (2021)) at 323. Through extensive experimentation, perseverance, and the unique insights and preferences of these talented scientists, the Mandl team successfully overcame the many challenges and discovered the novel lipid and mRNA formulations and methods for their use to raise an immune response against immunogens that are described and claimed in the Patents-in-Suit.

RESPONSE: To the extent the allegations of Paragraph 31 purport to rely on Exhibit 6, that exhibit speaks for itself. Defendants lack the knowledge or information sufficient to form a belief as to whether “the Mandl team successfully overcame the many challenges and discovered the novel lipid and mRNA formulations and methods for their use to raise an immune response against immunogens.” Defendants deny that the Accused Products infringe any valid and

enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

32. The Mandl team first described their inventions in provisional patent applications filed in July and August 2010.³ As stated therein, and in the Patents-in-Suit, “[t]he invention utilizes liposomes in which immunogen-encoding RNA is encapsulated. Thus the RNA is (as in a natural virus) separated from any external medium by the liposome’s bilayer[.]” *See, e.g.*, Exhibit 1 (’693 patent) at 2:2–5. “These liposomes are suitable for in vivo delivery of the RNA to a vertebrate cell and so they are useful as components in pharmaceutical compositions for immunizing subjects against various diseases.” *Id.* at 1:58–61.

RESPONSE: To the extent the allegations purport to rely on Exhibit 1, and Exhibits 83–89, those exhibits speak for themselves. Defendants deny that “[t]he Mandl team first described their inventions in provisional patent applications filed in July and August 2010.” Defendants further deny that the Patents-at-Issue are valid, enforceable, or infringed by Defendants. Defendants otherwise deny the remaining allegations of this Paragraph.

33. “Liposomes” of the inventions, as Defendants have explained to other tribunals, may be referred to as “lipid nanoparticles” (“LNPs”):

Geall [(Int’l Patent App. Pub. No. WO2012/006369 (“WO369”))⁴] explains that the liposomes of the invention can be formed “from a mixture of lipids” and provides useful liposomes ideally have a diameter in the range of 50-220nm. A [person of ordinary skill in the art] would have therefore understood Geall [(WO369)] as teaching the use of lipid nanoparticles (i.e., particles made of lipids that are nanosized, in the form of liposomes) for delivery of RNA.

³ *See* Exhibit 86 (U.S. Prov. Patent App. No. 61/361,830, filed July 6, 2010 (“’830 Prov.”)); Exhibit 87 (U.S. Prov. Patent App. No. 61/378,837, filed August 31, 2010 (“’837 Prov.”)); Exhibit 88 (U.S. Prov. Patent App. No. 61/378,826, filed August 31, 2010 (“’826 Prov.”)); Exhibit 89 (U.S. Prov. Patent App. No. 61/361,794, filed July 6, 2010 (“’794 Prov.”)). The ’693, ’694, ’534, ’401, and ’467 Patents-in-Suit (Exhibits 1–5) state a claim of priority to and incorporate by reference, the ’830 and ’837 Provs. The ’422 Patent-in-Suit (Exhibit 83) states a claim of priority to and incorporates by reference, the ’826 Prov. The ’475 and ’660 Patents-in-Suit (Exhibits 84 and 85) state a claim of priority to and incorporate by reference, the ’794 Prov.

⁴ Exhibit 90. The application published as WO369 is in the chain of priority of the ’475 and ’660 Patents-in-Suit and itself states a claim of priority to and incorporates the ’794 Prov.

See Exhibit 91 (August 28, 2023, Moon Declaration in IPR2023-01358 (“Moon Decl.”)) at 39 (citations omitted), citing Exhibit 90 (WO369) at 4:25, 5:8–9^{5,6}. Describing the invention using their preferred terminology, Defendants have stated: “WO 369 demonstrated that exogenous mRNA ... encoding a selection of proteins ... could be successfully encapsulated in LNPs, administered to large mammals, and expressed.” Exhibit 94 (January 10, 2024, Alabi Report 1 in *ModernaTx, Inc. v. Pfizer Ltd. et al.*, Case Nos. HP-2022-000022/27 (EWHC)) at 116.

RESPONSE: To the extent the allegations purport to rely on Exhibit 90, Exhibit 91, Exhibit 94, Exhibit 1, Exhibit 83, Exhibit 84, Exhibit 92, and Exhibit 93, those exhibits speak for themselves. Defendants deny that the Patents-at-Issue are valid, enforceable, or infringed by Defendants. Defendants otherwise deny the remaining allegations of this Paragraph.

34. Defendants have also repeatedly explained that “RNA” of the inventions includes “self-replicating RNA”⁷ (or “saRNA”) and conventional, non-self-replicating RNA. See Exhibit 96 (January 23, 2024, Paper 015 in IPR2023-01358) at 2 (WO369 “doesn’t limit its disclosure to saRNA”), 3 (similar). This is manifest from the limitation of “RNA” to “self-replicating RNA” only in dependent claims in the 2010 priority applications and the Patents-in-Suit,⁸ as Defendants have noted. See Exhibit 97 (July 25, 2023, BioNTech submission in EP3718565 Opposition) at 3 (WO369 “discloses that the mRNA, only of optional embodiments, is self-replicating (see dependent claim 9)”), citing Exhibit 90 (WO369) at 48. Indeed:

the Delivery Chemist would not consider the disclosure of WO 369 to be limited to saRNA. ... [T]he Delivery Chemist would consider that the LNPs of WO 369 could be used to efficiently encapsulate non-self-amplifying mRNA and successfully deliver it in vivo to

⁵ See, e.g., Exhibit 1 (’693 patent) at 2:29–30, 3:24–25; Exhibit 83 (’422 patent) at 2:45–46, 5:10–12; Exhibit 84 (’475 patent) at 4:11–12, 4:40–42.

⁶ See also Exhibit 92 (August 28, 2023, Petition for *Inter Partes* Review of U.S. Patent No. 10,702,600 in IPR2023-01358 (“IPR Petition”)) at 18–19; Exhibit 91 (Moon Decl.) at 8–9; Exhibit 93 (Int’l PCT App. Pub. No. WO2017/162266 (“WO266”)) at 109–112 (“As used herein, the term ‘nanoparticle’ refers to any particle having a diameter making the particle suitable for systemic, in particular parenteral, administration, of, in particular, nucleic acids, typically a diameter of 1000 nanometers (nm) or less. ... In some embodiments, a nanoparticulate composition is a lipid-containing pharmaceutical formulation, such as a liposome formulation or an emulsion.”).

⁷ “[A] form of mRNA which is capable of reproduction.” Exhibit 95 (July 15, 2024, BioNTech SE Paper in DE Utility Model 202021004130 Cancellation Proceeding) at 15.

⁸ See, e.g., Exhibit 88 (’826 Prov.) at 42, claims 1 (“RNA encoding an immunogen”) and 6 (“wherein the RNA is a self-replicating RNA”); Exhibit 86 (’830 Prov.) at 29, claims 1 and 3; Exhibit 87 (’837 Prov.) at 34, claims 1 and 5; Exhibit 89 (’794 Prov.) at 38, claims 1 and 9; Exhibit 1 (’693 patent), claims 1 and 29; Exhibit 2 (’694 patent), claims 1 and 11; Exhibit 3 (’534 patent), claims 1 and 33; Exhibit 4 (’401 patent), claims 1 and 28; Exhibit 5 (’467 patent), claims 1 and 15; Exhibit 83 (’422 patent) claims 1 and 5; Exhibit 84 (’475 patent) claims 1 and 32.

target cells to achieve antigen expression and a consequent immune response.

Exhibit 98 (February 26, 2024, Alabi Report 2 in *ModernaTx, Inc. v. Pfizer Ltd. et al.*, Case Nos. HP-2022-000022/27 (EWHC)) at 8.

RESPONSE: To the extent the allegations purport to rely on Exhibits 1–5, Exhibit 84, Exhibits 86–90, and Exhibit 95–98, those exhibits speak for themselves. Defendants deny that the Patents-at-Issue are valid, enforceable, or infringed by Defendants. Defendants otherwise deny the remaining allegations of this Paragraph.

35. According to Defendants, the Mandl team’s patent filings also “list[] in a clear and unambiguous, and easily identifiable manner possible immunogens that can be used in the context of LNP-formulated mRNA vaccines.” Exhibit 99 (July 25, 2023, Pfizer Paper in EP3718565 Opposition) at 24, citing Exhibit 90 (WO369) at 16, 19. For example, the encoded “immunogen” of the inventions, again as explained by Defendants, includes a coronavirus spike polypeptide:

Geall [(WO369)] discloses the use of RNA vaccines encoding the spike protein of a betacoronavirus. It “provides a method of raising an immune response in a large mammal comprising administering to the mammal a dose of between 2 µg and 100 µg of immunogen-encoding RNA.” ... Geall [(WO369)] instructs that the “immunogen will typically be a surface polypeptide, *e.g.* ... a spike glycoprotein”, and discloses that “[v]iral immunogens include, but are not limited to, those derived from a SARS coronavirus ... The coronavirus immunogen may be a spike polypeptide.”

See Exhibit 92 (IPR Petition) at 18 (citations omitted), citing Exhibit 100 (August 28, 2023, Griffin Decl. in IPR2023-01358) at 28–29 and Exhibit 90 (WO369) at Abstract, 16:6–7, 19:27–30.⁹

RESPONSE: To the extent the allegations purport to rely on Exhibit 99, Exhibit 90, Exhibit 92, Exhibit 100, Exhibit 84, Exhibit 1, and Exhibit 83, those exhibits speak for themselves. Defendants deny that the Patents-at-Issue are valid, enforceable, or infringed by Defendants. Defendants otherwise deny the remaining allegations of this Paragraph.

⁹ See, *e.g.*, Exhibit 84 (’475 patent) at Abstract, 13:63–65, 16:38–43; Exhibit 1 (’693 patent) at 9:44–46, 12:20–25, 16:7–11, 16:23–47; Exhibit 83 (’422 patent) at 9:13–15, 11:59–64, 15:45–49, 16:4–25, 41:64–42:8.

36. The United States government immediately recognized the value of the Mandl team's work. In the wake of the 2009 H1N1 flu pandemic virus outbreak, the Defense Advanced Research Projects Agency ("DARPA") awarded a contract to fund further research and development by the Mandl team into mRNA vaccine technology for quick deployment in response to new pandemic threats. Exhibit 13 (Lizotte, "Novartis Receives \$14M Award from DARPA," Global Biodefense, January 31, 2012) (describing award of DARPA Contract HR0011-12-3-0001).

RESPONSE: To the extent the allegations purport to rely on Exhibit 13, that exhibit speaks for itself. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 30 and therefore deny the remaining same.

B. Industry Recognition and Adoption

37. The Mandl team's seminal 2012 publication on this work has been cited over 500 times and viewed over 60,000 times. See Exhibit 11 (Geall *et al.*, "Nonviral delivery of self-amplifying RNA vaccines," *Proc. Natl. Acad. Sci.* 109(36), 14604-609 (2012) with supplementary information ("Geall (2012)")).¹⁰ In 2021, *Nature*, citing Geall (2012), identified the Mandl team as "the first team to combine LNPs with an RNA vaccine," and labeled this 2012 contribution the "First mRNA vaccine in lipid nanoparticles tested in mice" on a timeline of events in "The History of mRNA Vaccines." Exhibit 6 (Dolgin (2021)) at 323. Pfizer scientists, in a 2024 review article, adopted the 2021 *Nature* timeline, rephrasing the Geall (2012) entry as the "First LNP-encapsulated RNA vaccine in mice." Exhibit 101 (Jones *et al.*, "Breaking the mold with RNA—a 'RNAissance' of life science," *npj Genom. Med.* 9, article no. 2 (2024) ("Jones (2024)")) at 2.

RESPONSE: To the extent the allegations of Paragraph 37 purport to rely on Exhibit 11, Exhibit 6, and Exhibit 101, those exhibits speak for themselves. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

38. As recently recognized by the High Court of Justice of England and Wales:

The authors [of Geall (2012)] state that the platform has the potential to "address multiple disease targets" and that the "unique nucleic acid vaccine technology could enable a new generation of potent, versatile, and easily produced vaccines to address the health challenges of the 21st century." ... I agree with Pfizer/BioNTech on the significance of Geall 2012. Being CGK [(common general knowledge)], it would lead to the skilled team thinking that there was unlikely to be difficulty applying LNPs in the context of mRNA

¹⁰ Metrics available at <https://www.pnas.org/doi/full/10.1073/pnas.1209367109>.

(as opposed to siRNA) and, more importantly ... that LNPs could reasonably be tried for delivering mRNA for vaccine purposes for a range of pathogens: that is what “platform” implies.

Exhibit 102 (July 2, 2024, Judgment in *ModernaTx, Inc. v. Pfizer Ltd. et al.*, [2024] EWHC 1695 (Pat) in Case Nos. HP-2022-000022/27) at 123. Previously, and wholly consistent with that finding, in a 2022 presentation for healthcare professionals concerning its COVID-19 vaccines entitled “Overview of mRNA vaccine development,” Pfizer cited Geall (2012) for the following contribution: “Lipid nanoparticles were developed to protect the mRNA strands that encode the spike protein from degradation, thus helping them reach their target cells.” Exhibit 12 (Pfizer “Overview of mRNA vaccine development” presentation, dated August 2022 (“Pfizer 2022 Presentation”)¹¹).

RESPONSE: To the extent the allegations purport to rely on Exhibit 102 and Exhibit 12, those exhibits speak for themselves. To the extent there are any remaining allegations in this paragraph, denied.

39. This robust platform has proven suitable for obtaining an immune response from a wide range of immunogen-encoding mRNA molecules, manifest through its adoption by “[e]very mRNA company.” Exhibit 6 (Dolgin, “The Tangled History of mRNA Vaccines,” *Nature* 597, 318 (2021)) at 323.

RESPONSE: To the extent the allegations of Paragraph 39 purport to rely on Exhibit 6, that exhibit speaks for itself. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

C. GSK Biologicals’s Acquisition of the Mandl Team’s Inventions

40. At the time the Mandl team began working on mRNA vaccines, they were employed by Novartis AG subsidiaries. In 2015, GSK Biologicals acquired a substantial portion of Novartis AG’s global vaccines business. See Exhibit 14 (March 2, 2015, GSK press release).

RESPONSE: To the extent the allegations of Paragraph 40 purport to rely on Exhibit 14, that exhibit speaks for itself. Otherwise, at least because of the scope, breadth, and vagueness of

¹¹ Available at https://covid19.pfizerpro.com/api/vc/en/content/material/561b4c91-800b-4ec0-af5c-efddfd0aead8c/COVID19_PP-CVV-USA-0984_1.pdf?download=true; preserved April 10, 2024.

these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

41. In that transaction, GSK Biologicals obtained, among other things, the Mandl team's inventions, including all rights to the parent applications to the Patents-in-Suit and progeny, including the Patents-in-Suit.

RESPONSE: Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

42. As reflected in various published patent applications and issued patents, GSK has prosecuted patent claims to both conventional and self-amplifying mRNA liposomal vaccines and methods of their use around the world since the priority applications to the Patents-in-Suit were filed in 2010, including throughout 2020,¹² before Defendants allege information about the composition of the Accused Products was made public (D.I. 22 at 87 (¶ 56)).

RESPONSE: To the extent the allegations of Paragraph 42 purport to rely on Exhibit 103, Exhibit 104, and Exhibit 105, those exhibits speak for themselves. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

43. GSK continues to research and develop mRNA vaccines—both conventional and self-amplifying, including through various collaborations—and has several vaccine candidates currently advancing in human clinical trials.¹³

¹² See, e.g., Exhibit 103 (European Patent No. 2590626, issued October 29, 2015) at, e.g., claim 1 (“A liposome for *in vivo* delivery of RNA to a vertebrate cell...”) and 7 (“The liposome of any preceding claim, wherein the RNA molecule encodes (i) a RNA-dependent RNA polymerase which can transcribe RNA from the RNA molecule...”); Exhibit 104 (July 23, 2020, Publication No. US 2020/0230058 A1, of the application later issuing as the ’422 Patent-in-Suit) at, e.g., claim 1 (“a liposome within which RNA encoding an immunogen of interest is encapsulated”) and 7 (“wherein the RNA is a self-replicating RNA”); Exhibit 105 (European Patent No. 2729126, issued November 12, 2020) at, e.g., claim 1 (“A liposome in which immunogen encoding RNA is encapsulated...”) and claim 3 (“The liposome of any preceding claim, wherein the RNA is a self-replicating RNA...”).

¹³ See <https://www.gsk.com/en-gb/innovation/pipeline/>; [https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiulqCA-NGHAXWnAHkGHbNaDegQFnoECC0QAQ&url=https%3A%2F%2Fwww.gsk.com%2Fmedia%](https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiulqCA-NGHAXWnAHkGHbNaDegQFnoECC0QAQ&url=https%3A%2F%2Fwww.gsk.com%2Fmedia%2F)

RESPONSE: To the extent the allegations purport to rely on the webpages at footnote 13, those webpages speak for themselves. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

D. Defendants' Use and Knowledge of the Mandl Team's Patented Technology

44. On information and belief, Defendants did not begin investigating liposomal encapsulation and delivery of immunogen-encoding RNA for vaccination purposes until after the Mandl team's seminal work became public.

RESPONSE: Denied.

45. Defendants were aware of the Mandl team's mRNA vaccine innovations long before they ever developed and commercialized the Accused Products.

RESPONSE: Denied.

46. Indeed, years before marketing the Accused Products, Defendants hired former Novartis AG vaccines business employees who had first-hand knowledge of the Mandl team's innovations.

RESPONSE: At least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

47. Since at least 2013, publications on the Mandl team's mRNA vaccine work have been identified by patent examining authorities as relevant prior art to BioNTech's own patent applications. This art includes published predecessor applications to the Patents-in-Suit. *See, e.g.*, Exhibit 15 (June 14, 2013, Written Opinion of the International Searching Authority on application PCT/EP2013/000902). BioNTech has also cited the Mandl team's patent application publications within the text of its own mRNA LNP vaccine patent applications since at least 2016. *See, e.g.*, Exhibit 93 (WO266) at, *e.g.*, 110–114. *See also* Exhibits 17, 106, 107 (printouts of patent filings and patent applicants citing to patents or patent applications in each family of the Patents-in-Suit from the Derwent Patents Citation Index, preserved April 19, 2024, August 4, 2024, and August 4, 2024, respectively).¹⁴

[2F11102%2Fq1-2024-pipeline-assets-and-clinical-trials-report.pdf&usg=AOvVaw2DKoP_69C3GaSTBc_WSm4h&opi=89978449](#).

¹⁴ Information on the Derwent Patents Citation Index is available at <https://clarivate.com/products/ip-intelligence/ip-data-and-apis/derwent-patents-citation-index/>.

RESPONSE: To the extent the allegations of Paragraph 40 purport to rely on Exhibit 15, Exhibit 93, Exhibit 17, Exhibit 106, Exhibit 107, Exhibit 18, Exhibit 108, and Exhibit 109, those exhibits speak for themselves. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit.

48. BioNTech's familiarity with the families of patent applications describing and claiming the Mandl team's work prior to and during the COVID-19 pandemic is evidenced by various contemporaneous communications between GSK and BioNTech.

RESPONSE: At least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

49. And as noted, Pfizer recognized the contributions of the Mandl team in published scientific articles and presentations posted on its website concerning the development of its COVID-19 vaccines. *See, e.g.*, Exhibit 101 (Jones (2024)); Exhibit 12 (Pfizer 2022 Presentation).

RESPONSE: To the extent the allegations of Paragraph 49 purport to rely on Exhibit 101 and Exhibit 12, those exhibits speak for themselves. Defendants deny the remaining allegations of this Paragraph.

50. Defendants continue to advance mRNA vaccines—both conventional and self-amplifying—against various targets. *See* Exhibit 110 (excerpts from BioNTech 2023 Annual Report) at 105ff.; Exhibit 111 (excerpts from July 30, 2024, Pfizer Pipeline presentation¹⁵).

Similar information is available publicly through Google Patents. *See, e.g.*, Exhibit 18 (Google Patents, Cited By section, for the '534 patent, available at <https://patents.google.com/patent/US11666534B2/en?q=+11%2c666%2c534>; preserved August 3, 2023); Exhibit 108 (Google Patents, Cited By section, for the '422 patent, available at <https://patents.google.com/patent/US11759422B2/en?q=11%2c759%2c422>; preserved August 5, 2024); Exhibit 109 (Google Patents, Cited By section, for the '475 patent, available at <https://patents.google.com/patent/US11655475B2/en?q=11%2c655%2c475>; preserved August 5, 2024).

¹⁵ Available at <https://www.pfizer.com/science/drug-product-pipeline>.

RESPONSE: To the extent the allegations of Paragraph 50 purport to rely on Exhibit 110 and Exhibit 111, those exhibits speak for themselves. Defendants admit that they continue to advance mRNA vaccines. At least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 50 and therefore deny the same.

51. Defendants' COVID-19 mRNA vaccines exploit the fundamental technologies invented by the Mandl team and claimed in the Patents-in-Suit. Defendants leveraged their knowledge of the Mandl team's work to design and develop the Accused Products. But Defendants did not acquire a license to practice the GSK inventions before or since commercializing the Accused Products.

RESPONSE: Denied.

52. Defendants have had knowledge of and specific notice of their infringement of the Patents-in-Suit by the manufacture and sale of the Accused Products at least since April 24, 2024, as evidenced by communications with GSK. See Exhibits 81–82.

RESPONSE: To the extent the allegations of Paragraph 52 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny the remaining allegations of this Paragraph.

53. Defendants continue to infringe the Patents-in-Suit through the manufacture and sale of the Accused Products.

RESPONSE: Denied.

DEFENDANTS' INFRINGING ACTIVITIES

54. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

A. The Accused Products

55. Defendants' manufacture, use, sale, marketing, offer for sale, and/or importation of the following Accused Products infringe the Patents-in-Suit: all dosage forms of (1) the original monovalent Comirnaty® COVID-19 vaccine ("Comirnaty® (original monovalent)"); (2) the bivalent Comirnaty® COVID-19 original plus BA.1 variant vaccine ("Comirnaty® (bivalent BA.1)"); (3) the bivalent Comirnaty® COVID-19 original plus BA.4/5 variant vaccine

(“Comirnaty® (bivalent BA.4/5)”); and (4) the monovalent Comirnaty® COVID-19 XBB.1.5 variant vaccine (“Comirnaty® (monovalent XBB.1.5)”).

RESPONSE: Denied.

56. On information and belief, for each of the foregoing Accused Products, Defendants previously used and continue to use the same method of manufacture, composition of mRNA drug substance (apart from differences in the sequence encoding the immunogens), and composition of drug product when applying for regulatory authorization or approval by the Food and Drug Administration (“FDA”) in the United States and European Medicines Agency (“EMA”) in Europe.

RESPONSE: Denied.

57. Defendants, FDA and EMA have also referred to the Accused Products as “BNT162b2” vaccine products. *See, e.g.*, Exhibit 19 (December 10, 2020, Pfizer press release); Exhibit 20 (December 11, 2020, FDA Comirnaty® (original monovalent) Emergency Use Authorization (“EUA”) Review Memo); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report); Exhibit 72 (Schoenmaker *et al.*, “mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability,” *Intl. J. Pharm.* 601, 120586 (2021) (“Schoenmaker (2021)”) at 2, 3 (Table 1); D.I. 22 at 87 (¶ 56).

RESPONSE: To the extent the allegations of Paragraph 57 purport to rely on Exhibit 19, Exhibit 20, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants admit that the Pfizer-BioNTech COVID-19 vaccine has been referred to as BNT162b2. Defendants deny the remaining allegations of this Paragraph.

58. Comirnaty® (original monovalent) includes the active substance “tozinameran,” mRNA encoding a spike protein of the original (2019) strain of the SARS-CoV-2 coronavirus. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® European Public Assessment Report (“EPAR”) Product Information) at 2 (“Tozinameran is a single-stranded, 5’-capped messenger RNA (mRNA) ... encoding the viral spike (S) protein of SARS-CoV-2.”) and 79 (referring to the viral strain as “SARS-CoV-2 (Original)”; Exhibit 23 (Proposed International Nonproprietary Names List 124 – COVID-19) at 666.

RESPONSE: To the extent the allegations of Paragraph 58 purport to rely on Exhibit 22 and Exhibit 23, those exhibits speak for themselves. Defendants admit that Comirnaty® (original monovalent) contains the active substance tozinameran. Defendants deny the remaining allegations of this Paragraph.

59. The tozinameran mRNA active ingredient includes, among other things, a 5' cap, a 5' untranslated region (UTR), an open reading frame region coding for the spike protein, a 3' untranslated region, and a 3' polyA tail. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 2; Exhibit 23 (Proposed International Nonproprietary Names List 124 – COVID-19) at 666; Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: To the extent the allegations of Paragraph 59 purport to rely on Exhibit 22, Exhibit 23, and Exhibit 72, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

60. Comirnaty® (original monovalent) elicits an immune response to the viral spike protein of the original (2019) strain of SARS-CoV-2 coronavirus. *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 13; Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 8–16.

RESPONSE: To the extent the allegations of Paragraph 60 purport to rely on Exhibit 21 and Exhibit 22, those exhibits speak for themselves. Defendants admit that Comirnaty® (original monovalent), when properly administered, has been shown to elicit an immune response. Defendants deny the remaining allegations of this Paragraph.

61. In response to the emergence of new strains of SARS-CoV-2, Defendants advanced dosage forms of two bivalent vaccines for commercial marketing authorization or approval: the Comirnaty® (bivalent BA.1) vaccine; and the Comirnaty® (bivalent BA.4/5) vaccine. *See, e.g.*, Exhibit 24 (September 1, 2022, Pfizer press release) (reporting on Comirnaty® (bivalent BA.1); Exhibit 25 (November 4, 2022, Pfizer press release) (reporting on Comirnaty® (bivalent BA.4/5).

RESPONSE: To the extent the allegations of Paragraph 61 purport to rely on Exhibit 24 and Exhibit 25, those exhibits speak for themselves. Defendants admit that they sought regulatory approval for Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5). Defendants deny the remaining allegations of this Paragraph.

62. Both the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) vaccines contain the tozinameran mRNA active substance. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 79, 98; Exhibit 26 (December 7, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 6 (“The active substance tozinameran is already approved in the existing Comirnaty conditional marketing authorization. No changes to the information related to tozinameran are proposed.”); Exhibit 24 (September 1, 2022, Pfizer press release) (“Apart from the addition of the mRNA sequence of the Omicron BA.1 spike

protein, all other components of the vaccine remain unchanged.”); Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 5 (“The active substance tozinameran is already approved for the original Comirnaty vaccine formulations (EU/1/20/1528/001-005). No changes to the information related to tozinameran are proposed.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Apart from the addition of the mRNA sequence of the Omicron BA.4/BA.5 spike protein, all other components of the vaccine remain unchanged.”).

RESPONSE: To the extent the allegations of Paragraph 62 purport to rely on Exhibit 22, Exhibit 26, Exhibit 24, Exhibit 27, and Exhibit 25, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) contain tozinameran. Defendants deny the remaining allegations of this Paragraph.

63. In addition to tozinameran, the Comirnaty® (bivalent BA.1) vaccine also contains the active substance “riltozinameran,” mRNA encoding a viral spike protein of the Omicron BA.1 variant of SARS-CoV-2. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 79 (“Riltozinameran is a single-stranded, 5’-capped messenger RNA (mRNA) ... encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1).”); Exhibit 26 (December 7, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 6; Exhibit 28 (Proposed International Nonproprietary Names List 126 – COVID-19 Addendum) at 1147.

RESPONSE: To the extent the allegations of Paragraph 63 purport to rely on Exhibit 22, Exhibit 26, and Exhibit 28, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent BA.1) contains riltozinameran. Defendants deny the remaining allegations of this Paragraph.

64. On information and belief, apart from the open reading frame region coding for a viral spike protein of the SARS-CoV-2 Omicron BA.1 coronavirus variant, the components of the riltozinameran mRNA active ingredient are unchanged as compared to the tozinameran mRNA active ingredient as set forth above. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 79; Exhibit 28 (Proposed International Nonproprietary Names List 126 – COVID-19 Addendum) at 1147.

RESPONSE: To the extent the allegations of Paragraph 64 purport to rely on Exhibit 22 and Exhibit 28, those exhibits speak for themselves. Otherwise, at least because of the scope, breadth, and vagueness of these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

65. The Comirnaty® (bivalent BA.1) vaccine product elicits an immune response to the spike proteins of both the original SARS-CoV-2 strain and Omicron BA.1 SARS-CoV-2 variant. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 86–94; Exhibit 26 (December 7, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 62–66.

RESPONSE: To the extent the allegations of Paragraph 65 purport to rely on Exhibit 22 and Exhibit 26, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent BA.1), when properly administered, has been shown to elicit an immune response. Defendants deny the remaining allegations of this Paragraph.

66. In addition to tozinameran, the Comirnaty® (bivalent BA.4/5) vaccine also contains the active substance “famtozinameran,” mRNA encoding a viral spike protein of the Omicron BA.4/5 variant of SARS-CoV-2. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 98 (“Famtozinameran is a single-stranded, 5’-capped messenger RNA (mRNA) ... encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).”); Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 5; Exhibit 29 (March 2023, FDA Comirnaty® (bivalent BA.4/5) Fact Sheet and Prescribing Information), Prescribing Information at 52.

RESPONSE: To the extent the allegations of Paragraph 58 purport to rely on Exhibit 22, Exhibit 27, and Exhibit 29, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent BA.4/5) contains famtozinameran. Defendants deny the remaining allegations of this Paragraph.

67. On information and belief, apart from the open reading frame region coding for a viral spike protein of the SARS-CoV-2 Omicron BA.4/5 coronavirus variants, the components of the famtozinameran mRNA active ingredient are unchanged as compared to the tozinameran mRNA active ingredient as set forth above. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 98; Exhibit 30 (Proposed International Nonproprietary Names List 128 – COVID-19 Addendum) at 3.

RESPONSE: To the extent the allegations of Paragraph 67 purport to rely on Exhibit 22 and Exhibit 30, those exhibits speak for themselves. Defendants deny the remaining allegations of this Paragraph.

68. The Comirnaty® (bivalent BA.4/5) vaccine product elicits an immune response to the spike proteins of both the original SARS-CoV-2 strain and Omicron BA.4/5 SARS-CoV-2 variants. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product

Information) at 105–114; Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 24; Exhibit 29 (March 14, 2023, FDA Comirnaty® (bivalent BA.4/5) Fact Sheet and Prescribing Information), Prescribing Information at 52.

RESPONSE: To the extent the allegations of Paragraph 68 purport to rely on Exhibit 22, Exhibit 27, and Exhibit 29, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent BA.4/5), when properly administered, has been shown to elicit an immune response. Defendants deny the remaining allegations of this Paragraph.

69. In response to the continued evolution of SARS-CoV-2, Defendants subsequently advanced dosage forms of a new monovalent vaccine for commercial marketing authorization and/or approval: the Comirnaty® (monovalent XBB.1.5) vaccine. *See, e.g.*, Exhibit 31 (June 23, 2023, Pfizer press release).

RESPONSE: To the extent the allegations of Paragraph 69 purport to rely on Exhibit 31, that exhibit speaks for itself. Defendants admit that they sought regulatory approval for Comirnaty® (monovalent XBB.1.5). Defendants deny the remaining allegations of this Paragraph.

70. The Comirnaty® (monovalent XBB.1.5) vaccine contains a single mRNA active ingredient, “raxtozinameran,” which encodes a viral spike protein of the Omicron XBB.1.5 variant of SARS-CoV-2. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 190 (“Raxtozinameran is a single-stranded, 5’-capped messenger RNA (mRNA) ... encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).”); Exhibit 32 (Proposed International Nonproprietary Names List 129 – COVID-19) at 3; Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert) at 20.

RESPONSE: To the extent the allegations of Paragraph 70 purport to rely on Exhibit 22, Exhibit 32, and Exhibit 33, those exhibits speak for themselves. Defendants admit that Comirnaty® (bivalent XBB.1.5) contains raxtozinameran. Defendants deny the remaining allegations of this Paragraph.

71. On information and belief, apart from the open reading frame region coding for a viral spike protein of the SARS-CoV-2 Omicron XBB.1.5 coronavirus variant, the components of the raxtozinameran mRNA active ingredient are unchanged as compared to the tozinameran mRNA active ingredient as set forth above. *See, e.g.*, Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 190; Exhibit 32 (Proposed International Nonproprietary Names List 129 – COVID-19) at 3.

RESPONSE: To the extent the allegations of Paragraph 63 purport to rely on Exhibit 22 and Exhibit 32, those exhibits speak for themselves. Otherwise, at least because of the scope, breadth, and vagueness of this these allegations, Defendants lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

72. The Comirnaty® (monovalent XBB.1.5) vaccine product elicits an immune response to the spike protein of the Omicron XBB.1.5 SARS-CoV-2 variant. *See, e.g.,* Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 197–207; Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert) at 20.

RESPONSE: To the extent the allegations of Paragraph 64 purport to rely on Exhibit 22 and Exhibit 33, those exhibits speak for themselves. Defendants admit that Comirnaty® (monovalent XBB.1.5), when properly administered, has been shown to elicit an immune response. Defendants deny the remaining allegations of this Paragraph.

73. In addition to the mRNA active substance(s), all of Defendants’ accused Comirnaty® COVID-19 vaccines contain the following four lipid ingredients:

Chemical Name	Shorthand
(((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	“ALC-0315”
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	“ALC-0159”
1,2-distearoyl-sn-glycero-3-phosphocholine	“DSPC”
cholesterol	(N/A)

Exhibit 22 (December 15, 2023, EMA Comirnaty® EPAR Product Information) at 17, 95, 114, 208, 288, 304, 308, 324; Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19; Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert) at 53; Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert) at 20; Exhibit 72 (Schoenmaker (2021)) at 3 (Table 1), 8; D.I. 22 at 87 (¶ 56).

RESPONSE: To the extent the allegations of Paragraph 65 purport to rely on Exhibit 22, Exhibit 34, Exhibit 35, Exhibit 33, and Exhibit 72, those exhibits speak for themselves. Defendants otherwise lack the knowledge or information sufficient to form a belief as to the truth of the allegations of this Paragraph and therefore deny the same.

74. Each of the Accused Products comprises lipid formulations with the same relative molar percentages of the foregoing lipid ingredients. *See, e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“Each 0.3 mL dose of the COMIRNATY ... also includes the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl) bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol[.]”); Exhibit 26 (December 7, 2022, EMA (bivalent BA.1) Assessment Report) at 11; Exhibit 35 (July 14, 2023, FDA Comirnaty (bivalent BA.4/5) EUA Fact Sheet and Package Insert) at 53; Exhibit 33 (September 2023, Comirnaty® (monovalent XBB.1.5) vaccine Package Insert) at 20; Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: To the extent the allegations of Paragraph 66 purport to rely on Exhibit 34, Exhibit 26, Exhibit 35, Exhibit 33, and Exhibit 72, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

B. Defendants’ Infringement in the United States

75. On December 11, 2020, FDA granted the first Emergency Use Authorization (EUA) for the use of Defendants’ monovalent BNT162b2 original SARS-CoV-2 (2019) vaccine (later named Comirnaty®; here Comirnaty® (original monovalent)) to prevent COVID-19 caused by SARS-CoV-2. Exhibit 36 (December 11, 2020, FDA News Release); Exhibit 20 (December 11, 2020, FDA Comirnaty® (original monovalent) EUA Review Memo). The authorized regimen was a two-dose primary vaccination series administered 21 days apart in individuals 16 years of age and older. *Id.*

RESPONSE: To the extent the allegations of Paragraph 75 purport to rely on Exhibit 36 and Exhibit 20, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

76. On May 10, 2021, FDA expanded EUA for Comirnaty® (original monovalent) two-dose primary vaccination series to children and adolescents 12 years through 15 years of age. Exhibit 37 (May 10, 2021, FDA Comirnaty® (original monovalent) EUA Letter).

RESPONSE: To the extent the allegations of Paragraph 76 purport to rely on Exhibit 37, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

77. On August 12, 2021, FDA expanded EUA for Comirnaty® (original monovalent) to a third primary dose (at least 28 days after the second dose) for certain higher risk individuals 12 years of age or older. Exhibit 38 (August 12, 2021, FDA News Release); Exhibit 39 (August 12, 2021, FDA Comirnaty (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 77 purport to rely on Exhibit 38 and Exhibit 39, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

78. On August 23, 2021, FDA granted full approval of Defendants' BLA for Comirnaty® (original monovalent) COVID-19 vaccine two-dose primary vaccination series in individuals 16 years of age and older. Exhibit 8 (August 23, 2021, FDA Comirnaty® (original monovalent) Approval Letter).

RESPONSE: To the extent the allegations of Paragraph 78 purport to rely on Exhibit 8, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

79. On September 22, 2021, FDA expanded EUA for Comirnaty® (original monovalent) to a third dose (a first booster) six months after completion of the primary two-dose vaccination series for individuals 65 years of age or older, or certain other higher risk individuals 18 to 64 years of age. Exhibit 40 (September 22, 2021, FDA News Release); Exhibit 41 (September 22, 2021, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 79 purport to rely on Exhibit 40 and Exhibit 41, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

80. On October 29, 2021, FDA expanded EUA for Comirnaty® (original monovalent) two-dose primary vaccination series to children 5 through 11 years of age. Exhibit 42 (October 29, 2021, FDA News Release); Exhibit 43 (October 29, 2021, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 80 purport to rely on Exhibit 42 and Exhibit 43, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

81. On November 19, 2021, FDA expanded EUA for Comirnaty® (original monovalent) to a third dose (a first booster) for all individuals 18 years and older who had completed an authorized primary vaccination series. Exhibit 44 (November 19, 2021, FDA News Release); Exhibit 45 (November 19, 2021, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 81 purport to rely on Exhibit 44 and Exhibit 45, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

82. On December 9, 2021, FDA expanded EUA for Comirnaty® (original monovalent) to a third dose (a first booster) dose for all individuals 16 and 17 years of age who had completed an authorized primary vaccination series. Exhibit 46 (December 9, 2021, FDA News Release); Exhibit 47 (December 8, 2021, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 82 purport to rely on Exhibit 46 and Exhibit 47, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

83. On January 3, 2022, FDA expanded EUA for Comirnaty® (original monovalent) to a third dose (a first booster) for all individuals 12 years of age and older. Exhibit 48 (January 3, 2022, FDA News Release).

RESPONSE: To the extent the allegations of Paragraph 83 purport to rely on Exhibit 48, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

84. On March 29, 2022, FDA expanded EUA for Comirnaty® (original monovalent) to a fourth dose (a second booster) at least four months after receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine for individuals over 50 years of age and for immunocompromised patients 12 years of age and older. Exhibit 49 (March 29, 2022, FDA News Release).

RESPONSE: To the extent the allegations of Paragraph 84 purport to rely on Exhibit 49, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

85. On May 17, 2022, FDA expanded EUA for Comirnaty® (original monovalent) to a third dose (a first booster) for children 5 years through 11 years of age. Exhibit 50 (May 17,

2022, FDA News Release as preserved by The Wayback Machine, May 17, 2022¹⁶); Exhibit 51 (May 17, 2022, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 85 purport to rely on Exhibit 50 and Exhibit 51, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

86. On June 17, 2022, FDA expanded EUA for Comirnaty® (original monovalent) to a three-dose primary vaccination series for children 6 months through 4 years of age. Exhibit 52 (June 17, 2022, FDA News Release); Exhibit 53 (June 16, 2022, FDA Comirnaty® (original monovalent) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 86 purport to rely on Exhibit 52 and Exhibit 53, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

87. On August 31, 2022, FDA granted EUA for Comirnaty (bivalent BA.4/5) as a single booster dose in patients 12 years of age and older who had received a primary series or primary series and first booster of any authorized or approved COVID-19 vaccine. Exhibit 54 (August 31, 2022, FDA News Release as preserved by The Wayback Machine, September 1, 2022¹⁷); Exhibit 55 (August 31, 2022, FDA Comirnaty® (bivalent BA.4/5) EUA Review Memo). FDA also revised the EUA for Comirnaty® (original monovalent) to no longer include use as a booster dose in individuals 12 years of age and older. Exhibit 54 (August 31, 2022, FDA News Release as preserved by The Wayback Machine, September 1, 2022); Exhibit 55 (August 31, 2022, FDA Comirnaty® (bivalent BA.4/5) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 87 purport to rely on Exhibit 54 and Exhibit 55, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

88. On October 12, 2022, FDA expanded EUA for Comirnaty® (bivalent BA.4/5) as a booster dose in children 5 through 11 years of age who had received a primary series or primary series and booster of any authorized or approved COVID-19 vaccine. Exhibit 56 (October 12,

¹⁶ Available at <https://web.archive.org/web/20220517152524/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-vaccine-booster-dose>; preserved April 9, 2024.

¹⁷ Available at <https://web.archive.org/web/20220901002611/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use>; preserved April 9, 2024.

2022, FDA News Release as preserved by The Wayback Machine, October 13, 2022¹⁸); Exhibit 57 (October 11, 2022, FDA Comirnaty® (bivalent BA.4/5) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 88 purport to rely on Exhibit 56 and Exhibit 57, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

89. On December 8, 2022, FDA expanded EUA for Comirnaty® (bivalent BA.4/5) as the third dose in a primary series in children under 5 years of age who had received two primary doses of Comirnaty® (original monovalent) and revised the EUA for Comirnaty® (original monovalent) to no longer include its use as the third primary dose for this patient population. Exhibit 58 (December 8, 2022, FDA News Release as preserved by The Wayback Machine, December 9, 2022¹⁹); Exhibit 59 (December 8, 2022, FDA Comirnaty® (bivalent BA.4/5) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 89 purport to rely on Exhibit 58 and Exhibit 59, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

90. On March 14, 2023, FDA expanded EUA for Comirnaty® (bivalent BA.4/5) as a fourth dose (a first booster) dose in children 6 months through 4 years of age who had received a three-dose primary series of Comirnaty® (original monovalent or original monovalent followed by bivalent BA.4/5) vaccine. Exhibit 60 (March 14, 2023, FDA News Release); Exhibit 29 (March 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Prescribing Information).

RESPONSE: To the extent the allegations of Paragraph 90 purport to rely on Exhibit 60 and Exhibit 29, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

91. On April 18, 2023, FDA expanded EUA for Comirnaty® (bivalent BA.4/5) to be used for all doses (primary and booster) in most adults and pediatric populations as well as other dosage regimes for certain individuals based on age or immunocompromised status. Exhibit 61

¹⁸ Available at <https://web.archive.org/web/20221013015339/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-and-pfizer-biontech-bivalent-covid-19-vaccines>; preserved April 9, 2024.

¹⁹ Available at <https://web.archive.org/web/20221209225236/https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-updated-bivalent-covid-19-vaccines-children-down-6-months>; preserved April 9, 2024.

(April 18, 2023, FDA News Release). FDA also rescinded all authorizations for use of Comirnaty® (original monovalent) vaccine in the United States. *Id.*

RESPONSE: To the extent the allegations of Paragraph 91 purport to rely on Exhibit 61, that exhibit speaks for itself. Defendants otherwise deny the remaining allegations of this Paragraph.

92. On September 11, 2023, FDA granted full approval of Defendants' supplemental BLA for Comirnaty® (monovalent XBB.1.5) COVID-19 vaccine single dose regimen for individuals 12 years of age and older. Exhibit 62 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) Approval Letter). FDA also granted EUA for Comirnaty® (monovalent XBB.1.5) as a single dose for individuals 6 months through 11 years of age. Exhibit 63 (September 11, 2023, FDA News Release); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo). FDA also rescinded EUAs for the Comirnaty® (bivalent BA.4/5) vaccine. Exhibit 63 (September 11, 2023, FDA News Release); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo).

RESPONSE: To the extent the allegations of Paragraph 92 purport to rely on Exhibit 62, Exhibit 63, and Exhibit 64, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

93. Pursuant to these FDA authorizations and approvals, Defendants have offered to sell and continue to offer for sale, and have sold and continue to sell, the Accused Products in Delaware, the United States, and worldwide. *See, e.g.,* D.I. 22 at 27–28 (¶ 85).

RESPONSE: Paragraph 93 states a legal conclusion to which no response is required. Defendants admit that the Accused Products have been or are distributed in the United States, including in Delaware, pursuant to FDA approval or authorization. Defendants deny the remaining allegations of this Paragraph and deny infringement of any valid and enforceable claim of the Patents-in-Suit.

94. Defendants have directed and instructed, and continue to direct and instruct, the administration of the Accused Products in the United States, in accordance with the FDA authorized and approved uses of those products.

RESPONSE: Paragraph 94 states a legal conclusion to which no response is required. To the extent a response is required, Defendants deny the allegations of this Paragraph and deny infringement of any valid and enforceable claim of the Patents-in-Suit.

95. Defendants have made and continue to make, and have had made and continue to have made, the Accused Products in the United States. *See, e.g.*, D.I. 22 at 28 (¶ 87); Exhibit 8 (August 23, 2021, FDA Comirnaty® (original monovalent) Approval Letter) at 1; Exhibit 9 (excerpts from March 30, 2022, BioNTech SE 2021FY Annual Report (Form 20-F)) at 89; Exhibit 26 (December 7, 2022, EMA Comirnaty® BA.1 Assessment Report) at 13, 16–17; Exhibit 62 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) Approval Letter) at 1; Exhibit 27 (September 12, 2022, EMA Comirnaty® BA.4/5 Assessment Report) at 13, 16–17.

RESPONSE: Paragraph 95 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 95 purport to rely on Exhibit 8, Exhibit 9, Exhibit 26, Exhibit 62, and Exhibit 27, those exhibits speak for themselves. Defendants admit that the Accused Products have been or are manufactured in the United States. Defendants deny the remaining allegations of this Paragraph and deny infringement of any valid and enforceable claim of the Patents-in-Suit.

96. On information and belief, Accused Products manufactured by or for Defendants in the United States were and are still distributed for sale and sold both in the United States and outside the United States. *See, e.g.*, D.I. 22 at 28–29 (¶ 88); Exhibit 26 (December 7, 2022, EMA Comirnaty® BA.1 Assessment Report) at 13, 16–17; Exhibit 27 (September 12, 2022, EMA Comirnaty® BA.4/5 Assessment Report) at 13, 16–17; Exhibit 9 (excerpts from March 30, 2022, BioNTech SE 2021FY Annual Report (Form 20-F)) at 89.

RESPONSE: Paragraph 96 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 96 purport to rely on Exhibit 26, Exhibit 27, and Exhibit 9, those exhibits speak for themselves. Defendants admit that the Accused Products have been or are manufactured and distributed in the United States. Defendants deny that sales outside the United States are relevant to this litigation. Defendants deny the remaining allegations of this Paragraph and deny infringement of any valid and enforceable claim of the Patents-in-Suit.

97. Defendants have profited significantly from the inventions claimed in the Patents-in-Suit. From sales of the Accused Products alone, Defendant Pfizer reported over \$8 billion in

U.S. revenue (and over \$37 billion globally) in 2022 and over \$2 billion in U.S. revenue (and over \$11 billion globally) in 2023. Exhibit 65 (excerpts from February 23, 2023, Pfizer Inc. 2022FY Annual Report (Form 10-K)) at 33; Exhibit 66 (excerpts from February 22, 2024, Pfizer Inc. 2023FY Annual Report (Form 10-K)) at 38. Defendant BioNTech reported over €12 billion in revenues from shares of profits and milestones from sales of the Accused Products from collaboration partners (and over €17 billion in total COVID-19 vaccine revenue) in 2022 and over €3 billion in revenues from shares of profits from sales of the Accused Products from collaboration partners in 2023. Exhibit 67 (excerpts from March 27, 2023, BioNTech SE 2022FY Annual Report (Form 20-F)) at 162; Exhibit 110 (excerpts from March 20, 2024, BioNTech 2023FY Annual Report (Form 20-F)) at 165.

RESPONSE: To the extent the allegations of Paragraph 97 purport to rely on Exhibit 65, Exhibit 66, Exhibit 67, and Exhibit 110, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

98. Defendants stand to continue to profit significantly through continued infringement of GSK Biologicals's Patents-in-Suit without taking a license. In September 2023, Defendants set the list price of their Comirnaty® COVID-19 vaccine product at \$120 per dose, an approximately four-fold increase from the pandemic pricing. Exhibit 69 (September 12, 2023, *Reuters* article, "COVID vaccine manufacturers set list price between \$120-\$130 per dose"²⁰); Exhibit 70 (October 21, 2022, *Reuters* article, "Pfizer expects to hike U.S. COVID vaccine price to \$110-130 per dose"²¹) (noting original pandemic price of Comirnaty® COVID-19 vaccine was around \$30 per dose).

RESPONSE: To the extent the allegations of Paragraph 98 purport to rely on Exhibit 69 and Exhibit 70, those exhibits speak for themselves. Defendants otherwise deny the remaining allegations of this Paragraph.

COUNT I

(Infringement of the '693 Patent)

99. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

100. GSK Biologicals is the lawful owner by assignment of the '693 patent, which is entitled "Vaccine for Eliciting Immune Response Comprising RNA Encoding an Immunogen and

²⁰ Available at <https://www.reuters.com/business/healthcare-pharmaceuticals/covid-vaccine-manufacturers-set-list-price-between-120-130-per-dose-2023-09-12/>; preserved April 3, 2024.

²¹ Available at <https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-expects-price-covid-vaccine-110-130-per-dose-2022-10-20/>; preserved April 3, 2024.

Lipid Formulations Comprising Mole Percentage of Lipids” and was duly and legally issued by the U.S. Patent and Trademark Office on May 2, 2023. A true and correct copy of the ’693 patent is attached as Exhibit 1. The patent application issuing into the ’693 patent was published on November 17, 2022, as Publication No. US 2022/0362152 A1. See Exhibit 112.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,638,693 entitled “Vaccine for Eliciting Immune Response Comprising RNA Encoding an Immunogen and Lipid Formulations Comprising Mole Percentage of Lipids” on May 2, 2023, that Exhibit 1 purports to be a copy of the ’693 patent, that Publication No. U.S. 2022/0362152 A1 was published on November 17, 2022 and issued into the ’693 patent, and that Exhibit 112 purports to be a copy of Publication No. U.S. 2022/0362152 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

101. Each claim of the ’693 patent is valid and enforceable.

RESPONSE: Denied.

102. Defendants have directly infringed and continue to directly infringe one or more claims of the ’693 patent under 35 U.S.C. § 271(a), either literally or under the doctrine of equivalents, by making, using, offering to sell, or selling within the United States, or importing into the United States, each of the Accused Products embodying GSK Biologicals’s patented inventions as disclosed by and claimed in the ’693 patent, without authority or license to do so, during the term of the ’693 patent.

RESPONSE: Denied.

103. In addition or in the alternative, Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the ’693 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals’s patented inventions as disclosed by and claimed in the ’693 patent, without authority or license to do so, during the term of the ’693 patent.

RESPONSE: Denied.

104. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the ’693 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling

and/or offering for sale in the United States, and/or importing into the United States, each of the Accused Products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '693 patent, without authority or license to do so, during the term of the '693 patent, knowing that those products constitute a material part of the inventions of the '693 patent, knowing that those products are especially made or adapted to infringe the '693 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

105. For example, on information and belief, each of the Accused Products satisfies each and every element of at least claim 1 of the '693 patent. Defendants' actions with respect to each of the Accused Products have therefore infringed at least this exemplary claim of the '693 patent.

RESPONSE: Denied.

106. Claim 1 of the '693 patent recites:

A formulation comprising:

ribonucleic acid (RNA) molecules comprising a sequence that encodes an immunogen; and

lipids comprising: (a) from 20 mole % to 70 mole % cationic lipid, (b) an anionic or a zwitterionic lipid, (c) a polyethylene glycol-conjugated (PEG-conjugated) lipid, and (d) from 5 mole % to 80 mole % cholesterol; wherein:

the lipids encapsulate at least half of the RNA molecules;

the formulation is immunogenic in vivo by eliciting an antibody response against the immunogen in vivo; and

the cationic lipid comprises a tertiary amine and has a pKa from 6.07 to 7.6; and

whereby the pKa is determined at standard temperature and pressure by the following:

(1) admixing 400 μ L of 2 mM cationic lipid that is in ethanol and 800 μ L of 0.3 mM fluorescent probe 6-(p-toluidino)-2-naphthalenesulfonic acid (TNS), which is in 90 volume % ethanol and 10 volume % methanol, thereby obtaining a lipid/TNS mixture;

(2) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a first buffer consisting essentially of a sodium salt buffer comprising 20 mM sodium phosphate, 25 mM sodium citrate, 20 mM sodium acetate, and 150 mM sodium chloride, wherein the first buffer has a

pH from 4.44 to 4.52, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a first mixture, and dispensing 100 μ L of the first mixture in a first well of a 96-well plate, which has a clear bottom;

(3) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a second buffer consisting essentially of the sodium salt buffer, wherein the second buffer has a pH of 5.27, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a second mixture, and dispensing 100 μ L of the second mixture in a second well of the 96-well plate;

(4) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a third buffer consisting essentially of the sodium salt buffer, wherein the third buffer has a pH from 6.15 to 6.21, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a third mixture, and dispensing 100 μ L of the third mixture in a third well of the 96-well plate;

(5) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a fourth buffer consisting essentially of the sodium salt buffer, wherein the fourth buffer has a pH of 6.57, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a fourth mixture, and dispensing 100 μ L of the fourth mixture in a fourth well of the 96-well plate;

(6) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a fifth buffer consisting essentially of the sodium salt buffer, wherein the fifth buffer has a pH from 7.10 to 7.20, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a fifth mixture, and dispensing 100 μ L of the fifth mixture in a fifth well of the 96-well plate;

(7) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a sixth buffer consisting essentially of the sodium salt buffer, wherein the sixth buffer has a pH from 7.72 to 7.80, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a sixth mixture, and dispensing 100 μ L of the sixth mixture in a sixth well of the 96-well plate;

(8) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a seventh buffer consisting essentially of the sodium salt buffer, wherein the seventh buffer has a pH from 8.27 to 8.33, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a seventh mixture, and dispensing 100 μ L of the seventh mixture in a seventh well of the 96-well plate;

(9) admixing 7.5 μL of the lipid/TNS mixture and 242.5 μL of an eighth buffer consisting essentially of the sodium salt buffer, wherein the eighth buffer has a pH from 10.47 to 11.12, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining an eighth mixture, and dispensing 100 μL of the eighth mixture in an eighth well of the 96-well plate;

(10) measuring the fluorescence at a wavelength of 431 nm with an excitation wavelength of 322 nm and a cut-off below a wavelength of 420 nm of each of the first through eighth wells and an empty well of the 96-well plate, thereby obtaining a measured fluorescence for each of the p empty well and the first through eighth wells;

(11) subtracting the measured fluorescence of the empty well from each of the measured fluorescences of the first through eighth wells, thereby obtaining a blank-subtracted fluorescence for each of the first through eighth mixtures;

(12) normalizing each of the blank-subtracted fluorescences of the first through eighth mixtures to the blank-subtracted fluorescence of the first mixture thereby obtaining a relative fluorescence for each of the first through eighth mixtures, the relative fluorescence being 1 for the first mixture;

(13) obtaining a line of best fit of the pHs of the first through eighth buffers versus the respective relative fluorescences of the first through eighth mixtures; and

(14) defining the pKa as the pH on the line of best fit at which a relative fluorescence of 0.5 is obtained.

RESPONSE: Defendants admit that Claim 1 of the '693 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

107. Each of the Accused Products comprises a “formulation.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles[.]”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]”).

RESPONSE: Paragraph 107 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 107 purport to rely on Exhibit 34 and Exhibit 21, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in

Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

108. Each of the Accused Products comprises “ribonucleic acid (RNA) molecules comprising a sequence that encodes an immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 108 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 108 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

109. Each of the Accused Products comprises “lipids comprising: (a) ... [a] cationic lipid, (b) an anionic or a zwitterionic lipid, (c) a polyethylene glycol-conjugated (PEG-conjugated) lipid, and (d) ... cholesterol.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 109 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 109 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

110. ALC-0315 is a “cationic lipid.” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient

is a cationic lipid containing a tertiary amine"); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an "[i]onizable cationic lipid"); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 110 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 110 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

111. DSPC is a "zwitterionic lipid." See, *e.g.*, Exhibit 73 (DSPC Product Information, Polysciences) ("[DSPC] is a zwitterionic phospholipid that is used in the preparation of liposomes for transfection and drug delivery applications.").

RESPONSE: Paragraph 111 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 111 purport to rely on Exhibit 73, that exhibit speaks for itself. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

112. ALC-0159 is a "polyethylene glycol-conjugated (PEG-conjugated) lipid." See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 ("The ALC-0159 novel excipient is PEGylated lipid"); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) ("ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]"); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a "PEG-lipid"); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 112 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 112 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

113. Each of the Accused Products comprises "lipids comprising ... from 20 mole % to 70 mole % cationic lipid." See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying the quantity of each lipid

component); *see also* Exhibit 72 (Schoenmaker (2021)) at 3, Table 1 (reporting ionizable cationic lipid ALC-0315 makes up 46.3 mole % of the lipids present in Comirnaty® products); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 113 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 113 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

114. Each of the Accused Products comprises “lipids comprising ... from 5 mole % to 80 mole % of cholesterol.” *See* paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying the quantity of each lipid component); *see also* Exhibit 72 (Schoenmaker (2021)) at 3, Table 1 (reporting cholesterol makes up 42.7 mole % of the lipids present in Comirnaty® products); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 114 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 114 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

115. On information and belief, the lipids of each of the Accused Products “encapsulate at least half of the RNA molecules.” *See* paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 115 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 115 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in

Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

116. Each of the Accused Products is “immunogenic in vivo by eliciting an antibody response against the immunogen in vivo” at least when used in accordance with the FDA and EMA authorized and approved indications. See paragraphs 55–92, above; *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 24 (September 1, 2022, Pfizer press release) (“[T]he bivalent vaccine with mRNA encoding the wild-type and the BA.1 spike proteins provides [] neutralizing antibody titers against the Omicron BA.1 and BA.4/BA.5 sublineages[.]”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 116 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 116 purport to rely on Exhibit 21, Exhibit 24, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

117. On information and belief, when employing the “fluorescent probe 6-(p-toluidino)-2-naphthalenesulfonic acid (TNS)” and following steps (1) to (14) of claim 1 of the ’693 patent to “obtain[] a relative fluorescence” in each of the described pH-buffered mixtures and “defining the pKa as the pH on the line of best fit at which a relative fluorescence of 0.5 is obtained,” the cationic lipid used in each of the Accused Products—ALC-0315—exhibits a pKa falling between 6.07 and 7.6. See, *e.g.*, Exhibit 75 (McKenzie *et al.*, “mRNA synthesis and encapsulation in ionizable lipid nanoparticles,” *Current Protocols* 3, e898 (2023)) at 19 (reporting a pKa of 6.284 for ALC-0315 in a TNS assay); Exhibit 76 (International PCT Application Publication Number WO 2017/075531 A1) at 48 and 50, Table 3 (reporting a pKa of 6.09 for ALC-0315 (cationic lipid “No. 3”) in a TNS assay); Exhibit 77 (Tilstra *et al.*, “Iterative Design of Ionizable Lipids for Intramuscular mRNA

Delivery,” *J. Am. Chem. Soc.* 145, 2294–2304 (2023) with supplementary information) at Figure S11 (reporting a pKa of 6.27 for ALC-0315 in a TNS assay).

RESPONSE: Paragraph 117 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 117 purport to rely on Exhibit 75, Exhibit 76, and Exhibit 77, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

118. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 118 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 118 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

119. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. *See, e.g.*, Exhibit 78 (www.comirnaty.com as preserved by The Wayback Machine, August, 27, 2021²²); Exhibit 79 (www.comirnaty.com/eua-bivalent as

²² Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

preserved by The Wayback Machine, September, 22, 2022²³); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 119 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 119 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

120. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '693 patent.

RESPONSE: Denied.

121. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '693 patent.

RESPONSE: Denied.

122. None of the Accused Products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

123. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '693 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

²³ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

RESPONSE: Denied.

124. GSK has suffered and continues to suffer damages from Defendants' infringement of the '693 patent.

RESPONSE: Denied.

125. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '693 patent.

RESPONSE: Denied.

126. Defendants have had knowledge of the '693 patent and specific notice of its infringement at least since April 24, 2024, by communications between GSK and Defendants. See Exhibits 81–82.

RESPONSE: Paragraph 126 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 126 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

127. Defendants' infringement of the '693 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on April 24, 2024. *See id.*

RESPONSE: Denied.

128. Defendants' conduct with respect to the '693 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT II

(Infringement of the '694 Patent)

129. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

130. GSK Biologicals is the lawful owner by assignment of the '694 patent, which is entitled "Vaccine for Eliciting Immune Response Comprising Lipid formulations and RNA Encoding Multiple Immunogens" and was duly and legally issued by the U.S. Patent and

Trademark Office on May 2, 2023. A true and correct copy of the '694 patent is attached as Exhibit 2. The patent application issuing into the '694 patent was published on November 3, 2022, as Publication No. US 2022/0347097 A1. See Exhibit 113.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,638,694 entitled "Vaccine for Eliciting Immune Response Comprising Lipid Formulations and RNA Encoding Multiple Immunogens" on May 2, 2023, that Exhibit 2 purports to be a copy of the '694 patent, that Publication No. U.S. 2022/0347097 A1 was published on November 3, 2022 and issued into the '694 patent, and that Exhibit 113 purports to be a copy of Publication No. U.S. 2022/0347097 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

131. Each claim of the '694 patent is valid and enforceable.

RESPONSE: Denied.

132. Defendants have directly infringed and continue to directly infringe one or more claims of the '694 patent under 35 U.S.C. § 271(a), either literally or under the doctrine of equivalents, by making, using, offering to sell, or selling the United States, or importing into the United States, each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '694 patent, without authority or license to do so, during the term of the '694 patent.

RESPONSE: Denied.

133. In addition or in the alternative, Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '694 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Comirnaty® (bivalent BA.4/5) product embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '694 patent, without authority or license to do so, during the term of the '694 patent.

RESPONSE: Denied.

134. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '694 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '694 patent, without authority or license to do so, during the term of the '694 patent, knowing that those products

constitute a material part of the inventions of the '694 patent, knowing that those products are especially made or adapted to infringe the '694 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

135. For example, on information and belief, each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products satisfies each and every element of at least claim 1 of the '694 patent. Defendants' actions with respect to the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products have therefore infringed at least this exemplary claim of the '694 patent.

RESPONSE: Denied.

136. Claim 1 of the '694 patent recites:

A formulation comprising:

a first species of ribonucleic acid (RNA) molecules comprising a sequence that encodes a first immunogen;

a second species of RNA molecules comprising a sequence that encodes a second immunogen; and

lipids comprising: (a) a cationic lipid, (b) an anionic lipid or a zwitterionic lipid, (c) a polyethylene glycol-conjugated (PEG-conjugated) lipid, and (d) a cholesterol, wherein:

the lipids encapsulate at least half of the first species of RNA molecules and at least half of the second species of RNA molecules;

the cationic lipid comprises a tertiary amine and has a pKa from 6.07 to 7.6; and

the formulation is immunogenic in vivo by eliciting an antibody response against the first immunogen and the second immunogen in vivo; and

whereby the pKa is determined at standard temperature and pressure by the following:

(1) admixing 400 μ L of 2 mM of the cationic lipid that is in ethanol and 800 μ L of 0.3 mM of fluorescent probe 6-(p-toluidino)-2-naphthalenesulfonic acid (TNS), which is in 90 volume % ethanol and 10 volume % methanol, thereby obtaining a lipid/TNS mixture;

(2) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a first buffer consisting essentially of a sodium salt buffer consisting

of 20 mM sodium phosphate, 25 mM sodium citrate, 20 mM sodium acetate, and 150 mM sodium chloride, wherein the first buffer has a pH from 4.44 to 4.52, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a first mixture, and dispensing 100 μ L of the first mixture in a first well of a 96-well plate, which has a clear bottom;

(3) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a second buffer consisting essentially of the sodium salt buffer, wherein the second buffer has a pH of 5.27, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a second mixture, and dispensing 100 μ L of the second mixture in a second well of the 96-well plate;

(4) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a third buffer consisting essentially of the sodium salt buffer, wherein the third buffer has a pH from 6.15 to 6.21, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a third mixture, and dispensing 100 μ L of the third mixture in a third well of the 96-well plate;

(5) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a fourth buffer consisting essentially of the sodium salt buffer, wherein the fourth buffer has a pH of 6.57, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a fourth mixture, and dispensing 100 μ L of the fourth mixture in a fourth well of the 96-well plate;

(6) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a fifth buffer consisting essentially of the sodium salt buffer, wherein the fifth buffer has a pH from 7.10 to 7.20, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a fifth mixture, and dispensing 100 μ L of the fifth mixture in a fifth well of the 96-well plate;

(7) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a sixth buffer consisting essentially of the sodium salt buffer, wherein the sixth buffer has a pH from 7.72 to 7.80, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining a sixth mixture, and dispensing 100 μ L of the sixth mixture in a sixth well of the 96-well plate;

(8) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of a seventh buffer consisting essentially of the sodium salt buffer, wherein the seventh buffer has a pH from 8.27 to 8.33, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide,

thereby obtaining a seventh mixture, and dispensing 100 μ L of the seventh mixture in a seventh well of the 96-well plate;

(9) admixing 7.5 μ L of the lipid/TNS mixture and 242.5 μ L of an eighth buffer consisting essentially of the sodium salt buffer, wherein the eighth buffer has a pH from 10.47 to 11.12, which has been adjusted with 12N hydrochloric acid or 6N sodium hydroxide, thereby obtaining an eighth mixture, and dispensing 100 μ L of the eighth mixture in an eighth well of the 96-well plate;

(10) measuring the fluorescence at a wavelength of 431 nm with an excitation wavelength of 322 nm and a cut-off below a wavelength of 420 nm of each of the first through eighth wells and an empty well of the 96-well plate, thereby obtaining a measured fluorescence for each of the empty well and the first through eighth wells;

(11) subtracting the fluorescence of the empty well from each of the measured fluorescences of the first through eighth wells, thereby obtaining a blank-subtracted fluorescence for each of the first through eighth mixtures;

(12) normalizing each of the blank-subtracted fluorescences of the first through eighth mixtures to the blank-subtracted fluorescence of the first mixture, thereby obtaining a relative fluorescence for each of the first through eighth mixtures, the relative fluorescence being 1 for the first mixture;

(13) obtaining a line of best fit of the pHs of the first through eighth buffers versus the respective relative fluorescences of the first through eighth mixtures; and

(14) determining the pKa as the pH on the line of best fit at which a relative fluorescence of 0.5 is obtained.

RESPONSE: Defendants admit that Claim 1 of the '694 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

137. Each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products comprises a “formulation.” See paragraphs 55–92, above; e.g., Exhibit 26 (July 12, 2022, EMA Comirnaty® (original BA.1) Assessment Report) at 5 (“The Bivalent vaccine is formulated in Tris/Sucrose[.]”); Exhibit 29 (March 2023, FDA Comirnaty® (bivalent BA.4/5) Fact Sheet and Prescribing Information), Prescribing Information at 52 (“The modRNA in the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is formulated in lipid particles[.]”); Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 4 (“The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs).”).

RESPONSE: Paragraph 137 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 137 purport to rely on Exhibit 26, Exhibit 29, and Exhibit 27, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

138. Each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products comprises “a first species of ribonucleic acid (RNA) molecules comprising a sequence that encodes a first immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 26 (July 12, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 6 (“The active substance tozinameran is already approved in the existing Comirnaty® conditional marketing authorization. No changes to the information related to tozinameran are proposed.”); Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 5 (“The active substance tozinameran is already approved for the original Comirnaty® vaccine formulations (EU/1/20/1528/001 -005). No changes to the information related to tozinameran are proposed.”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 138 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 138 purport to rely on Exhibit 26, Exhibit 27, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

139. Each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products comprises “a second species of RNA molecules comprising a sequence that encodes a second immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 26 (July 12, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 6 (“Riltozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1).”); Exhibit 27 (September 12, 2022, EMA Comirnaty® (bivalent BA.4/5) Assessment Report) at 5 (“Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).”).

RESPONSE: Paragraph 139 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 139 purport to rely on Exhibit 26 and Exhibit 27, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

140. Each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products comprises “lipids comprising: (a) a cationic lipid, (b) an anionic or a zwitterionic lipid, (c) a polyethylene glycol-conjugated (PEG-conjugated) lipid, and (d) cholesterol.” See paragraphs 55–92, above; *e.g.*, Exhibit 26 (July 12, 2022, EMA Comirnaty® (bivalent BA.1) Assessment Report) at 11 (identifying lipid ingredients); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert) at 53 (identifying lipid ingredients) ; Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 140 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 140 purport to rely on Exhibit 26, Exhibit 35, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

141. ALC-0315 is a “cationic lipid” that “comprises a tertiary amine.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine”); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an “[i]onizable cationic lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 141 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 141 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any

valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

142. DSPC is a “zwitterionic lipid.” *See, e.g.*, Exhibit 73 (DSPC Product Information, Polysciences) (“[DSPC] is a zwitterionic phospholipid that is used in the preparation of liposomes for transfection and drug delivery applications.”).

RESPONSE: Paragraph 142 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 142 purport to rely on Exhibit 73, that exhibit speaks for itself. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

143. ALC-0159 is a “polyethylene glycol-conjugated (PEG-conjugated) lipid.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 (“The ALC-0159 novel excipient is PEGylated lipid”); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) (“ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]”); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a “PEG-lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 143 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 143 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

144. On information and belief, the lipids of each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products “encapsulate at least half of the first species of RNA molecules and at least half of the second species of RNA molecules.” *See* paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 144 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 144 purport to rely on Exhibit 34 and Exhibit 72, those

exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

145. On information and belief, when employing the “fluorescent probe 6-(p-toluidino)-2-naphthalenesulfonic acid (TNS)” and following steps (1) to (14) of claim 1 of the ’694 patent to “obtain[] a relative fluorescence” in each of the described pH-buffered mixtures and “determining the pKa as the pH on the line of best fit at which a relative fluorescence of 0.5 is obtained,” the cationic lipid used in each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products—ALC-0315—exhibits a pKa falling between 6.07 and 7.6. *See, e.g.*, Exhibit 75 (McKenzie *et al.*, “mRNA synthesis and encapsulation in ionizable lipid nanoparticles,” *Current Protocols* 3, e898 (2023)) at 19 (reporting a pKa of 6.284 for ALC-0315 in a TNS assay); Exhibit 76 (International PCT Application Publication Number WO 2017/075531 A1) at 48 and 50, Table 3 (reporting a pKa of 6.09 for ALC-0315 (cationic lipid “No. 3”) in a TNS assay); Exhibit 77 (Tilstra *et al.*, “Iterative Design of Ionizable Lipids for Intramuscular mRNA Delivery,” *J. Am. Chem. Soc.* 145, 2294–2304 (2023) with supplementary information) at Figure S11 (reporting a pKa of 6.27 for ALC-0315 in a TNS assay).

RESPONSE: Paragraph 145 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 145 purport to rely on Exhibit 75, Exhibit 76, and Exhibit 77, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

146. Each of the Comirnaty® (bivalent BA.1) and Comirnaty® (bivalent BA.4/5) products is “immunogenic in vivo by eliciting an antibody response against the first immunogen and the second immunogen in vivo” at least when used in accordance with the FDA and EMA authorized and approved indications. *See* paragraphs 55–92, above; *e.g.*, Exhibit 24 (September 1, 2022, Pfizer press release) (“[T]he bivalent vaccine with mRNA encoding the wild-type and the BA.1 spike proteins provides [] neutralizing antibody titers against the Omicron BA.1 and BA.4/BA.5 sublineages[.]”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”).

RESPONSE: Paragraph 146 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 146 purport to rely on Exhibit 24 and Exhibit 25, those

exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

147. Defendants packaged, promoted, and sold Comirnaty® (bivalent BA.4/5) in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized indications. *See* paragraphs 75–98, above; *e.g.*, Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert).

RESPONSE: Paragraph 147 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 147 purport to rely on Exhibit 35, that exhibit speaks for itself. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

148. Defendants created and disseminated by means separate from the packaging and package inserts of Comirnaty® (bivalent BA.4/5), supporting materials, instructions, and/or technical information that instructed health care practitioners on the use of Comirnaty® (bivalent BA.4/5) in the United States in accordance with the FDA authorized indications. *See, e.g.*, Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September 22, 2022²⁴).

RESPONSE: Paragraph 140 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 140 purport to rely on Exhibit 79, that exhibit speaks for itself. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

149. Defendants have been and are aware that the use of Comirnaty® (bivalent BA.4/5) in the United States in accordance with the FDA authorized indications identified above in paragraphs 75–98 infringed at least exemplary claim 1 of the '694 patent.

²⁴ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

RESPONSE: Denied.

150. Defendants have been and are aware that healthcare providers used Comirnaty® (bivalent BA.4/5) in the United States in accordance with the FDA authorized indications identified above in paragraphs 75–98 and thereby infringed at least exemplary claim 1 of the '694 patent.

RESPONSE: Denied.

151. None of the Comirnaty® (bivalent BA.1) or Comirnaty® (bivalent BA.4/5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized indications identified above in paragraphs 75–98.

RESPONSE: Denied.

152. Defendants actively, knowingly, and specifically intended to induce, and induced, infringement of at least claim 1 of the '694 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, the Comirnaty® (bivalent BA.4/5) product to healthcare providers, with the knowledge and intent that healthcare providers would use the Comirnaty® (bivalent BA.4/5) products supplied by Defendants according to the FDA authorized infringing indications.

RESPONSE: Denied.

153. GSK has suffered and continues to suffer damages from Defendants' infringement of the '694 patent.

RESPONSE: Denied.

154. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '694 patent.

RESPONSE: Denied.

155. Defendants have had knowledge of the '694 patent and specific notice of its infringement at least since April 24, 2024, by communications between GSK and Defendants. See Exhibits 81–82.

RESPONSE: Paragraph 155 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 155 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

156. Defendants' infringement of the '694 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on April 24, 2024. *See id.*

RESPONSE: Denied.

157. Defendants' conduct in infringing the '694 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT III

(Infringement of the '534 Patent)

158. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

159. GSK Biologicals is the lawful owner by assignment of the '534 patent, which is entitled "Methods of Administering Lipid Formulations with Viral Immunogens" and was duly and legally issued by the U.S. Patent and Trademark Office on June 6, 2023. A true and correct copy of the '534 patent is attached as Exhibit 3. The patent application issuing into the '534 patent was published on April 28, 2022, as Publication No. US 2022/0125727 A1. *See* Exhibit 114.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,666,534 entitled "Methods of Administering Lipid Formulations with Viral Immunogens" on June 6, 2023, that Exhibit 3 purports to be a copy of the '534 patent, that Publication No. U.S. 2022/0125727 A1 was published on April 28, 2022 and issued into the '534 patent, and that Exhibit 114 purports to be a copy of Publication No. U.S. 2022/0125727 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

160. Each claim of the '534 patent is valid and enforceable.

RESPONSE: Denied.

161. Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '534 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty®

(bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '534 patent, without authority or license to do so, during the term of the '534 patent.

RESPONSE: Denied.

162. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '534 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '534 patent, without authority or license to do so, during the term of the '534 patent, knowing that those products constitute a material part of the inventions of the '534 patent, knowing that those products are especially made or adapted to infringe the '534 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

163. For example, on information and belief, the FDA authorized and approved uses for each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products satisfies each and every element of at least claim 1 of the '534 patent. Defendants' actions with respect to each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products have therefore infringed at least this exemplary claim of the '534 patent.

RESPONSE: Denied.

164. Claim 1 of the '534 patent recites:

A method of eliciting an immune response against an immunogen in a subject, the method comprising:

administering to the subject an immunologically effective unit dose of a formulation comprising:

ribonucleic acid (RNA) molecules comprising a sequence that encodes the immunogen, wherein the immunogen comprises a respiratory syncytial virus immunogen, an Epstein-Barr virus immunogen, a cytomegalovirus immunogen, a coronavirus spike polypeptide immunogen, an influenza virus A immunogen, a Varicella zoster virus immunogen, or a flavivirus immunogen; and

lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol;

wherein the lipids encapsulate at least half of the RNA molecules;
and

wherein the immune response against the immunogen comprises an
antibody response against the immunogen.

RESPONSE: Defendants admit that Claim 1 of the '534 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

165. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises a “formulation.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles[.]”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]”).

RESPONSE: Paragraph 165 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 165 purport to rely on Exhibit 34 and Exhibit 21, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

166. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “ribonucleic acid (RNA) molecules comprising a sequence that encodes [an] immunogen, wherein the immunogen comprises ... a coronavirus spike polypeptide immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 166 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 166 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses

contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

167. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol.” See paragraphs 55–92, above, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 167 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 167 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

168. ALC-0315 is a “tertiary amine cationic lipid.” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine”); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an “[i]onizable cationic lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 168 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 168 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

169. ALC-0159 is a “polyethylene glycol-conjugated (PEG-conjugated) lipid.” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 (“The ALC-0159 novel excipient is PEGylated lipid”); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) (“ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2

vaccine[.]”); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a “PEG-lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 169 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 169 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

170. On information and belief, the lipids of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products “encapsulate at least half of the mRNA molecules.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 170 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 170 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

171. Use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in accordance with the FDA authorized and approved indications comprises “administering to the subject an immunologically effective unit dose” that “elicit[s] an immune response” against “a coronavirus spike polypeptide immunogen” comprising “an antibody response against the immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® original Assessment Report) at 58 (“The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating,

“preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 171 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 171 purport to rely on Exhibit 21, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

172. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 172 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 172 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

173. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. See, *e.g.*, Exhibit 78 (www.comirnaty.com as preserved by

The Wayback Machine, August, 27, 2021²⁵); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022²⁶); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 173 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 173 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

174. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '534 patent.

RESPONSE: Denied.

175. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '534 patent.

RESPONSE: Denied.

176. None of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

177. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '534 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent),

²⁵ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

²⁶ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

178. GSK has suffered and continues to suffer damages from Defendants' infringement of the '534 patent.

RESPONSE: Denied.

179. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '534 patent.

RESPONSE: Denied.

180. Defendants have had knowledge of the '534 patent and specific notice of its infringement at least since April 24, 2024, by communications between GSK and Defendants. See Exhibits 81–82.

RESPONSE: Paragraph 180 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 180 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

181. Defendants' infringement of the '534 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on April 24, 2024. *See id.*

RESPONSE: Denied.

182. Defendants' conduct with respect to the '534 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT IV

(Infringement of the '401 Patent)

183. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

184. GSK Biologicals is the lawful owner by assignment of the '401 patent, which is entitled "Methods of Administering Lipid Formulations with Immunogens" and was duly and legally issued by the U.S. Patent and Trademark Office on September 26, 2023. A true and correct copy of the '401 patent is attached as Exhibit 4. The patent application issuing into the '401 patent was published on April 28, 2022, as Publication No. US 2022/0125724 A1. See Exhibit 115.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,766,401 entitled "Methods of Administering Lipid Formulations with Immunogens" on September 26, 2023, that Exhibit 4 purports to be a copy of the '401 patent, that Publication No. U.S. 2022/0125724 A1 was published on April 28, 2022 and issued into the '401 patent, and that Exhibit 115 purports to be a copy of Publication No. U.S. 2022/0125724 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

185. Each claim of the '401 patent is valid and enforceable.

RESPONSE: Denied.

186. Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '401 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '401 patent, without authority or license to do so, during the term of the '401 patent.

RESPONSE: Denied.

187. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '401 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '401 patent, without authority or license to do so, during the term of the '401 patent, knowing that those products constitute a material part of the inventions of the '401 patent, knowing that those products are especially made or adapted to infringe the '401 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

188. For example, on information and belief, the FDA authorized and approved uses for each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products satisfies each and every element of at least claim 1 of the '401 patent. Defendants' actions with respect to each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products have therefore infringed at least this exemplary claim of the '401 patent.

RESPONSE: Denied.

189. Claim 1 of the '401 patent recites:

A method of eliciting an immune response against an immunogen in a human or a cow, the method comprising:

administering to the human or the cow an immunologically effective unit dose of a formulation comprising:

RNA molecules comprising a sequence that encodes the immunogen; and

lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol; and

wherein the lipids encapsulate at least half of the RNA molecules; and the immune response against the immunogen comprises an antibody response against the immunogen.

RESPONSE: Defendants admit that Claim 1 of the '401 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

190. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises a "formulation." See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 ("The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles[.]"); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 ("The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]").

RESPONSE: Paragraph 190 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 190 purport to rely on Exhibit 34 and Exhibit 21, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and

enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

191. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “RNA molecules comprising a sequence that encodes [an] immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 191 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 191 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

192. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 192 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 192 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

193. ALC-0315 is a “tertiary amine cationic lipid.” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315

novel excipient is a cationic lipid containing a tertiary amine"); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an "[i]onizable cationic lipid"); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 193 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 193 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

194. ALC-0159 is a "polyethylene glycol-conjugated (PEG-conjugated) lipid." See, e.g., Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 ("The ALC-0159 novel excipient is PEGylated lipid"); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) ("ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]"); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a "PEG-lipid"); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 194 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 194 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

195. On information and belief, the lipids of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products "encapsulate at least half of the mRNA molecules." See paragraphs 55–92, above; e.g., Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 ("The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen."); see also Exhibit 72 (Schoenmaker (2021)) at 4 ("In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%."); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 195 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 195 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in

Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

196. Use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in accordance with the FDA authorized or approved uses comprises “administering to [a] human ... an immunologically effective unit dose” that “elicit[s] an immune response” against a coronavirus spike polypeptide “immunogen” comprising “an antibody response against the immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 196 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 196 purport to rely on Exhibit 21, Exhibit 25, Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

197. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 197 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 197 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

198. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. *See, e.g.*, Exhibit 78 (www.comirnaty.com as preserved by The Wayback Machine, August, 27, 2021²⁷); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022²⁸); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 198 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 198 purport to rely on Exhibit 78, Exhibit 79 and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

199. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '401 patent.

RESPONSE: Denied.

200. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent

²⁷ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

²⁸ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '401 patent.

RESPONSE: Denied.

201. None of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

202. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '401 patent by packaging, promoting, selling or otherwise supplying directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

203. GSK has suffered and continues to suffer damages from Defendants' infringement of the '401 patent.

RESPONSE: Denied.

204. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '401 patent.

RESPONSE: Denied.

205. Defendants have had knowledge of the '401 patent and specific notice of its infringement at least since April 24, 2024, by communications between GSK and Defendants. See Exhibits 81–82.

RESPONSE: Paragraph 205 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 205 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

206. Defendants' infringement of the '401 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on April 24, 2024. *See id.*

RESPONSE: Denied.

207. Defendants' conduct with respect to the '401 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT V

(Infringement of the '467 Patent)

208. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

209. GSK Biologicals is the lawful owner by assignment of the '467 patent, which is entitled "Lipid Formulations with Immunogens" and was duly and legally issued by the U. S. Patent and Trademark Office on October 17, 2023. A true and correct copy of the '467 patent is attached as Exhibit 5. The patent application issuing into the '467 patent was published on April 28, 2022, as Publication No. US 2022/0125722 A1. *See Exhibit 116.*

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,786,467 entitled "Lipid Formulations with Immunogens" on October 17, 2023, that Exhibit 5 purports to be a copy of the '467 patent, that Publication No. U.S. 2022/0125722 A1 was published on April 28, 2022 and issued into the '467 patent, and that Exhibit 116 purports to be a copy of Publication No. U.S. 2022/0125722 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph

210. Each claim of the '467 patent is valid and enforceable.

RESPONSE: Denied.

211. Defendants have directly infringed and continue to directly infringe one or more claims of the '467 patent under 35 U.S.C. § 271(a), either literally or under the doctrine of equivalents, by making, using, offering to sell, or selling, within the United States, or importing into the United States, each of the Accused Products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '467 patent, without authority or license to do so, during the term of the '467 patent.

RESPONSE: Denied.

212. In addition or in the alternative, Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '467 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '467 patent, without authority or license to do so, during the term of the '467 patent.

RESPONSE: Denied.

213. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '467 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Accused Products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '467 patent, without authority or license to do so, during the term of the '467 patent, knowing that those products constitute a material part of the inventions of the '467 patent, knowing that those products are especially made or adapted to infringe the '467 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

214. For example, on information and belief, each of the Accused Products satisfies each and every element of at least claim 1 of the '467 patent. Defendants' actions with respect to each of the Accused Products have therefore infringed at least this exemplary claim of the '467 patent.

RESPONSE: Denied.

215. Claim 1 of the '467 patent recites:

A formulation comprising:

ribonucleic acid (RNA) molecules comprising a sequence that

encodes an immunogen; and

lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol;

wherein the formulation is immunogenic in vivo by eliciting an antibody response against the immunogen in vivo;

wherein the lipids encapsulate at least half of the RNA molecules.

RESPONSE: Defendants admit that Claim 1 of the '467 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

216. Each of the Accused Products comprises a “formulation.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles[.]”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]”).

RESPONSE: Paragraph 216 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 216 purport to rely on Exhibit 34 and Exhibit 21, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

217. Each of the Accused Products comprises “ribonucleic acid (RNA) molecules comprising a sequence that encodes an immunogen.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 217 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 217 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

218. Each of the Accused Products comprises “lipids comprising a tertiary amine cationic lipid, a polyethylene glycol-conjugated (PEG-conjugated) lipid, and cholesterol.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent)

Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 218 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 218 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

219. ALC-0315 is a “tertiary amine cationic lipid.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine”); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an “[i]onizable cationic lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 219 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 219 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

220. ALC-0159 is a “polyethylene glycol-conjugated (PEG-conjugated) lipid.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 (“The ALC-0159 novel excipient is PEGylated lipid”); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) (“ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]”); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a “PEG-lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 220 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 220 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any

valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

221. Each of the Accused Products is “is immunogenic in vivo by eliciting an antibody response against the immunogen in vivo” at least when used in accordance with the FDA and EMA authorized and approved indications. See paragraphs 55–92, above at, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 24 (September 1, 2022, Pfizer press release) (“[T]he bivalent vaccine with mRNA encoding the wild-type and the BA.1 spike proteins provides [] neutralizing antibody titers against the Omicron BA.1 and BA.4/BA.5 sublineages[.]”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 221 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 221 purport to rely on Exhibit 21, Exhibit 24, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

222. On information and belief, the lipids of each of the Accused Products “encapsulate at least half of the RNA molecules.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 222 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 222 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in

Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

223. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 223 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 223 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

224. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. See, *e.g.*, Exhibit 78 (www.comirnaty.com as preserved by The Wayback Machine, August, 27, 2021²⁹); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022³⁰); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

²⁹ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

³⁰ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

RESPONSE: Paragraph 224 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 224 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

225. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '467 patent.

RESPONSE: Denied.

226. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '467 patent.

RESPONSE: Denied.

227. None of the Accused Products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

228. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '467 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

229. GSK has suffered and continues to suffer damages from Defendants' infringement of the '467 patent.

RESPONSE: Denied.

230. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '467 patent.

RESPONSE: Denied.

231. Defendants have had knowledge of the '467 patent and specific notice of its infringement at least since April 24, 2024, by communications between GSK and Defendants. See Exhibits 81–82.

RESPONSE: Paragraph 231 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 231 purport to rely on Exhibits 81–82, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

232. Defendants' infringement of the '467 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on April 24, 2024. *See id.*

RESPONSE: Denied.

233. Defendants' conduct with respect to the '467 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT VI

(Infringement of the '422 Patent)

234. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

235. GSK Biologicals is the lawful owner by assignment of the '422 patent, which is entitled "PEGylated Liposomes for Delivery of Immunogen-Encoding RNA" and was duly and legally issued by the U.S. Patent and Trademark Office on September 19, 2023. A true and correct copy of the '422 patent is attached as Exhibit 83. The patent application issuing into the '422 patent was published on July 23, 2020, as Publication No. US 2020/0230058 A1. *See* Exhibit 104.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,759,422 entitled "PEGylated Liposomes for Delivery of Immunogen-Encoding RNA"

on September 19, 2023, that Exhibit 83 purports to be a copy of the '422 patent, that Publication No. U.S. 2020/0230058 A1 was published on July 23, 2020 and issued into the '422 patent, and that Exhibit 104 purports to be a copy of Publication No. U.S. 2020/0230058 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

236. Each claim of the '422 patent is valid and enforceable.

RESPONSE: Denied.

237. Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '422 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '422 patent, without authority or license to do so, during the term of the '422 patent.

RESPONSE: Denied.

238. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '422 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '422 patent, without authority or license to do so, during the term of the '422 patent, knowing that those products constitute a material part of the inventions of the '422 patent, knowing that those products are especially made or adapted to infringe the '422 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

239. For example, on information and belief, the FDA authorized and approved uses for each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products satisfies each and every element of at least claim 1 of the '422 patent. Defendants' actions with respect to each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products have therefore infringed at least this exemplary claim of the '422 patent.

RESPONSE: Denied.

240. Claim 1 of the '422 patent recites:

A method for raising a protective immune response in a vertebrate, the method comprising administering to the vertebrate an effective amount of a liposome within which at least one ribonucleic acid (RNA) that encodes an immunogen of interest is encapsulated, wherein the immunogen of interest elicits in the vertebrate a protective immune response against a bacterium, a virus, a fungus, a parasite, or an allergen, wherein the liposome comprises at least one lipid that includes a polyethylene glycol (PEG) moiety, wherein the PEG moiety is present on at least the exterior of the liposome, wherein the average molecular mass of the PEG moiety is between 1 kDa and 3 kDa, wherein the at least one lipid that includes the PEG moiety is not a 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)].

RESPONSE: Defendants admit that Claim 1 of the '422 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

241. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “a liposome.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]”); *see also* Exhibit 72 (Schoenmaker (2021)); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 241 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 241 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

242. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “at least one ribonucleic acid (RNA) that encodes an immunogen of interest.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent)

Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 242 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 242 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

243. The liposomes of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprise “at least one lipid that includes a polyethylene glycol (PEG) moiety.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 243 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 243 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

244. ALC-0159 (2-[(polyethylene glycol)-2000]-N,N ditetradecylacetamide) is a “lipid that includes a polyethylene glycol (PEG) moiety, wherein the PEG moiety is present on at least the exterior of the liposome, wherein the average molecular mass of the PEG moiety is between 1 kDa and 3 kDa, wherein the at least one lipid that includes the PEG moiety is not a 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)].” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 (“The ALC-0159 novel excipient is PEGylated lipid ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface.”); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) (“ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]”); Exhibit 72 (Schoenmaker (2021))

at 8 (“The PEG-molecules at the surface prevent the individual LNPs from aggregating.”), Fig. 6 (identifying ALC-0159 to be a “PEG-lipid n~45 (PEG2000)”; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 244 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 244 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

245. On information and belief, the “at least one ribonucleic acid (RNA)” is “encapsulated” “within” the liposomes of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products. See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 245 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 245 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

246. Use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in accordance with the FDA authorized or approved uses comprises “[a] method for raising a protective immune response in a vertebrate, the method comprising administering to the vertebrate an effective amount” of each product “wherein the immunogen of interest elicits in the vertebrate, a protective immune response against ... a virus.” See paragraphs 55–92, above; *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing anti body and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA

Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 246 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 246 purport to rely on Exhibit 21, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

247. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 247 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 247 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

248. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. See, *e.g.*, Exhibit 78 (www.comirnaty.com as preserved by

The Wayback Machine, August, 27, 2021³¹); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022³²); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 248 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 248 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

249. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '422 patent.

RESPONSE: Denied.

250. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '422 patent.

RESPONSE: Denied.

251. None of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

252. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '422 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent),

³¹ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

³² Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/eua-bivalent>; preserved on April 5, 2024.

Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

253. GSK has suffered and continues to suffer damages from Defendants' infringement of the '422 patent.

RESPONSE: Denied.

254. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '422 patent.

RESPONSE: Denied.

255. Defendants have had knowledge of the '422 patent and specific notice of its infringement at least since August 13, 2024, by communications between GSK and Defendants. See Exhibits 117–118.

RESPONSE: Paragraph 255 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 255 purport to rely on Exhibits 117–118, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

256. Defendants' infringement of the '422 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on August 13, 2024. See *id.*

RESPONSE: Denied.

257. Defendants' conduct with respect to the '422 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT VII

(Infringement of the '475 Patent)

258. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

259. GSK Biologicals is the lawful owner by assignment of the '475 patent, which is entitled "Immunisation of Large Mammals with Low Doses of RNA" and was duly and legally issued by the U.S. Patent and Trademark Office on May 23, 2023. A true and correct copy of the '475 patent is attached as Exhibit 84. The patent application issuing into the '475 patent was published on February 13, 2020, as Publication No. US 2020/0048636 A1. See Exhibit 119.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,655,475 entitled "Immunisation of Large Mammals with Low Doses of RNA" on May 23, 2023, that Exhibit 84 purports to be a copy of the '475 patent, that Publication No. U.S. 2020/0048636 A1 published on February 13, 2020 and issued into the '475 patent, and that Exhibit 119 purports to be a copy of Publication No. U.S. 2020/0048636 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

260. Each claim of the '475 patent is valid and enforceable.

RESPONSE: Denied.

261. Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '475 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '475 patent, without authority or license to do so, during the term of the '475 patent.

RESPONSE: Denied.

262. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '475 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '475 patent, without authority or license to do so, during the term of the '475 patent, knowing that those products constitute a material part of the inventions of the '475 patent, knowing that those products are especially made or adapted to infringe the '475 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

263. For example, on information and belief, the FDA authorized and approved uses for each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products satisfies each and every element of at least claim 1 of the '475 patent. Defendants' actions with respect to each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products have therefore infringed at least this exemplary claim of the '475 patent.

RESPONSE: Denied.

264. Claim 1 of the '475 patent recites:

A method of eliciting an antibody response against an immunogen by an immune system in a large mammal, the method comprising administering to the large mammal at least two unit doses; each unit dose comprising a composition comprising liposomes and messenger ribonucleic acid (mRNA) molecules; the mRNA molecules comprising a poly-adenosine monophosphate (poly(A)) tail and a sequence that encodes the immunogen; the immunogen comprising a respiratory syncytial virus (RSV) surface fusion glycoprotein (F protein) immunogen, an Epstein-Barr virus (EBV) glycoprotein immunogen, a cytomegalovirus (CMV) glycoprotein immunogen, a human papillomavirus (HPV) 16 immunogen, a coronavirus spike polypeptide immunogen, an influenza virus immunogen, a Varicella zoster virus (VZV) glycoprotein immunogen, or a flavivirus immunogen; each unit dose comprising between 2 µg and 100 µg of the mRNA molecules; the at least two unit doses being sequential and at least 1 week apart; the administering comprising contacting the composition with skeletal muscle; the liposomes comprising a cationic lipid comprising a tertiary amine; the liposomes encapsulating at least half of the mRNA molecules; and the large mammal being a human, a horse, a cow, or a pig.

RESPONSE: Defendants admit that Claim 1 of the '475 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

265. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises "a composition comprising liposomes." *See paragraphs 55–92, above; e.g., Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 ("The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen."); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 ("The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]"); see also Exhibit 72 (Schoenmaker (2021)); D.I. 22 at 87 (¶ 56).*

RESPONSE: Paragraph 265 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 265 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

266. The liposomes of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprise “a cationic lipid comprising a tertiary amine.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 266 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 266 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

267. ALC-0315 is a “cationic lipid comprising a tertiary amine.” See, *e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine”); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an “[i]onizable cationic lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 267 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 267 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

268. The compositions of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprise “messenger ribonucleic acid (mRNA) molecules; the mRNA molecules comprising a poly-adenosine monophosphate (poly(A)) tail and a sequence that encodes the immunogen; the immunogen comprising ... a coronavirus spike polypeptide immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 268 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 268 purport to rely on Exhibit 34, Exhibit 21 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

269. On information and belief, the liposomes of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products “encapsulat[e] at least half of the mRNA molecules.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 269 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 269 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

270. Use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in accordance with the FDA authorized

or approved uses comprises “[a] method of eliciting an antibody response against an immunogen by an immune system in a large mammal, the method comprising administering to the large mammal at least two unit doses” of the composition of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, “each unit dose comprising between 2 µg and 100 µg of the mRNA molecules; the at least two unit doses being sequential and at least 1 week apart; the administering comprising contacting the composition with skeletal muscle; ... and the large mammal being a human.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 1–7, 19 (Sections 1. Indications and Usage, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert) at 4–9, 52 (Sections 1. Emergency Use Authorization, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert) at 2, 20 (Sections 1. Indications and Usage, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing anti body and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 270 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 270 purport to rely on Exhibit 34, Exhibit 35, Exhibit 33, Exhibit 21, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

271. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet

and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 271 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 271 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

272. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. *See, e.g.*, Exhibit 78 (www.comirnaty.com as preserved by The Wayback Machine, August, 27, 2021³³); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022³⁴); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 272 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 272 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

273. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '475 patent.

³³ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

³⁴ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/euabivalent>; preserved on April 5, 2024.

RESPONSE: Denied.

274. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '475 patent.

RESPONSE: Denied.

275. None of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

276. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '475 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

277. GSK has suffered and continues to suffer damages from Defendants' infringement of the '475 patent.

RESPONSE: Denied.

278. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '475 patent.

RESPONSE: Denied.

279. Defendants have had knowledge of the '475 patent and specific notice of its infringement at least since August 13, 2024, by communications between GSK and Defendants. *See Exhibits 117–118.*

RESPONSE: Paragraph 279 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 279 purport to rely on Exhibits 117–118, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and

enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

280. Defendants' infringement of the '475 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on August 13, 2024. *See id.*

RESPONSE: Denied.

281. Defendants' conduct with respect to the '475 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

COUNT VIII

(Infringement of the '660 Patent)

282. GSK incorporates each of the preceding paragraphs as if fully set forth herein.

RESPONSE: Defendants incorporate by reference each of their preceding responses.

283. GSK Biologicals is the lawful owner by assignment of the '660 patent, which is entitled "Immunisation of Large Mammals with Low Doses of RNA" and was duly and legally issued by the U.S. Patent and Trademark Office on December 26, 2023. A true and correct copy of the '660 patent is attached as Exhibit 85. The patent application issuing into the '660 patent was published on April 13, 2023, as Publication No. US 2023/0112809 A1. *See* Exhibit 120.

RESPONSE: Defendants admit that the U.S. Patent and Trademark Office issued U.S. Pat. No. 11,851,660 entitled "Immunisation of Large Mammals with Low Doses of RNA" on December 26, 2023, that Exhibit 85 purports to be a copy of the '660 patent, that Publication No. U.S. 2023/0112809 A1 published on April 13, 2023 and issued into the '660 patent, and that Exhibit 120 purports to be a copy of Publication No. U.S. 2023/0112809 A1, but deny that the patent is valid, enforceable, or infringed by Defendants. Defendants deny any remaining allegations of this Paragraph.

284. Each claim of the '660 patent is valid and enforceable.

RESPONSE: Denied.

285. Defendants have induced, and continue to induce, direct infringement by third parties of one or more claims of the '660 patent under 35 U.S.C. § 271(b), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '660 patent, without authority or license to do so, during the term of the '660 patent.

RESPONSE: Denied.

286. In addition or in the alternative, Defendants have contributed, and continue to contribute, to the direct infringement by third parties of one or more claims of the '660 patent under 35 U.S.C. § 271(c), either literally or under the doctrine of equivalents, by making, selling and/or offering for sale in the United States, and/or importing into the United States, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products embodying GSK Biologicals's patented inventions as disclosed by and claimed in the '660 patent, without authority or license to do so, during the term of the '660 patent, knowing that those products constitute a material part of the inventions of the '660 patent, knowing that those products are especially made or adapted to infringe the '660 patent, and knowing that those products are not staple articles or commodities of commerce suitable for substantial non-infringing use.

RESPONSE: Denied.

287. For example, on information and belief, the FDA authorized and approved uses for each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products satisfies each and every element of at least claim 1 of the '660 patent. Defendants' actions with respect to each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products have therefore infringed at least this exemplary claim of the '660 patent.

RESPONSE: Denied.

288. Claim 1 of the '660 patent recites:

A method of eliciting an antibody response against a coronavirus spike polypeptide immunogen by an immune system in a large mammal, the method comprising administering intramuscularly to the large mammal at least two unit doses, each unit dose comprising a composition comprising lipid particles and messenger ribonucleic acid (mRNA) molecules; the at least two unit doses being sequential and at least 1 week apart; the administering comprising contacting the composition with skeletal muscle; the mRNA molecules comprising a sequence that encodes the coronavirus spike polypeptide immunogen; each unit dose comprising between 2 µg and 100 µg of the mRNA molecules; the lipid particles comprising: i) a polyethylene glycol-ylated lipid, ii) cholesterol, iii) an anionic

phospholipid or a zwitterionic phospholipid, and iv) a cationic lipid; the cationic lipid comprising a tertiary amine; the lipid particles encapsulating at least half of the mRNA molecules; and the large mammal being a human or a cow.

RESPONSE: Defendants admit that Claim 1 of the '660 patent appears to include the above language. Defendants otherwise deny the remaining allegations of this Paragraph.

289. Each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprises “a composition comprising lipid particles.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles[.]”); *see also* Exhibit 72 (Schoenmaker (2021)); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 289 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 289 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

290. The lipid particles of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprise “: i) a polyethylene glycol-ylated lipid, ii) cholesterol, iii) an anionic phospholipid or a zwitterionic phospholipid, and iv) a cationic lipid; the cationic lipid comprising a tertiary amine.” See paragraphs 55–92, above at, *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (identifying lipid ingredients); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 290 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 290 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and

enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

291. ALC-0159 (2-[(polyethylene glycol)-2000]-N,N ditetradecylacetamide) is a “polyethylene glycol-ylated lipid.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 24 (“The ALC-0159 novel excipient is PEGylated lipid”); Exhibit 74 (ALC-0159 Product Information, Echelon Biosciences) (“ALC-0159 is a PEGylated lipid which has been used to form lipid nanoparticles for delivery of RNA. ALC-0159 is one of the components in the BNT162b2 vaccine[.]”); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (identifying ALC-0159 to be a “PEG-lipid n~45 (PEG2000)”).

RESPONSE: Paragraph 291 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 291 purport to rely on Exhibit 21, Exhibit 74, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

292. DSPC is a “zwitterionic phospholipid.” *See, e.g.*, Exhibit 73 (DSPC Product Information, Polysciences) (“[DSPC] is a zwitterionic phospholipid that is used in the preparation of liposomes for transfection and drug delivery applications.”).

RESPONSE: Paragraph 292 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 292 purport to rely on Exhibit 73, that exhibit speaks for itself. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

293. ALC-0315 is a “cationic lipid; the cationic lipid comprising a tertiary amine.” *See, e.g.*, Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 23–24 (“The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine”); Exhibit 71 (ALC-0315 Product Information, Cayman Chemical) (providing structure); Exhibit 72 (Schoenmaker (2021)) at Fig. 6 (providing structure and identifying ALC-0315 as an “[i]onizable cationic lipid”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 293 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 293 purport to rely on Exhibit 21, Exhibit 71, and Exhibit 72, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any

valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

294. The compositions of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products comprise “messenger ribonucleic acid (mRNA) molecules; ... the mRNA molecules comprising a sequence that encodes the coronavirus spike polypeptide immunogen.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“COMIRNATY ... contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2.”); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 15 (“The active substance consists of ... mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2[.]”); Exhibit 72 (Schoenmaker (2021)) at 2–4; D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 294 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 294 purport to rely on Exhibit 34, Exhibit 21, and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

295. On information and belief, the lipid particles of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products “encapsulat[e] at least half of the mRNA molecules.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 19 (“The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 antigen.”); *see also* Exhibit 72 (Schoenmaker (2021)) at 4 (“In mRNA-LNP formulations, such as those used in mRNA vaccines ... encapsulation efficiencies ... are typically > 90%.”); D.I. 22 at 87 (¶ 56).

RESPONSE: Paragraph 295 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 295 purport to rely on Exhibit 34 and Exhibit 72, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

296. Use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in accordance with the FDA authorized or approved uses comprises “[a] method of eliciting an antibody response against a coronavirus spike polypeptide immunogen by an immune system in a large mammal, the method comprising administering intramuscularly to the large mammal at least two unit doses” of the composition of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, “the at least two unit doses being sequential and at least 1 week apart; the administering comprising contacting the composition with skeletal muscle; ... each unit dose comprising between 2 µg and 100 µg of the mRNA molecules; ... and the large mammal being a human.” See paragraphs 55–92, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent) Package Insert) at 1–7, 19 (Sections 1. Indications and Usage, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert) at 4–9, 52 (Sections 1. Emergency Use Authorization, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert) at 2, 20 (Sections 1. Indications and Usage, 2. Dosage and Administration, 3. Dosage Forms and Strengths, 11. Description); Exhibit 21 (February 19, 2021, EMA Comirnaty® (original monovalent) Assessment Report) at 58 (“The vaccine elicits both neutralizing anti body and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.”); Exhibit 25 (November 4, 2022, Pfizer press release) (“Among the overall study population who received the Omicron BA.4/BA.5-adapted bivalent vaccine, there was a substantially higher increase in Omicron BA.4/BA.5-neutralizing antibody titers compared to pre-booster levels.”); Exhibit 64 (September 11, 2023, FDA Comirnaty® (monovalent XBB.1.5) EUA Review Memo) at 17–18 (extrapolating immunological response from the prior Comirnaty® COVID-19 vaccine products and stating, “preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.”).

RESPONSE: Paragraph 296 states a legal conclusion to which no response is required.

To the extent the allegations of Paragraph 296 purport to rely on Exhibit 34, Exhibit 35, Exhibit 33, Exhibit 21, Exhibit 25, and Exhibit 64, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 55 through 92. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

297. Defendants packaged, promoted, and sold, and continue to package promote and sell, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States with FDA-approved packaging and package inserts comprising labeling and prescribing information that instruct health care practitioners on their use in accordance with the FDA authorized and approved indications. See paragraphs 75–98, above; *e.g.*, Exhibit 34 (April 2023, FDA Comirnaty® (original monovalent)

Package Insert); Exhibit 35 (July 14, 2023, FDA Comirnaty® (bivalent BA.4/5) EUA Fact Sheet and Package Insert); Exhibit 33 (September 2023, FDA Comirnaty® (monovalent XBB.1.5) Package Insert).

RESPONSE: Paragraph 297 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 297 purport to rely on Exhibit 34, Exhibit 35, and Exhibit 33, those exhibits speak for themselves. Defendants incorporate by reference their responses contained in Paragraphs 75 through 98. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

298. Defendants created and disseminated, and continue to create and disseminate, by means separate from the packaging and package inserts of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products, supporting materials, instructions, and/or technical information that instruct health care practitioners on the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications. *See, e.g.*, Exhibit 78 (www.comirnaty.com as preserved by The Wayback Machine, August, 27, 2021³⁵); Exhibit 79 (www.comirnaty.com/eua-bivalent as preserved by The Wayback Machine, September, 22, 2022³⁶); Exhibit 80 (www.comirnaty.com/eua-six-months-to-eleven-years; preserved April 5, 2024).

RESPONSE: Paragraph 298 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 298 purport to rely on Exhibit 78, Exhibit 79, and Exhibit 80, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

299. Defendants have been and are aware that the use of each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5)

³⁵ Available at <https://web.archive.org/web/20210827220339/https://www.comirnaty.com/>; preserved on April 5, 2024.

³⁶ Available at <https://web.archive.org/web/20220922181232/https://www.comirnaty.com/euabivalent>; preserved on April 5, 2024.

products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 infringes at least exemplary claim 1 of the '660 patent.

RESPONSE: Denied.

300. Defendants have been and are aware that healthcare providers use each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products in the United States in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98 and thereby infringe at least exemplary claim 1 of the '660 patent.

RESPONSE: Denied.

301. None of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products is a staple article or commodity of commerce suitable for use in the United States other than in accordance with the FDA authorized and approved indications identified above in paragraphs 75–98.

RESPONSE: Denied.

302. Defendants actively, knowingly, and specifically intended to induce, and induced, and continue to actively, knowingly, and specifically intend to induce, and induce, infringement of at least claim 1 of the '660 patent by packaging, promoting, selling or otherwise supplying, directly or indirectly, each of the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products to healthcare providers, with the knowledge and intent that healthcare providers will use the Comirnaty® (original monovalent), Comirnaty® (bivalent BA.4/5), and Comirnaty® (monovalent XBB.1.5) products supplied by Defendants according to the FDA authorized and approved infringing indications.

RESPONSE: Denied.

303. GSK has suffered and continues to suffer damages from Defendants' infringement of the '660 patent.

RESPONSE: Denied.

304. GSK is entitled to an award of monetary damages, including a reasonable royalty, for Defendants' infringement of the '660 patent.

RESPONSE: Denied.

305. Defendants have had knowledge of the '660 patent and specific notice of its infringement at least since August 13, 2024, by communications between GSK and Defendants. See Exhibits 117–118.

RESPONSE: Paragraph 305 states a legal conclusion to which no response is required. To the extent the allegations of Paragraph 305 purport to rely on Exhibits 117–118, those exhibits speak for themselves. Defendants deny that the Accused Products infringe any valid and enforceable claim of the Patents-in-Suit. Defendants otherwise deny the remaining allegations of this Paragraph.

306. Defendants’ infringement of the ’660 patent has been and continues to be willful and deliberate at least since they received specific notice of their infringement from GSK on August 13, 2024. *See id.*

RESPONSE: Denied.

307. Defendants’ conduct with respect to the ’660 patent makes this case exceptional under 35 U.S.C. § 285.

RESPONSE: Denied.

PRAYER FOR RELIEF

Defendants deny all allegations not expressly admitted herein. The remainder of Plaintiffs’ First Amended Complaint is a prayer for relief and does not require a response. To the extent any response is required, Defendants deny that Plaintiffs are entitled to any of the remedies or relief included in clauses (A) through (H) of Plaintiffs’ Prayer for Relief.

DEMAND FOR JURY TRIAL

Defendants join Plaintiffs’ request for a trial by jury on all claims so triable in this action.

AFFIRMATIVE DEFENSES

Further answering the First Amended Complaint, Defendants assert the following defenses without assuming any burden that they would not otherwise have, including without admitting or acknowledging that they bear the burden of proof as to any of them. Defendants reserve the right to amend their answer in accordance with the Federal Rules of Civil Procedure and Local Civil

Rules of the U.S. District Court for the District of Delaware to assert additional defenses as further information is obtained.

FIRST AFFIRMATIVE DEFENSE
(NON-INFRINGEMENT OF THE ASSERTED PATENTS)

Defendants have not infringed any valid and enforceable claim of the Patents-in-Suit, either directly or indirectly, and/or either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(INVALIDITY OF THE ASSERTED PATENTS)

Each and every claim of the Patents-in-Suit is invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, 112 and/or 256 and/or any other judicially created requirements for patentability and enforceability of patent and/or in view of the defenses recognized in 35 U.S.C. § 282.

THIRD AFFIRMATIVE DEFENSE
(PATENT MISUSE)

Plaintiffs have sought to enforce the Patents-in-Suit for products and acts that Plaintiffs know are outside the claims of the Patents-in-Suit, rendering the Patents-in-Suit unenforceable on account of patent misuse.

FOURTH AFFIRMATIVE DEFENSE
(FAILURE TO STATE A CLAIM)

Plaintiffs' First Amended Complaint fails to state a claim on which relief can be granted.

FIFTH AFFIRMATIVE DEFENSE
(PROSECUTION LACHES)

Plaintiffs are barred by the doctrine of prosecution laches from enforcing the Patents-in-Suit against Defendants, as Plaintiffs unreasonably and inexcusably delayed prosecuting the patent applications that led to the Patents-in-Suit, prejudicing Defendants.

SIXTH AFFIRMATIVE DEFENSE
(NO WILLFUL INFRINGEMENT)

Defendants have not willfully infringed, and do not willfully infringe, any valid and enforceable claim of any of the Patents-in-Suit.

SEVENTH AFFIRMATIVE DEFENSE
(NO EXCEPTIONAL CASE)

Defendants' actions in defending this case or otherwise do not give rise to an exceptional case in Plaintiffs' favor under 35 U.S.C. § 285.

EIGHTH AFFIRMATIVE DEFENSE
(PROSECUTION DISCLAIMER AND ESTOPPEL)

Plaintiffs are barred, based on statements, representations, and admissions made during prosecution of the patent applications resulting in the Patents-in-Suit or related patent applications, from asserting any interpretation of any valid and enforceable claims of the Patents-in-Suit that would be broad enough to cover any Accused Product alleged to infringe the Patents-in-Suit, either literally or by application of the doctrine of equivalents, or under any theory of infringement.

NINTH AFFIRMATIVE DEFENSE
(LACK OF STANDING)

Plaintiffs do not hold all substantial right, title, and interest to the Patents-in-Suit and lack standing to bring or maintain this lawsuit in connection with the Patents-in-Suit. Plaintiffs have failed to adequately plead or prove that each Plaintiff has ownership, control, and/or exclusive rights to the Patents-in-Suit in their First Amended Complaint.

TENTH AFFIRMATIVE DEFENSE
(ESTOPPEL, WAIVER, ACQUIESCENCE, AND UNCLEAN HANDS)

Plaintiffs' claims and/or requested relief are barred by one or more of the doctrines of estoppel, waiver, acquiescence, and unclean hands from enforcing or claiming damages with respect to any claim of the Patents-in-Suit.

ELEVENTH AFFIRMATIVE DEFENSE
(35 U.S.C. § 271(e)(1))

Aspects of Defendants’ alleged infringement of the Asserted Patents are reasonably related to Defendants’ development and submission of information to the FDA for the Emergency Use Authorization and the Biologics License Application regarding Comirnaty®, and such claims against Defendants are barred by the safe harbor of 35 U.S.C. § 271(e)(1).

TWELFTH AFFIRMATIVE DEFENSE
(LIMITATIONS ON DAMAGES)

Pursuant to the requirements of 35 U.S.C. §§ 286–287, GSK’s ability to recover any purported damages for any alleged infringement is limited or barred.

THIRTEENTH AFFIRMATIVE DEFENSE
(NO COSTS)

Plaintiffs are barred by 35 U.S.C. § 288 from recovering any costs associated with this action.

FOURTEENTH AFFIRMATIVE DEFENSE
(ADDITIONAL DEFENSES)

Defendants reserve the right to assert further defenses in the event that discovery indicates that such defenses would be appropriate.

COUNTERCLAIMS

Pursuant to Rule 13 of the Federal Rules of Civil Procedure, Pfizer Inc. (“Pfizer”) and Pharmacia & Upjohn Co. LLC (“Pharmacia”) (collectively, “Pfizer”) and BioNTech SE, BioNTech Manufacturing GmbH (“BioNTech Manufacturing”), and BioNTech US Inc. (“BioNTech US”) (collectively, “BioNTech,” and together with Pfizer, “Counterclaimants” or “Defendants”), by and through their attorneys, bring the following Counterclaims against GlaxoSmithKline Biologicals SA (“GSK Biologicals”) and GlaxoSmithKline LLC (“GSK LLC”) (collectively, “GSK” or “Counterclaim-Defendants” or “Plaintiffs”):

1. Counterclaimants on personal knowledge as to their own acts, and on information and belief as to all others based on their own and their attorneys' investigation, and without admitting the allegations of Counterclaim-Defendants other than those expressly admitted herein, bring the following Counterclaims against GSK for declaratory judgment that United States Patent Nos. 11,638,693 (the "'693 Patent"), 11,638,694 (the "'694 Patent"), 11,666,534 (the "'534 Patent"), 11,766,401 (the "'401 Patent"), 11,786,467 (the "'467 Patent"), 11,759,422 (the "'422 Patent"), 11,655,475 (the "'475 Patent"), and 11,851,660 (the "'660 Patent") (collectively, the "Asserted Patents" or "Patents-in-Suit") are invalid, unenforceable, and not infringed by Counterclaimants.

2. These Counterclaims are brought by BioNTech and Pfizer who partnered together, and continue to work together, to address the greatest public health threat the United States and the world has faced in at least a century: the COVID-19 pandemic. Now, BioNTech and Pfizer must also face threats of a groundless patent infringement suit by a company, GSK, who was unable to bring to market any product in the U.S. to help in the fight against COVID-19. Instead, GSK looked to a patent portfolio it had previously acquired from Novartis AG, located a pending family that had been in prosecution for over a decade, and filed new applications in an attempt to create claims that would encompass Pfizer and BioNTech's vaccine after the details of that vaccine became publicly available.

3. BioNTech and Pfizer partnered together to develop, manufacture, and secure regulatory approval for a vaccine that proved to be effective in preventing severe disease, hospitalization, and death from COVID-19 infection. BioNTech and Pfizer did so at great risk to their companies, by investing considerable sums of money and countless hours in an effort to address this global pandemic. BioNTech and Pfizer successfully developed a product, proved its

efficacy, established global manufacturing and supply chains, and gained regulatory approval in record time. Through their efforts they were able to help the United States and the world begin to move past the COVID-19 public health crisis.

4. Unlike BioNTech's and Pfizer's efforts, GSK's failed. Although GSK's First Amended Complaint repeatedly refers to the alleged innovations of the "Mandl team," neither that team nor anyone at GSK marketed a COVID-19 vaccine for the U.S.

5. Further, the only people from the "Mandl team" identified as purported inventors on the applications that led to the Asserted Patents are Andrew Geall for each Asserted Patent and Ayush Verma for the '422 Patent. None of the Asserted Patents list Mandl or any other members of the "Mandl team" as an inventor.

6. In an attempt to profit from the success of BioNTech and Pfizer through threats of patent infringement, GSK began to prosecute the applications to obtain the patents asserted in its original Complaint after detailed information regarding Pfizer and BioNTech's vaccine was publicly known.

7. The patents asserted in GSK's original Complaint only describe liposomes and self-replicating RNA. They do not describe the lipid nanoparticle formulation or mRNA of Pfizer and BioNTech's COVID-19 vaccine.

8. Despite seeing Defendants' Answer, Affirmative Defenses, and Counterclaims in response to its original Complaint, GSK has not attempted to address the flaws concerning the original patents asserted that only describe liposomes and self-replicating RNA. Instead, GSK has continued to expand the scope of this litigation by filing a First Amended Complaint to add three patents that issued before the original Complaint was filed—patents that GSK also began to

actively prosecute only after information regarding Pfizer and BioNTech's vaccine was publicly known.

9. The three new patents asserted in GSK's First Amended Complaint are similarly flawed. They only describe liposomes and self-replicating RNA, and they do not describe the lipid nanoparticle formulation or mRNA of Pfizer and BioNTech's COVID-19 vaccine.

10. GSK is attempting to expand the scope of the Asserted Patents beyond anything that was invented by the Mandl team, Andrew Geall, or Ayush Verma to accuse Pfizer and BioNTech's vaccine of infringement.

11. GSK is seeking damages for a product that it did not invent.

12. BioNTech and Pfizer bring these Counterclaims to resolve GSK's meritless allegations.

13. Counterclaimants repeat and incorporate by reference each of the foregoing paragraphs of Defendants' Answer, Affirmative Defenses, and Counterclaims in Response to First Amended Complaint for Patent Infringement, as if fully set forth herein.

THE PARTIES

14. Pfizer is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 66 Hudson Boulevard East, New York, New York 10001.

15. Pharmacia is a limited liability company organized and existing under the laws of the State of Delaware, with its principal place of business at 100 Route 206 N. Peapack, New Jersey 07977.

16. BioNTech SE is a corporation organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, D-55131 Mainz, Germany.

17. BioNTech Manufacturing GmbH is a limited liability company organized and existing under the laws of Germany, with its principal place of business at An der Goldgrube 12, D-55131 Mainz, Germany.

18. BioNTech US Inc. is a corporation organized and existing under the laws of Delaware, with its principal place of business at 40 Erie St., Suite 110, Cambridge, MA 02139.

19. According to its First Amended Complaint, GSK Biologicals is a corporation organized and existing under the laws of Belgium, with its principal place of business at Avenue Fleming 20, 1300 Wavre, Belgium.

20. According to its First Amended Complaint, GSK LLC is a limited liability corporation organized and existing under the laws of Delaware, with its principal place of business at 2929 Walnut Street, Suite 1700, Philadelphia, PA 19104.

JURISDICTION AND VENUE

21. This Court has subject matter jurisdiction over these Counterclaims for declaratory judgment pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202 based on an actual controversy among the parties arising under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

22. Personal jurisdiction over GSK Biologicals is proper because, among other things, it has consented to the personal jurisdiction of the Court by commencing its action for patent infringement in this judicial district, as set forth in its First Amended Complaint.

23. Personal jurisdiction over GSK LLC is proper because, among other things, it has consented to the personal jurisdiction of the Court by commencing its action for patent infringement in this judicial district, as set forth in its First Amended Complaint.

24. Venue is proper in this judicial district based on the choice of forum by GSK Biologicals and GSK LLC and under 28 U.S.C. § 1391(b)–(c).

25. There is an actual and justiciable controversy among the parties concerning non-infringement and invalidity of the Asserted Patents.

CASE AND CONTROVERSY

26. The '693 Patent, titled "Vaccine for Eliciting Immune Response Comprising RNA Encoding an Immunogen and Lipid Formulations Comprising Mole Percentage of Lipids," states an issue date of May 2, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '693 Patent is attached to the First Amended Complaint as Exhibit 1 (D.I. 26-1).

27. The '694 Patent, titled "Vaccine for Eliciting Immune Response Comprising Lipid Formulations and RNA Encoding Multiple Immunogens," states an issue date of May 2, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '694 Patent is attached to the First Amended Complaint as Exhibit 2 (D.I. 26-2).

28. The '534 Patent, titled "Methods of Administering Lipid Formulations with Viral Immunogens," states an issue date of June 6, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '534 Patent is attached to the First Amended Complaint as Exhibit 3 (D.I. 26-3).

29. The '401 Patent, titled "Methods of Administering Formulations with Immunogens," states an issue date of September 26, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '401 Patent is attached to the First Amended Complaint as Exhibit 4 (D.I. 26-4).

30. The '467 Patent, titled "Lipid Formulations with Immunogens," states an issue date of October 17, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '467 Patent is attached to the First Amended Complaint as Exhibit 5 (D.I. 26-5).

31. The '422 Patent, titled "Pegylated Liposomes for Delivery of Immunogen-Encoding RNA," states an issue date of September 19, 2023 and names as inventors Andrew Geall and Ayush Verma. Upon information and belief, a true and correct copy of the '422 Patent is attached to the First Amended Complaint as Exhibit 83 (D.I. 26-83).

32. GSK asserted the '422 Patent only after seeing Defendants' Answer, Affirmative Defenses, and Counterclaims to the original Complaint filed on July 24, 2024.

33. The '475 Patent, titled "Immunisation of Large Mammals with Low Doses of RNA," states an issue date of May 23, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '475 Patent is attached to the First Amended Complaint as Exhibit 84 (D.I. 26-84).

34. GSK asserted the '475 Patent only after seeing Defendants' Answer, Affirmative Defenses, and Counterclaims to the original Complaint filed on July 24, 2024.

35. The '660 Patent, titled "Immunisation of Large Mammals with Low Doses of RNA," states an issue date of December 26, 2023 and names as inventor Andrew Geall. Upon information and belief, a true and correct copy of the '660 Patent is attached to the First Amended Complaint as Exhibit 85 (D.I. 26-85).

36. GSK asserted the '660 Patent only after seeing Defendants' Answer, Affirmative Defenses, and Counterclaims to the original Complaint filed on July 24, 2024.

37. According to the First Amended Complaint, GSK Biologicals purports to be the owner by assignment of all Asserted Patents.

38. According to the First Amended Complaint, GSK LLC purports to be the exclusive distributor of any products covered by the Asserted Patents in the United States.

39. An actual, substantial, and justifiable controversy, within the meaning of 28 U.S.C. §§ 2201 and 2202, exists between Counterclaimants and Counterclaim-Defendants.

40. Counterclaimants are entitled to a judicial determination and declaration that they have not infringed and are not infringing the Asserted Patents and that the Asserted Patents are invalid, unenforceable, and not infringed.

PFIZER AND BIONTECH'S DEVELOPMENT OF COMIRNATY®

41. In December of 2019, it was discovered that an outbreak of pneumonia among people who had visited the Huanan Seafood Wholesale Market in Wuhan, China was caused by a novel coronavirus, eventually designated by the World Health Organization as SARS-CoV-2 with the disease it causes reclassified as Coronavirus disease 2019 (“COVID-19”).

42. COVID-19 quickly spread around the world and tore through populations that were immunologically naïve, threatening the collapse of the healthcare system and the loss of life at scales not seen since the advent of modern medicine. What began first as small area lockdowns to prevent the transmission of disease and temporary stay-at-home orders eventually became society altering restrictions. Many saw that the only path out of the pandemic was the development of successful vaccines against the disease.

43. On January 10, 2020, the Chinese Center for Disease Control published the genetic sequence of SARS-CoV-2.

44. BioNTech scientists had been working in the field of mRNA technology since at least the founding of the company in 2008. BioNTech was working on messenger RNA (“mRNA”)-based clinical vaccine candidates by the early- to mid-2010s. BioNTech was earning itself a reputation as an industry leader in mRNA technology.

45. To combat the pandemic, BioNTech scientists set to work on developing a COVID-19 disease vaccine. BioNTech was able to do so by building on its existing development work

and experience with mRNA-based clinical vaccine candidates. BioNTech eventually identified a product candidate as a potential mRNA-based vaccine that would protect against COVID-19.

46. In March 2020, Pfizer and BioNTech began a collaborative effort focused on bringing a COVID-19 disease vaccine to market. The vaccine that ultimately emerged from this partnership was a novel mRNA vaccine now known as Comirnaty®.

47. Clinical trials of Pfizer/BioNTech vaccine candidates began in late April of 2020, with preliminary Phase 3 results demonstrating their safety and efficacy published in just over six months.

48. On November 20, 2020, Pfizer, on behalf of itself and BioNTech, submitted its clinical trial data as part of its Emergency Use Authorization (“EUA”) request to the Food and Drug Administration (“FDA”) for administering its mRNA vaccine to people 16 years of age and older.

49. On December 10, 2020, the FDA granted the first EUA for a COVID-19 vaccine to Pfizer and BioNTech’s mRNA vaccine (now known as Comirnaty®) with vaccinations rolling out immediately thereafter, reflecting the fastest development of a vaccine in history.

50. The FDA provided Pfizer and BioNTech’s vaccine with full approval on August 23, 2021.

51. Since being granted EUA, millions of doses of Comirnaty® have been administered worldwide, resulting in countless numbers of lives saved while easing the strain of an otherwise uncontrollable pandemic. During this same time, GSK Biologicals and GSK LLC did not develop or sell any COVID-19 vaccine.

52. On April 25, 2024, GSK sued Counterclaimants for infringement of the ’693 Patent, ’694 Patent, ’534 Patent, ’401 Patent, and ’467 Patent, alleging that Counterclaimants had

incorporated the claimed subject matter of those patents into the Comirnaty® vaccine in an infringing manner.

53. On August 14, 2024, after Defendants' Answer and Counterclaims were filed on July 24, 2024, GSK filed its First Amended Complaint for infringement of the originally asserted patents, adding infringement allegations for the '422 Patent, the '475 Patent, and the '660 Patent, and alleging that Counterclaimants had also incorporated the claimed subject matter of those patents into the Comirnaty® vaccine in an infringing manner.

54. In view of the foregoing, a conflict of asserted rights has arisen between Counterclaimants and GSK with respect to noninfringement, invalidity, and unenforceability of the claims of the '693 Patent, '694 Patent, '534 Patent, '401 Patent, '467 Patent, '422 Patent, '475 Patent, and '660 Patent.

**GSK'S ACQUISITION AND SUBSEQUENT PROSECUTION OF THE FAMILY OF
U.S. PATENT APPLICATION NO. 13/808,080 AFTER PFIZER AND
BIONTECH'S VACCINE WAS PUBLICLY DISCLOSED**

55. On July 6, 2010, well before the beginning of the COVID-19 pandemic, Novartis Vaccines and Diagnostics, Inc. ("Novartis Vaccines") filed the first provisional application in a *first* family of patents now asserted by GSK against Pfizer and BioNTech, U.S. Provisional Patent Application No. 61/361,830 (the "'830 Application"), entitled "Tertiary Amine Liposomes for RNA Delivery," with claims that state "[a] **liposome having a lipid bilayer encapsulating an aqueous core**, wherein: (i) the lipid bilayer comprises a lipid having a tertiary amine and a pKa in the range of 5.0 to 7.6; and (ii) the aqueous core includes a RNA which encodes an immunogen." (Emphasis added). The specification states "[t]he RNA is +-stranded" and "[p]referred +-stranded RNAs are **self-replicating**." (Emphasis added). Encapsulation of non-self-replicating mRNA is not reported.

56. On August 31, 2010, Novartis Vaccines filed the second provisional application in this family, U.S. Provisional Patent Application No. 61/378,837 (the “’837 Application”), entitled “Liposomes with Lipids Having Advantageous pKa for RNA Delivery,” with claims that state “[a] **liposome having a lipid bilayer encapsulating an aqueous core**, wherein: (i) the lipid bilayer comprises a lipid having a pKa in the range of 5.0 to 7.6; and (ii) the aqueous core includes a RNA which encodes an immunogen.” (Emphasis added). The specification states “[t]he RNA is +-stranded” and “[p]referred +-stranded RNAs are **self-replicating**.” (Emphasis added). Encapsulation of non-self-replicating mRNA is not reported.

57. On March 14, 2013, Novartis Vaccines filed the first non-provisional patent application in this family, U.S. Patent Application No. 13/808,080 (the “’080 Application”), entitled “Liposomes with Lipids Having an Advantageous pKa Value for RNA Delivery,” which originally claimed after a preliminary amendment “[a] **liposome having a lipid bilayer encapsulating an aqueous core**, wherein: (i) the lipid bilayer comprises having a pKa in the range of 5.0 to 7.6; and (ii) the aqueous core includes a **RNA** which encodes an immunogen.” (Emphasis added).

58. On April 1, 2013, Novartis Vaccines purported to assign the ’080 Application to Novartis AG.

59. On December 16, 2014, the Examiner issued final rejections under 35 U.S.C. § 103(a) for all pending claims as obvious in light of Maclachlan et al., (WO2005/120152), in view of Martinon et al., (Eur. J. Immunol., 1993, 23:1719–1722), finding that “Maclachlan provides multiple embodiments of siRNAs encapsulated in liposomes comprising the cationic lipid DLinDMA.”

60. On information and belief, a few months later in March 2015, GSK acquired Novartis AG's vaccines business (excluding influenza vaccines). (Exhibit A.)

61. On June 22, 2016, assignment documents were filed with the U.S. Patent & Trademark Office purporting that the '080 Application was assigned to GSK Biologicals as of June 15, 2016.

62. On June 16, 2015, to overcome the Examiner's rejections, the applicant, now GSK Biologicals, amended the claims to recite that "the aqueous core comprises a **self-replicating RNA** which encodes a polypeptide immunogen." (Emphasis added). Thus, GSK limited the claims to self-replicating RNA to overcome the prior art.

63. Thereafter, between June 2015 and December 2020, GSK Biologicals filed three requests for continued examination. During that period, all of the claims filed in connection with the '080 Application were directed to "liposomes" and "self-replicating RNA." Each request for continued examination resulted in a final rejection for all pending claims.

64. While GSK Biologicals was still prosecuting the '080 Application, Pfizer and BioNTech were granted Emergency Use Authorization for their COVID-19 vaccines on December 10, 2020.

65. On April 9, 2021, the composition of the Pfizer and BioNTech COVID-19 vaccine was published in *Nature*. (Exhibit B.)

66. On August 23, 2021, FDA provided full approval to Pfizer and BioNTech for the first COVID-19 vaccine.

67. Just two months after Pfizer and BioNTech's COVID-19 vaccine received FDA full approval, on October 28, 2021, GSK Biologicals filed a fourth request for continued examination and amended the claims of the '080 Application to include "**RNA molecules**" rather

than “**self-replicating RNA molecules.**” (Emphasis added). The claims continued to include “liposomes,” reciting “[a] pharmaceutical composition being immunogenic *in vivo* and comprising: **liposomes** and RNA molecules; the **liposomes** being suitable for *in vivo* cellular delivery of the RNA molecules.” (Emphasis added).

68. On December 22, 2021, GSK Biologicals filed six new non-provisional patent applications in this family: U.S. Patent Application Nos. 17/560,019 (the “’019 Application”), 17/560,052 (the “’052 Application”), 17/560,059 (the “’059 Application”), 17/560,092 (the “’092 Application”), 17/560,116 (the “’116 Application”), 17/560,138 (the “’138 Application”). Each of the applications sought claims reciting “RNA” wherein “the lipids encapsulate” the RNA molecules.

69. On June 23, 2022, GSK Biologicals filed five new non-provisional patent applications in this family: U.S. Patent Application Nos. 17/808,519 (the “’519 Application”), 17/848,294 (the “’294 Application”), 17/848,299 (the “’299 Application”), 17/848,325 (the “’325 Application”), and 17/848,337 (the “’337 Application”). Each of the applications sought claims reciting “RNA” wherein “the lipids encapsulate” the RNA molecules or “[a] formulation comprising . . . RNA . . . and lipids.”

70. Of the eleven applications filed on December 22, 2021 and June 23, 2022, five issued as the Asserted Patents—the ’693 Patent and ’694 Patent issued on May 2, 2023, the ’534 Patent issued on June 6, 2023, the ’401 Patent issued on September 26, 2023, and the ’467 Patent issued on October 17, 2023. The Asserted Patents each issued with claims reciting “RNA” wherein “the lipids encapsulate” the RNA molecules.

**GSK'S ACQUISITION AND SUBSEQUENT PROSECUTION OF THE FAMILY OF
U.S. PATENT APPLICATION NO. 13/808,153 AFTER PFIZER AND
BIONTECH'S VACCINE WAS PUBLICLY DISCLOSED**

71. On July 6, 2010, Novartis Vaccines also filed the first provisional application in a *second* family of patents now asserted by GSK against Pfizer and BioNTech, U.S. Provisional Patent Application No. 61/361,794 (the “’794 Application”), entitled “Immunisation with Low Doses of RNA,” with claim 1 stating “[a] method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2µg and 100 µg of immunogen-encoding **RNA**,” claim 6 stating “[t]he method of any preceding claim, wherein the RNA is administered in combination with a delivery system,” and claim 7 stating “[t]he method of claim 6, wherein the delivery systems comprises: (i) **liposomes**; (ii) non-toxic and bio-degradable polymer microparticles; and/or (iii) a submicron cationic oil-in-water emulsion.” (Emphasis added). Encapsulation of non-self-replicating mRNA is not reported.

72. On February 26, 2013, Novartis Vaccines filed the first non-provisional patent application in this family, U.S. Patent Application No. 13/808,153 (the “’153 Application”), entitled “Immunisation of Large Mammals with Low Doses of RNA,” which originally claimed after a preliminary amendment “[a] method of raising an immune response in a large mammal, comprising administering to the mammal a dose of between 2µg and 100 µg of immunogen-encoding **RNA**,” claim 6 stating “[t]he method of claim 1, wherein the RNA is administered in combination with a delivery system,” and claim 7 stating “[t]he method of claim 6, wherein the delivery systems comprises: (i) **liposomes**; (ii) non-toxic and bio-degradable polymer microparticles; and/or (iii) a submicron cationic oil-in-water emulsion.” (Emphasis added).

73. On March 5, 2013, assignment documents were filed with the U.S. Patent & Trademark Office purporting that the ’153 Application was assigned to Novartis AG as of March 4, 2013.

74. On April 27, 2014, the Examiner issued final rejections under 35 U.S.C. § 103(a) for all pending claims as obvious, finding in part that “Martinon et al. (1993), teach a composition for immunizing mice against influenza virus comprising mRNA encapsulated in a liposome.”

75. On October 7, 2014, to attempt to overcome the Examiner’s rejections, Novartis AG amended the claims to recite “[a] method eliciting an antibody response and/or a cell-mediated immune response in a large mammal, comprising administering to the mammal a dose of between 2 μ g and 100 μ g of a **self-replicating RNA** encoding an immunogen, wherein the RNA is formulated with a delivery system that comprises: (i) **liposomes**; (ii) non-toxic and biodegradable polymer microparticles; (iii) a submicron cationic oil-in-water emulsion; or (iv) a combination thereof.” (Emphasis added). Thus, Novartis AG limited the scope of the claims to a method of administering a self-replicating RNA to overcome the prior art.

76. On March 27, 2016, assignment documents were filed with the U.S. Patent & Trademark Office purporting that the ’153 Application was assigned to GSK Biologicals as of March 18, 2016.

77. After **seven requests for continued examination**, the ’153 Application issued as U.S. Pat. No. 10,487,332 on November 26, 2019, with claim 1 reciting “[a] method of eliciting an antibody response and/or a cell-mediated immune response in a large mammal, comprising administering to the mammal a dose of between 2 μ g and 100 μ g of a **self-replicating RNA** encoding an immunogen, wherein the large mammal is a human, horse, cattle or pig and the RNA is formulated with a non-viral delivery system that comprises **liposomes** comprising a cationic lipid comprising a tertiary amine, wherein the **self-replicating RNA**: i) cannot perpetuate itself in infectious form and ii) includes no modified nucleotides other than a 5’ cap.” (Emphasis added).

78. On October 18, 2019, GSK Biologicals filed the second non-provisional patent applications in this family, U.S. Patent Application No. 16/656,929 (the “’929 Application”), entitled “Immunisation of Large Mammals with Low Doses of RNA,” which originally claimed after a preliminary amendment “a **self-replicating RNA** encoding an immunogen, wherein the RNA is formulated with a non-viral delivery system comprising a cationic lipid, wherein the delivery system is selected from the group consisting of cationic nanoemulsion and liposomes.” (Emphasis added).

79. On October 29, 2021, two months after FDA provided full approval to Pfizer and BioNTech for the first COVID-19 vaccine, GSK Biologicals canceled the pending claims and added new claims, now claiming “an immunogenic composition comprising **lipid particles** and **messenger ribonucleic acid (mRNA) molecules**” and “a composition comprising **liposomes** and **mRNA molecules**.” (Emphasis added).

80. The ’929 Application issued as the ’475 Patent on May 23, 2023, with claim 1 reciting “a composition comprising **liposomes** and **messenger ribonucleic acid (mRNA) molecules**.” (Emphasis added).

81. On December 13, 2022, GSK Biologicals filed six additional non-provisional patent applications, including U.S. Patent Application No. 18/065,267 (the “’267 Application”), entitled “Immunisation of Large mammals with Low Doses of RNA,” which originally claimed after a preliminary amendment “a composition comprising **lipid particles** and **messenger ribonucleic acid (mRNA) molecules**.” (Emphasis added).

82. The ’267 Application issued as the ’660 Patent on December 26, 2023, with claims 1 reciting “a composition comprising **lipid particles** and **messenger ribonucleic acid (mRNA) molecules**.” (Emphasis added).

**GSK'S ACQUISITION AND SUBSEQUENT PROSECUTION OF THE FAMILY OF
U.S. PATENT APPLICATION NO. 13/819,077**

83. On August 31, 2010, Novartis Vaccines also filed the first provisional application in a *third* family of patents now asserted by GSK against Pfizer and BioNTech, U.S. Provisional Patent Application No. 61/378,826 (the “’826 Application”), entitled “Pegylated Liposomes for Delivery of RNA,” with claims that state “[a] liposome within which **RNA** encoding an immunogen of interest is encapsulated, wherein the liposome comprises at least one lipid which includes a polyethylene glycol moiety, such that polyethylene glycol is present on the liposome’s exterior, wherein the average molecular mass of the polyethylene glycol is between 1kDa and 3kDa.” (Emphasis added). Encapsulation of non-self-replicating mRNA is not reported.

84. On February 26, 2013, Novartis Vaccines filed the first non-provisional patent application in this family, U.S. Patent Application No. 13/819,077 (the “’077 Application”), entitled “Pegylated Liposomes for Delivery of Immunogen Encoding RNA,” which originally claimed after a preliminary amendment “[a] liposome within which **RNA** encoding an immunogen of interest is encapsulated, wherein the liposome comprises at least one lipid which includes a polyethylene glycol moiety, such that polyethylene glycol is present on the liposome’s exterior, wherein the average molecular mass of the polyethylene glycol is between 1kDa and 3kDa.” (Emphasis added).

85. On March 5, 2013, assignment documents were filed with the U.S. Patent & Trademark Office purporting that the ’077 Application was assigned to Novartis AG as of March 1, 2013.

86. On January 8, 2015, the Examiner issued final rejections under 35 U.S.C. § 103(a) for all pending claims as obvious in light of Sankaran et al., (WO 1996/08235), in view of

MacLachlan et al. (US 2006/0240093), finding that “MacLachlan teaches small interfering RNA encapsulated in a lipid particle having a diameter suitable for therapeutic delivery.”

87. On June 8, 2015, to attempt to overcome the Examiner’s rejections, Novartis AG amended the claims to recite “[a] large unilamellar liposome with in which a **self-replicating RNA** encoding a polypeptide immunogen of interest is encapsulated, wherein the liposome comprises a lipid comprising a cationic head group, a lipid comprising a zwitterionic head group, and at least one lipid that is attached with a polyethylene glycol moiety, such that polyethylene glycol is present on the liposome’s exterior, wherein the average molecular mass of the polyethylene glycol (PEG) moiety is between 1kDa and 3kDa.” (Emphasis added). Thus, Novartis AG limited the scope of the claims to a self-replicating RNA to overcome the prior art.

88. On June 22, 2016, assignment documents were filed with the U.S. Patent & Trademark Office purporting that the ’077 Application was assigned to GSK Biologicals as of June 15, 2016. On June 5, 2017, assignment documents were filed with the U.S. Patent & Trademark Office purporting to correct the application number recorded on the previous assignment.

89. Thereafter, between June 2016 and July 2019, GSK Biologicals filed four requests for continued examination. During that period, all of the claims filed in connection with the ’077 Application were directed to “self-replicating RNA.” Each request for continued examination resulted in a final rejection for all pending claims. On April 21, 2020, the ’077 Application was abandoned.

90. On April 1, 2020, only two weeks after BioNTech and Pfizer had announced they were co-developing an mRNA vaccine for COVID-19, GSK Biologicals filed the second non-provisional patent application in this family, U.S. Patent Application No. 16/837,115 (the “’115

Application”), entitled “Pegylated Liposomes for Delivery of Immunogen-Encoding RNA,” with claims that state “[a] method for raising a protective immune response in a vertebrate, comprising the step of administering to the vertebrate an effective amount of a liposome within which **RNA** encoding an immunogen of interest is encapsulated, wherein the liposome comprises at least one lipid which includes a polyethylene glycol moiety, such that polyethylene glycol is present on the liposome’s exterior, wherein the average molecular mass of the polyethylene glycol is between 1kDa and 3kDa.” (Emphasis added).

91. GSK Biologicals filed two requests for continued examination and amended the claims further on August 16, 2022 and March 15, 2023.

92. The ’115 Application issued as the ’422 Patent on September 19, 2023, with claim 1 reciting “a liposome within which at least one ribonucleic acid (RNA) that encodes an immunogen of interest is encapsulated.”

**PFIZER AND BIONTECH ARE PREJUDICED BY THE DELAY IN PROSECUTION
OF GSK AND ITS PREDECESSORS-IN-INTEREST**

93. Following the first provisional application’s filing on July 6, 2010 for the ’080 Application family, GSK Biologicals (collectively with its predecessors-in-interest Novartis Vaccines and Novartis AG, “Applicant”) unreasonably delayed in filing the applications that issued as the ’693 Patent, ’694 Patent, ’534 Patent, ’401 Patent, and ’467 Patent for over eleven years. Additionally, Applicant unreasonably delayed pursuing the claims of the ’693 Patent, ’694 Patent, ’534 Patent, ’401 Patent, and ’467 Patent for over eleven years before it pursued claims reciting “RNA” wherein “the lipids encapsulate” the RNA molecules.

94. Following the provisional application’s filing on July 6, 2010 for the ’153 Application family, Applicant unreasonably delayed in filing the applications that issued as the ’475 Patent and ’660 Patent for over nine years and twelve years, respectively. Additionally,

Applicant unreasonably delayed pursuing the claims of the '660 Patent for over a decade before it pursued claims reciting "lipid particles." Following the amendment to the claims of the '153 Application on October 7, 2014, Applicant unreasonably delayed pursuing the claims of the '475 Patent and '660 Patent for over seven years before it pursued claims reciting "RNA."

95. Following the provisional application's filing on August 31, 2010 for the '077 Application family, Applicant unreasonably delayed in filing the application that led to the '422 Patent for over nine years. Additionally, following the amendment to the claims of the '077 Application on June 8, 2015, Applicant unreasonably delayed pursuing the claims of the '422 Patent for over four years before it pursued claims reciting "RNA."

96. It was not until the details of Pfizer and BioNTech's COVID-19 vaccine became publicly available that GSK pursued the patent claims it now asserts against them from the '634 Patent, '694 Patent, '534 Patent, '401 Patent, '467 Patent, '475 Patent, and '660 Patent.

97. As a result of Applicant's unexplained and unreasonable delay, Pfizer and BioNTech have been prejudiced. For example, Pfizer and BioNTech invested time and resources in the development of the Accused Products during Applicant's delay. Pfizer and BioNTech developed the first COVID-19 vaccine to combat COVID-19. Rather than market its own vaccine in the U.S., GSK filed applications at the Patent Office in an attempt to cover Pfizer and BioNTech's successful innovations.

98. The final issued claims in the Asserted Patents are not supported by the written description. The final claims reference "RNA" or "mRNA," whereas the specifications only describe self-replicating RNA and do not provide written description or enablement support for all RNA or mRNA molecules. The claims also reference not only "liposomes," but "lipid particles" or that the "lipids encapsulate the" RNA, whereas the specifications only describe specific

liposome formulations and do not provide written description or enablement support for all lipid-containing formulations that encapsulate RNA.

99. Pfizer and BioNTech are also prejudiced because certain prior art may no longer be available now that over a decade has passed since Applicant filed the first provisional applications. As a result of its delay, Applicant was able to draft claims in view of new information and products that did not exist at the time of its initial filing.

**GSK IMPROPERLY SEEKS TO PROFIT FROM PFIZER AND
BIONTECH'S COMIRNATY® COVID-19 VACCINE**

100. GSK's belated efforts to improperly expand its patent portfolio try to capitalize on Pfizer and BioNTech's success.

101. GSK now seeks to profit not from technology GSK or its predecessors invented, but rather from improperly contorting the specification and/or claims of the families of its recent patent applications to what it alleges covers Comirnaty®.

102. GSK does not report having made and used an LNP encapsulating non-self-replicating mRNA in any of the Asserted Patents.

103. GSK's alleged lipid technology is not a COVID-19 vaccine.

104. GSK's alleged lipid technology has never been included in a COVID-19 vaccine.

105. GSK is seeking damages for an invention that it did not create, and which it did not prosecute at the Patent Office until the composition of Comirnaty® was publicly available.

COUNT I – DECLARATION OF NON-INFRINGEMENT ('693 PATENT)

106. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

107. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial,

and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '693 Patent. GSK has accused Counterclaimants of activities that it claims infringe the '693 Patent.

108. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '693 Patent.

109. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '693 Patent.

110. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT II – DECLARATION OF NON-INFRINGEMENT ('694 PATENT)

111. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

112. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '694 Patent. GSK has accused Counterclaimants of activities that it claims infringe the '694 Patent.

113. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '694 Patent.

114. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '694 Patent.

115. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT III – DECLARATION OF NON-INFRINGEMENT ('534 PATENT)

116. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

117. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '534 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '534 Patent.

118. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '534 Patent.

119. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '534 Patent.

120. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT IV – DECLARATION OF NON-INFRINGEMENT ('401 PATENT)

121. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

122. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between

Counterclaimants and Counterclaim-Defendants concerning the infringement of the '401 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '401 Patent.

123. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '401 Patent.

124. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '401 Patent.

125. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT V – DECLARATION OF NON-INFRINGEMENT ('467 PATENT)

126. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

127. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '467 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '467 Patent.

128. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '467 Patent.

129. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '467 Patent.

130. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT VI – DECLARATION OF NON-INFRINGEMENT ('422 PATENT)

131. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

132. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '422 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '422 Patent.

133. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '422 Patent.

134. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '422 Patent.

135. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT VII – DECLARATION OF NON-INFRINGEMENT ('475 PATENT)

136. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

137. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '475 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '475 Patent.

138. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '475 Patent.

139. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '475 Patent.

140. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT VIII – DECLARATION OF NON-INFRINGEMENT ('660 PATENT)

141. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

142. This Counterclaim arises under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy having adverse legal interest of sufficient immediacy and reality to warrant the issuance of a declaration of rights by the Court exists between Counterclaimants and Counterclaim-Defendants concerning the infringement of the '660 Patent. GSK has accused Counterclaimants of activities that they claim infringe the '660 Patent.

143. Counterclaimants do not and have not infringed, either directly or indirectly, any valid and enforceable claim of the '660 Patent.

144. Counterclaimants are entitled to a declaratory judgment from this Court that they do not and have not infringed any claim of the '660 Patent.

145. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT IX – DECLARATION OF INVALIDITY ('693 PATENT)

146. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

147. The claims of the '693 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

148. Counterclaimants are entitled to a declaratory judgment from this Court that the '693 Patent is invalid.

149. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT X – DECLARATION OF INVALIDITY ('694 PATENT)

150. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

151. The claims of the '694 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

152. Counterclaimants are entitled to a declaratory judgment from this Court that the '694 Patent is invalid.

153. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XI – DECLARATION OF INVALIDITY ('534 PATENT)

154. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

155. The claims of the '534 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

156. Counterclaimants are entitled to a declaratory judgment from this Court that the '534 Patent is invalid.

157. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XII – DECLARATION OF INVALIDITY ('401 PATENT)

158. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

159. The claims of the '401 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

160. Counterclaimants are entitled to a declaratory judgment from this Court that the '401 Patent is invalid.

161. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XIII – DECLARATION OF INVALIDITY ('467 PATENT)

162. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

163. The claims of the '467 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patent and/or in view of the defenses recognized in 35 U.S.C. § 282.

164. Counterclaimants are entitled to a declaratory judgment from this Court that the '467 Patent is invalid.

165. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XIV – DECLARATION OF INVALIDITY ('422 PATENT)

166. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

167. The claims of the '422 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

168. Counterclaimants are entitled to a declaratory judgment from this Court that the '422 Patent is invalid.

169. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XV – DECLARATION OF INVALIDITY ('475 PATENT)

170. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

171. The claims of the '475 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

172. Counterclaimants are entitled to a declaratory judgment from this Court that the '475 Patent is invalid.

173. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XVI – DECLARATION OF INVALIDITY ('660 PATENT)

174. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

175. The claims of the '660 Patent are invalid for failure to satisfy one or more of the provisions set forth in 35 U.S.C. §§ 100 *et seq.*, including, without limitation, the requirements of 35 U.S.C. §§ 101, 102, 103, and/or 112 and/or any other judicially created requirements of patentability and enforceability of patents and/or in view of the defenses recognized in 35 U.S.C. § 282.

176. Counterclaimants are entitled to a declaratory judgment from this Court that the '660 Patent is invalid.

177. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XVII – DECLARATION OF PATENT MISUSE ('693 PATENT)

178. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

179. GSK has sought to enforce and/or license the '693 Patent for products and acts it knows are outside the claims of the '693 Patent.

180. For at least six years prior to December 22, 2021, all claims sought in the '080 Application family specified that the RNA was self-replicating RNA.

181. Prior to December 22, 2021, all claims sought were directed to a "liposome" encapsulating RNA.

182. All embodiments encapsulating an RNA in the '693 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

183. The liposomes that are disclosed as encapsulating an RNA in the '693 Patent are different from the LNP formulation used in Comirnaty®.

184. GSK only began prosecuting the claims of the '693 Patent, directed to "RNA" where "the lipids encapsulate" the RNA, after the composition of Comirnaty® was published and years after the alleged priority date of the '693 Patent.

185. There is no written description or enablement support for the breadth of the claims of the '693 Patent in its specification.

186. GSK's conduct in seeking to license and enforce the '693 Patent against products and acts that it knows to be outside the scope of the claims of the '693 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

187. GSK has engaged in a course of conduct that seeks to broaden the scope of the '693 Patent with anticompetitive effect.

188. GSK's misuse of the '693 Patent renders it unenforceable.

189. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XVIII – DECLARATION OF PATENT MISUSE ('694 PATENT)

190. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

191. GSK has sought to enforce and/or license the '694 Patent for products and acts it knows are outside the claims of the '694 Patent.

192. For at least six years prior to December 22, 2021, all claims sought in the '080 Application family specified that the RNA was self-replicating RNA.

193. Prior to December 22, 2021, all claims sought were directed to a “liposome” encapsulating RNA.

194. All embodiments encapsulating an RNA in the '694 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

195. The liposomes that are disclosed as encapsulating an RNA in the '694 Patent are different from the LNP formulation used in Comirnaty®.

196. GSK only began prosecuting the claims of the '694 Patent, directed to “RNA” where “the lipids encapsulate” the RNA after the composition of Comirnaty® was published and years after the alleged priority date of the '694 Patent.

197. There is no written description or enablement support for the breadth of the claims of the '694 Patent in its specification.

198. GSK's conduct in seeking to license and enforce the '694 Patent against products and acts that it knows to be outside the scope of the claims of the '694 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

199. GSK has engaged in a course of conduct that seeks to broaden the scope of the '694 Patent with anticompetitive effect.

200. GSK's misuse of the '693 Patent renders it unenforceable.

201. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XIX – DECLARATION OF PATENT MISUSE ('534 PATENT)

202. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

203. GSK has sought to enforce and/or license the '534 Patent for products and acts it knows are outside the claims of the '534 Patent.

204. For at least six years prior to December 22, 2021, all claims sought in the '080 Application family specified that the RNA was self-replicating RNA.

205. Prior to December 22, 2021, all claims sought were directed to a "liposome" encapsulating RNA.

206. All embodiments encapsulating an RNA in the '534 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

207. The liposomes that are disclosed as encapsulating an RNA in the '534 Patent are different from the LNP formulation used in Comirnaty®.

208. GSK only began prosecuting the claims of the '534 Patent, directed to "RNA" where "the lipids encapsulate" the RNA after the composition of Comirnaty® was published and years after the alleged priority date of the '534 Patent.

209. There is no written description or enablement support for the breadth of the claims of the '534 Patent in its specification.

210. GSK's conduct in seeking to license and enforce the '534 Patent against products and acts that it knows to be outside the scope of the claims of the '534 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

211. GSK has engaged in a course of conduct that seeks to broaden the scope of the '534 Patent with anticompetitive effect.

212. GSK's misuse of the '534 Patent renders it unenforceable.

213. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XX – DECLARATION OF PATENT MISUSE ('401 PATENT)

214. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

215. GSK has sought to enforce and/or license the '401 Patent for products and acts it knows are outside the claims of the '401 Patent.

216. For at least six years prior to December 22, 2021, all claims sought in the '080 Application family specified that the RNA was self-replicating RNA.

217. Prior to December 22, 2021, all claims sought were directed to a "liposome" encapsulating RNA.

218. All embodiments encapsulating an RNA in the '401 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

219. The liposomes that are disclosed as encapsulating an RNA in the '401 Patent are different from the LNP formulation used in Comirnaty®.

220. GSK only began prosecuting the claims of the '401 Patent, directed to “RNA” where “the lipids encapsulate” the RNA after the composition of Comirnaty® was published and years after the alleged priority date of the '401 Patent.

221. There is no written description or enablement support for the breadth of the claims of the '401 Patent in its specification.

222. GSK's conduct in seeking to license and enforce the '401 Patent against products and acts that it knows to be outside the scope of the claims of the '401 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

223. GSK has engaged in a course of conduct that seeks to broaden the scope of the '401 Patent with anticompetitive effect.

224. GSK's misuse of the '401 Patent renders it unenforceable.

225. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXI – DECLARATION OF PATENT MISUSE ('467 PATENT)

226. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

227. GSK has sought to enforce and/or license the '467 Patent for products and acts it knows are outside the claims of the '467 Patent.

228. For at least six years prior to December 22, 2021, all claims sought in the '080 Application family specified that the RNA was self-replicating RNA.

229. Prior to December 22, 2021, all claims sought were directed to a “liposome” encapsulating RNA.

230. All embodiments encapsulating an RNA in the '467 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

231. The liposomes that are disclosed as encapsulating an RNA in the '467 Patent are different from the LNP formulation used in Comirnaty®.

232. GSK only began prosecuting the claims of the '467 Patent, directed to “RNA” where “the lipids encapsulate” the RNA after the composition of Comirnaty® was published and years after the alleged priority date of the '467 Patent.

233. There is no written description or enablement support for the breadth of the claims of the '467 Patent in its specification.

234. GSK's conduct in seeking to license and enforce the '467 Patent against products and acts that it knows to be outside the scope of the claims of the '467 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

235. GSK has engaged in a course of conduct that seeks to broaden the scope of the '467 Patent with anticompetitive effect.

236. GSK's misuse of the '467 Patent renders it unenforceable.

237. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXII – DECLARATION OF PATENT MISUSE ('422 PATENT)

238. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

239. GSK has sought to enforce and/or license the '422 Patent for products and acts it knows are outside the claims of the '422 Patent.

240. For at least four years prior to April 1, 2020, all claims sought in the '077 Application family specified that the RNA was self-replicating RNA.

241. All embodiments encapsulating an RNA in the '422 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

242. The liposomes that are disclosed as encapsulating an RNA in the '422 Patent are different from the LNP formulation used in Comirnaty®.

243. GSK only began prosecuting the claims of the '422 Patent, directed to “messenger ribonucleic acid (mRNA) molecules” after BioNTech and Pfizer announced they were co-developing an mRNA vaccine for COVID-19 and years after the alleged priority date of the '422 Patent.

244. There is no written description or enablement support for the breadth of the claims of the '422 Patent in its specification.

245. GSK's conduct in seeking to license and enforce the '422 Patent against products and acts that it knows to be outside the scope of the claims of the '422 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

246. GSK has engaged in a course of conduct that seeks to broaden the scope of the '422 Patent with anticompetitive effect.

247. GSK's misuse of the '422 Patent renders it unenforceable.

248. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXIII – DECLARATION OF PATENT MISUSE ('475 PATENT)

249. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

250. GSK has sought to enforce and/or license the '475 Patent for products and acts it knows are outside the claims of the '475 Patent.

251. For at least seven years prior to October 29, 2021, all claims sought in the '153 Application family specified that the RNA was self-replicating RNA.

252. All embodiments encapsulating an RNA in the '475 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

253. The liposomes that are disclosed as encapsulating an RNA in the '475 Patent are different from the LNP formulation used in Comirnaty®.

254. GSK only began prosecuting the claims of the '475 Patent, directed to “messenger ribonucleic acid (mRNA) molecules” after the composition of Comirnaty® was published and years after the alleged priority date of the '475 Patent.

255. There is no written description or enablement support for the breadth of the claims of the '475 Patent in its specification.

256. GSK's conduct in seeking to license and enforce the '475 Patent against products and acts that it knows to be outside the scope of the claims of the '475 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

257. GSK has engaged in a course of conduct that seeks to broaden the scope of the '475 Patent with anticompetitive effect.

258. GSK's misuse of the '475 Patent renders it unenforceable.

259. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXIV – DECLARATION OF PATENT MISUSE ('660 PATENT)

260. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

261. GSK has sought to enforce and/or license the '660 Patent for products and acts it knows are outside the claims of the '660 Patent.

262. For at least seven years prior to October 29, 2021, all claims sought in the '153 Application family specified that the RNA was self-replicating RNA.

263. All embodiments encapsulating an RNA in the '660 Patent disclose only self-replicating RNA molecules as the RNA, unlike the non-self-replicating mRNA used in Comirnaty®.

264. The liposomes that are disclosed as encapsulating an RNA in the '660 Patent are different from the LNP formulation used in Comirnaty®.

265. GSK only began prosecuting the claims of the '660 Patent, directed to “messenger ribonucleic acid (mRNA) molecules” after the composition of Comirnaty® was published and years after the alleged priority date of the '660 Patent.

266. There is no written description or enablement support for the breadth of the claims of the '660 Patent in its specification.

267. GSK's conduct in seeking to license and enforce the '660 Patent against products and acts that it knows to be outside the scope of the claims of the '660 Patent and outside the scope of what was actually invented is an attempt to seek an improper economic benefit.

268. GSK has engaged in a course of conduct that seeks to broaden the scope of the '660 Patent with anticompetitive effect.

269. GSK's misuse of the '660 Patent renders it unenforceable.

270. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXV – DECLARATION OF PROSECUTION LACHES ('693 PATENT)

271. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

272. After the provisional '830 Application was filed on July 6, 2010, GSK unreasonably delayed over eleven years until June 23, 2022 to file the '519 Application that issued as the '693 Patent.

273. After amending the claims of the '080 Application on June 16, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over six years in pursuing the claims of the '693 Patent related to “RNA” as opposed to “self-replicating RNA.”

274. The '080 Application was filed on January 2, 2013, yet GSK unreasonably delayed for over eight years in pursuing the claims of the '693 Patent related to RNA where “the lipids encapsulate” the RNA as opposed to “liposomes” encapsulating the RNA.

275. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '693 Patent, Counterclaimants have been prejudiced.

276. The '693 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

277. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXVI – DECLARATION OF PROSECUTION LACHES ('694 PATENT)

278. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

279. After the provisional '830 Application was filed on July 6, 2010, GSK unreasonably delayed over eleven years until June 23, 2022 to file the '299 Application that issued as the '694 Patent.

280. After amending the claims of the '080 Application on June 16, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over six years in pursuing the claims of the '694 Patent related to “RNA” as opposed to “self-replicating RNA.”

281. The '080 Application was filed on January 2, 2013, yet GSK unreasonably delayed for over eight years in pursuing the claims of the '694 Patent related to RNA where “the lipids encapsulate” the RNA as opposed to “liposomes” encapsulating the RNA.

282. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '694 Patent, Counterclaimants have been prejudiced.

283. The '694 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

284. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXVII – DECLARATION OF PROSECUTION LACHES ('534 PATENT)

285. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

286. After the provisional '830 Application was filed on July 6, 2010, GSK unreasonably delayed over eleven years until December 22, 2021 to file the '138 Application that issued as the '534 Patent.

287. After amending the claims of the '080 Application on June 16, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over six years in pursuing the claims of the '534 Patent related to “RNA” as opposed to “self-replicating RNA.”

288. The '080 Application was filed on January 2, 2013, yet GSK unreasonably delayed for over eight years in pursuing the claims of the '534 Patent related to RNA where “the lipids encapsulate” the RNA as opposed to “liposomes” encapsulating the RNA.

289. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '534 Patent, Counterclaimants have been prejudiced.

290. The '534 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

291. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXVIII – DECLARATION OF PROSECUTION LACHES ('401 PATENT)

292. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

293. After the provisional '830 Application was filed on July 6, 2010, GSK unreasonably delayed over eleven years until December 22, 2021 to file the '059 Application that issued as the '401 Patent.

294. After amending the claims of the '080 Application on June 16, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over six years in pursuing the claims of the '401 Patent related to “RNA” as opposed to “self-replicating RNA.”

295. The '080 Application was filed on January 2, 2013, yet GSK unreasonably delayed for over eight years in pursuing the claims of the '401 Patent related to RNA where “the lipids encapsulate” the RNA as opposed to “liposomes” encapsulating the RNA.

296. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '401 Patent, Counterclaimants have been prejudiced.

297. The '401 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

298. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXIX – DECLARATION OF PROSECUTION LACHES ('467 PATENT)

299. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

300. After the provisional '830 Application was filed on July 6, 2010, GSK unreasonably delayed over eleven years until December 22, 2021 to file the '019 Application that issued as the '467 Patent.

301. After amending the claims of the '080 Application on June 16, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over six years in pursuing the claims of the '467 Patent related to “RNA” as opposed to “self-replicating RNA.”

302. The '080 Application was filed on January 2, 2013, yet GSK unreasonably delayed for over eight years in pursuing the claims of the '467 Patent related to RNA where “the lipids encapsulate” the RNA as opposed to “liposomes” encapsulating the RNA.

303. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '467 Patent, Counterclaimants have been prejudiced.

304. The '467 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

305. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXX – DECLARATION OF PROSECUTION LACHES ('422 PATENT)

306. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

307. After the provisional '826 Application was filed on August 31, 2010, GSK unreasonably delayed over nine years until April 1, 2020 to file the '115 Application that issued as the '422 Patent.

308. After amending the claims of the '077 Application on June 8, 2015 to recite “self-replicating RNA,” GSK unreasonably delayed for over four years in pursuing the claims of the '422 Patent related to “RNA” as opposed to “self-replicating RNA.”

309. As a result of Applicant’s unexplained and unreasonable delay in prosecuting the claims of the '422 Patent, Counterclaimants have been prejudiced.

310. The '422 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

311. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys’ fees incurred in connection with this matter.

COUNT XXXI – DECLARATION OF PROSECUTION LACHES ('475 PATENT)

312. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

313. After the provisional '794 Application was filed on July 6, 2010, GSK unreasonably delayed over nine years until October 18, 2019 to file the '929 Application that issued as the '475 Patent.

314. After amending the claims of the '153 Application on October 7, 2014 to recite “self-replicating RNA,” GSK unreasonably delayed for over seven years in pursuing the claims of the '475 Patent related to “RNA” as opposed to “self-replicating RNA.”

315. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '475 Patent, Counterclaimants have been prejudiced.

316. The '475 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

317. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

COUNT XXXII – DECLARATION OF PROSECUTION LACHES ('660 PATENT)

318. Counterclaimants incorporate by reference each of the preceding paragraphs as if fully set forth herein.

319. After the provisional '794 Application was filed on July 6, 2010, GSK unreasonably delayed over twelve years until December 13, 2022 to file the '267 Application that issued as the '660 Patent.

320. After amending the claims of the '153 Application on October 7, 2014 to recite “self-replicating RNA,” GSK unreasonably delayed for over seven years in pursuing claims related to “RNA” as opposed to “self-replicating RNA.”

321. The '153 Application was filed on February 26, 2013 yet GSK unreasonably delayed for over eight years in pursuing the claims of the '660 Patent related to a “composition comprising lipid particles” as opposed to “liposomes.”

322. As a result of Applicant's unexplained and unreasonable delay in prosecuting the claims of the '660 Patent, Counterclaimants have been prejudiced.

323. The '660 Patent is unenforceable against Counterclaimants under the doctrine of prosecution laches.

324. This is an exceptional case under 35 U.S.C. § 285, entitling Counterclaimants to an award of attorneys' fees incurred in connection with this matter.

JURY DEMAND

Counterclaimants request a trial by jury on all claims so triable in this action.

RELIEF REQUESTED

WHEREFORE, Counterclaimants respectfully request that the Court enter a Judgment and Order in their favor and against Counterclaim-Defendants as follows:

- (a) Dismissing GSK's First Amended Complaint with prejudice and denying each and every prayer for relief contained therein;
- (b) Declaring that Counterclaimants do not infringe any claim of the Asserted Patents;
- (c) Declaring that the manufacture, use, offer to sell, and sale of Comirnaty® within the United States, and its importation into the United States, does not infringe any claim of the Asserted Patents;
- (d) Declaring that the claims of the Asserted Patents are invalid;
- (e) Declaring that the claims of the Asserted Patents are unenforceable;
- (f) Preliminarily and permanently enjoining GSK and its agents, representatives, attorneys, and those persons in active concert or participation with them who receive actual notice thereof from threatening or initiating infringement litigation against Counterclaimants or any of their customers, dealers, or suppliers, or any prospective or present sellers, dealers, distributors, or customers of Counterclaimants, or charging any of them either orally or in writing with infringement of the Asserted Patents;
- (g) Awarding Counterclaimants their attorneys' fees, together with costs and disbursements, including because this case is exceptional under 35 U.S.C. § 285; and
- (h) Awarding such other and further relief as the Court deems justified.

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August 30, 2024

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CERTIFICATE OF SERVICE

I hereby certify that on August 30, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on August 30, 2024, upon the following in the manner indicated:

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Exhibit A

02 March 2015

GSK completes major three-part transaction with Novartis

GSK has acquired Novartis's global Vaccines business (excluding influenza vaccines) for an initial cash consideration of \$5.25 billion

Issued: London UK – LSE Announcement

£4 billion to be returned to shareholders

Q1 Results & Investor Meeting to be held on 6 May 2015

GlaxoSmithKline plc (LSE/NYSE: GSK) announces that its three-part transaction with Novartis has completed today. As a result of this transaction, GSK has acquired Novartis's global Vaccines business (excluding influenza vaccines) for an initial cash consideration of \$5.25 billion; has created a new world-leading Consumer Healthcare joint venture with Novartis in which GSK will have majority control and an equity interest of 63.5%; and has divested its Oncology business for an aggregate cash consideration of \$16 billion.

The net after tax proceeds of the transaction received by GSK today are estimated to be \$7.8 billion. This reflects the full consideration of \$16 billion paid today by Novartis for GSK's Oncology portfolio and related assets. Under the terms of the transaction, up to \$1.5 billion of that purchase price may have to be returned to Novartis if certain conditions relating to the COMBI-d Trial are not met. Following the positive results from this study announced on 6 February 2015, GSK believes these conditions will be satisfied.

As a result, following today's completion, GSK plans to use the transaction proceeds to fund the full amount of the previously announced capital return of £4 billion to shareholders. Subject to shareholder approval, the capital return is expected to be implemented through a B share scheme, which will provide capital treatment for all UK tax-resident shareholders. Further details on the capital return will be sent to shareholders in due course.

In light of the timing of closing the transaction, the Company intends to report its first quarter results for 2015 and hold an Investor Meeting on 6 May 2015, at which it will provide 2015 earnings guidance and profile the medium and long-term shape and opportunities for the enlarged Group.

Sir Andrew Witty, CEO, GSK said: "Completion of this transaction represents a major step forward in the Group's strategy to create a stronger and more balanced set of businesses across Pharmaceuticals, Consumer Healthcare and Vaccines. We will now be focused on rapidly implementing our integration plans to realise the growth and synergy opportunities we see in the new Consumer Healthcare and Vaccines businesses. We look forward to sharing more details of this with our shareholders on 6 May."

BioNTech-Pfizer Exhibit 1313

GSK – one of the world’s leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit our [about us section](#).

Additional information

Whilst completion of the transaction with Novartis has taken place today, there are certain jurisdictions in which the transfer of relevant assets to or by GSK will only take place following receipt of additional market-specific approvals or other matters relevant to those jurisdictions. The arrangements in relation to these jurisdictions are considered immaterial in the context of the transaction.

Terms defined in GSK’s shareholder circular of 20 November 2014 have the same meaning where used in this announcement.

Information regarding forward-looking statements

This announcement includes statements that are, or may be deemed to be, “forward-looking statements”. These forward-looking statements can be identified by the use of forward-looking terminology, including the terms “believes”, “estimates”, “plans”, “projects”, “anticipates”, “expects”, “intends”, “may”, “will”, or “should” or, in each case, their negative or other variations or comparable terminology, or by discussions of strategy, plans, objectives, goals, future events or intentions. These forward-looking statements include all matters that are not historical facts. They appear in a number of places throughout this announcement and include, but are not limited to, statements regarding GSK’s intentions, beliefs or current expectations concerning, among other things, GSK’s business, results of operations, financial position, prospects, growth, strategies and the industry in which it operates as well as those of the Novartis businesses that are the subject of the transaction. By their nature, forward-looking statements involve risk and uncertainty because they relate to future events and circumstances. Forward-looking statements are not guarantees of future performance and the actual results of GSK’s operations and financial position, and the development of the markets and the industry in which GSK operates, may differ materially from those described in, or suggested by, the forward-looking statements contained in this announcement. The same applies in respect of the Novartis Businesses that are the subject of the transaction. In addition, even if the results of operations, financial position and the development of the markets and the industry in which GSK operates are consistent with the forward-looking statements contained in this announcement, those results or developments may not be indicative of results or developments in subsequent periods. A number of factors could cause results and developments to differ materially from those expressed or implied by the forward-looking statements including, without limitation, general economic and business conditions, industry trends, competition, changes in regulation, currency fluctuations, changes in its business strategy, political and economic uncertainty and other factors discussed in this announcement.

Forward-looking statements may, and often do, differ materially from actual results. Any forward-looking statements in this announcement speak only as of their respective dates, reflect GSK’s current view with respect to future events and are subject to risks relating to future events and other risks, uncertainties and assumptions relating to GSK’s operations, results of operations and growth strategy. You should specifically consider the factors identified in this document, in addition to the risk factors that may affect GSK’s operations which are described under “Risk Factors” in the Company’s 2014 Annual Report on Form 20-F, which could cause actual results to differ before making any decision in relation to the Transaction as well as those of the Novartis businesses that are the subject of the transaction. Subject to the requirements of the FCA, the London Stock Exchange, the Listing Rules and the Disclosure and Transparency Rules (and/or any regulatory requirements) or applicable law, GSK explicitly disclaims any obligation or undertaking publicly to release the result of any revisions to any forward-looking statements in this announcement that may occur due to any change in GSK’s expectations or to reflect events or circumstances after the date of this announcement.

Exhibit B



Contents lists available at ScienceDirect

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Review

mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability

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ABSTRACT

A drawback of the current mRNA-lipid nanoparticle (LNP) COVID-19 vaccines is that they have to be stored at (ultra)low temperatures. Understanding the root cause of the instability of these vaccines may help to rationally improve mRNA-LNP product stability and thereby ease the temperature conditions for storage. In this review we discuss proposed structures of mRNA-LNPs, factors that impact mRNA-LNP stability and strategies to optimize mRNA-LNP product stability. Analysis of mRNA-LNP structures reveals that mRNA, the ionizable cationic lipid and water are present in the LNP core. The neutral helper lipids are mainly positioned in the outer, encapsulating, wall. mRNA hydrolysis is the determining factor for mRNA-LNP instability. It is currently unclear how water in the LNP core interacts with the mRNA and to what extent the degradation prone sites of mRNA are protected through a coat of ionizable cationic lipids. To improve the stability of mRNA-LNP vaccines, optimization of the mRNA nucleotide composition should be prioritized. Secondly, a better understanding of the milieu the mRNA is exposed to in the core of LNPs may help to rationalize adjustments to the LNP structure to preserve mRNA integrity. Moreover, drying techniques, such as lyophilization, are promising options still to be explored.

1. Introduction

Of the many COVID-19 vaccines under development, the two vaccines that have shown the most promising results in preventing COVID-19 infection represent a new class of vaccine products: they are composed of messenger ribonucleic acid (mRNA) strands encapsulated in lipid nanoparticles (LNPs). The efficacy of these mRNA vaccines developed by BioNTech/Pfizer and Moderna is about 95% (Baden et al., 2021; Polack et al., 2020) and they were the first mRNA vaccines to receive ‘emergency use authorization’ (by FDA) and ‘conditional approval’ by EMA. These mRNA COVID-19 vaccines encode the viral Spike (S) glycoprotein of SARS-CoV-2 that includes two proline substitutions (K986P and V987P mutations), in order to stabilize the prefusion conformation of the glycoprotein (Wrapp et al., 2020). Upon intramuscular (IM) administration, the LNP system enables the uptake by host cells and the delivery of mRNA inside the cytosol, where the

translation of the mRNA sequence into the S protein occurs in the ribosomes. After post-translation processing by the host cells, the S protein is presented as a membrane-bound antigen in its prefusion conformation at the cellular surface, providing the antigen target for B cells. In addition, part of the temporally produced Spike proteins enter antigen presentation pathways, providing antigen recognition by T cells via MHC presentation of T-cell epitopes (Verbeke et al., 2021). The EMA assessment report formulates the mechanism of action of mRNA vaccines at the injection site as follows: ‘Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs (EMA, 2020a).’ Because of this inherent innate immune activity, it is not necessary to formulate the mRNA vaccines with additional adjuvants. Interestingly, Pfizer/

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BioNTech and Moderna specifically use nucleoside-modified mRNA that decrease (rather than increase) the inherent mRNA immunogenicity, underlining the need to properly balance the innate immune activity of mRNA vaccines (see below). The *in vivo* antigen production post-administration that can be achieved with mRNA vaccines, together with the self-adjuvant properties of mRNA-LNP vaccines, ultimately leads to the efficient generation of neutralizing antibody responses and cellular immunity, decreasing the risk of developing COVID-19 for the vaccine recipients.

mRNA vaccines have several benefits over other types of vaccines. A general advantage of mRNA vaccines is that their development is relatively fast, as mRNA-LNPs are a true platform technology. After identification of the protective protein antigen(s) and sequencing the corresponding gene(s), the mRNA can be made within weeks (Jackson et al., 2020). As the mRNAs encoding different antigens are chemically and physically highly similar, formulation design and manufacturing processes of new mRNA vaccines follow the same steps (Petsch et al., 2012). Compared to replication deficient viral vectors, mRNA vaccines may be more efficacious for COVID-19 prevention. Unlike viral vector-based vaccines, they don't generate immunity against the carrier. In this regard mRNA vaccines are similar to deoxyribonucleic acid (DNA)-based vaccines. DNA vaccines, however, still have a minute chance of potential genome integration. Moreover, in contrast to mRNA vaccines, DNA vaccines have shown rather low immunogenicity in early clinical trials, possibly because DNA-based vaccines need to gain access to the nucleus to exert their action, complicating efficient delivery. Overall, flexible design, standardized production processes and relatively short-lived cytoplasmic presence make mRNA vaccines very powerful, especially in a pandemic situation with rapidly mutating viruses.

However, one of the greatest challenges encountered when developing mRNA vaccines is their poor stability. Currently, most mRNA vaccines are administered IM, where the mRNA that is taken up by host cells leads to antigen expression (Hassett et al., 2019). Early research on mRNA vaccines has demonstrated that naked mRNA is quickly degraded after administration (Pardi et al., 2015; Wayment-Steele et al., 2020). Consequently, over the last few years efforts were made to improve the *in vivo* stability of mRNA after administration. This led to ways to optimize the mRNA structure by slowing down its degradation (see under section 'mRNA stability'). Another successful and currently widely used approach is to encapsulate and protect the mRNA in LNPs (Pardi et al., 2015). This reduces premature mRNA degradation after administration and enhances delivery to the cytosol of antigen-presenting cells (Liang et al., 2017; Lindsay et al., 2019).

Although progress has been made to enhance the stability *in vivo* and efficacy of mRNA-LNP vaccines, much less attention has been paid to their stability during storage (Crommelin et al., 2021). In order to effectively distribute a vaccine worldwide, it should have a sufficiently long shelf life, preferably at refrigerator temperatures (2–8 °C) or above. Currently, hardly any data is available in the public domain on what happens when mRNA-LNP formulations are stored for long periods of time. Moreover, it is unclear to what extent entrapping mRNA within LNPs influences the storage stability of the mRNA vaccine. Additionally, very little is known about the structure and morphology of LNPs formulated with mRNA, the chemical stability of the LNP components and the colloidal stability of the mRNA-LNP system. What is known now is that in order to store the current mRNA COVID-19 vaccines for longer periods of time, they have to be frozen. The current mRNA COVID-19 vaccines of Moderna and BioNTech/Pfizer have to be kept between –15 and –25 °C and between –60 and –90 °C, respectively (EMA, 2020a, 2021). To date, the degradation processes and the reasons why storage temperature requirements differ, are not fully understood.

The requirement of storing the mRNA-LNPs in a frozen state hampers vaccine distribution. Especially, the very low temperature of –60 to –90 °C is a major obstacle when it comes to vaccine transport, storage and distribution among end-users worldwide. Most other vaccines can be stored at 2–8 °C. Clearly, there is a need and opportunity to find ways

of stabilizing mRNA-LNP vaccines to allow non-frozen storage. This review provides an overview of approaches to make mRNA vaccines more stable, so that they can be stored longer at less extreme temperatures. To explore the topic, the characteristics of mRNA-LNP vaccines and their influence on storage stability are discussed. This information is used to identify the reasons for mRNA vaccine instability and to explore technological options for stability improvement.

2. Overview of mRNA vaccines

The composition of mRNA-LNP vaccines is fundamental to their stability. In the development of vaccines against SARS-CoV-2, a variety of different mRNA vaccine candidates have been created. Currently, there are 10 different mRNA COVID-19 vaccines that have progressed to clinical trials (World Health Organization, 2021). The SARS-CoV-2 mRNA vaccines either use conventional mRNA or self-amplifying mRNA (SAM). There are currently three 'conventional' mRNA vaccines in use or in advanced clinical trials that encode the full S protein. These are the mRNA-1273 vaccine by Moderna, BNT162b2/Comirnaty by BioNTech/Pfizer and CVnCoV by CureVac (Table 1). A detailed comparison of these three mRNA COVID-19 vaccines including their differences and similarities in mRNA structure and LNP design has been provided in several other reviews (Kim et al., 2021; Verbeke et al., 2021). The following sections aim to give an overview of the function and characteristics of the mRNA component and the LNP delivery system in these vaccines, as they play a critical role in the stability of mRNA vaccines, both upon *in vivo* administration and during storage.

2.1. mRNA engineering for optimum *in vivo* stability and translation capacity

Because of the negative charges on its phosphate groups, mRNA is a polyanionic macromolecule in pH ranges typically used for parenterals (Lipfert et al., 2014). A first obstacle for mRNA vaccines is that naked mRNA is quickly degraded upon injection by ribonucleases (RNase), which are abundant in the extracellular environment. Second, the internalization of mRNA inside the cell is detected by intracellular RNA sensors, including endosomal Toll-like receptors (TLR) and cytoplasmic nucleic acid sensors. Binding of mRNA to these host defense receptors activates innate immune pathways, leading to the expression of hundreds of genes. One the one hand, this may provide an adjuvant effect on the vaccine potency. On the other hand, it establishes an antiviral state in cells, which strongly reduces the mRNA intracellular stability and translation (Pepini et al., 2017). Following internalization, mRNA strands need to be recruited into the ribosomes to enable the expression of the encoded protein. The protein synthesis rate and the functional half-life of mRNA can be drastically increased through mRNA engineering. The typical elements of an mRNA strand for inclusion in an mRNA vaccine are schematically presented in Fig. 1.

Many efforts have been made to increase the *in vivo* stability and translation capacity of the mRNA molecule, while avoiding unwanted innate immune activation. One prevalent idea is that this can be achieved by optimizing the regulatory regions of the mRNA: the 5' cap, poly-A tail and untranslated regions (UTRs). The UTRs are parts of the mRNA that flank the coding region of the mRNA and regulate its stability and translation. The poly-A tail also regulates stability, as its shortening and eventual removal leads to mRNA degradation. The 5' cap structure is important for protein production and the recruitment of translation initiation factors (Pardi et al., 2018). Furthermore, mRNA with maximized GC (guanine-cytosine) content in combination with codon optimization, i.e., selection of 'frequent codons' in the coding region, leads to enhanced stability and translation (Thess et al., 2015). Another critical determinant is the secondary structure of mRNA, which can be stabilized by changing the primary sequence through codon optimizations and computational tools. Building secondary structures in the mRNA –except in the 5' UTR region– by choosing 'highly structured

Table 1

Information about the three mRNA-LNP drug products that are presently used or in clinical phase III trials. For comparison reasons, drug product information for Onpattro (an siRNA-LNP drug product) has been added.

Category	siRNA	Pfizer-BioNTech mRNA vaccine	Moderna mRNA vaccine	Curevac mRNA vaccine candidate
Name product	Onpattro * patisiran	BNT162b2; Comirnaty	mRNA-1273	CVnCoV
mRNA dose; route of administration	0.3 mg/kg, intravenous	30 µg; intramuscular	100 µg; intramuscular	12 µg; intramuscular
Lipid nanoparticle components	DLin-MC3-DMA: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) PEG2000-DMG = Alpha-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene Cholesterol	0.43 mg ALC-0315 = (4-hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 0.05 mg ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 0.09 mg 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) 0.2 mg Cholesterol	SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate} PEG2000-DMG = 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) Cholesterol	Cationic lipid (Acuitas Therapeutics) Phospholipid Cholesterol PEG-lipid conjugate
Molar lipid ratios (%) ionizable cationic lipid : neutral lipid : cholesterol : PEG-ylated lipid	50:10:38.5:1.5	46.3:9.4:42.7:1.6	50:10:38.5:1.5	50:10:38.5:1.5
Molar N/P ratios ^a	3	6	6 ^b	6 ^b
Buffer	Potassium phosphate, monobasic, anhydrous Sodium phosphate, dibasic, heptahydrate pH ~ 7	0.01 mg Potassium dihydrogen phosphate 0.07 mg Disodium hydrogen phosphate dihydrate pH 7–8	Tris (tromethamine) pH 7–8	? pH
Other excipients	Sodium chloride Water for injection	0.01 mg Potassium chloride 0.36 mg Sodium chloride 6 mg Sucrose Water for injection	Sodium acetate Sucrose Water for injection	Saline

*NDA 210922 ONPATTRO (patisiran) Lipid Complex Injection; Addendum to Drug Product Quality Review (FDA, 2017).

^a N = ionizable cationic lipid (nitrogen), P = nucleotide (phosphate).

^b Estimate.

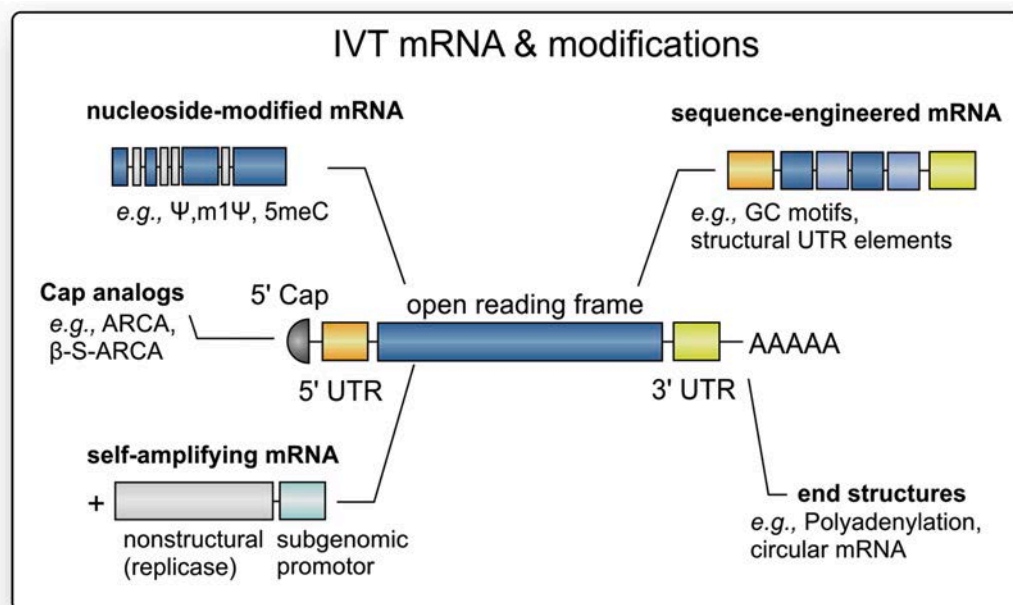


Fig. 1. Structural elements of *in vitro* transcribed (IVT) mRNA. Each of these elements can be optimized and modified in order to modulate the stability, translation capacity, and immune-stimulatory profile of mRNA. Courtesy of Verbeke et al. (2019).

coding sequences' leads to higher translation *in vivo* as well, because of a longer functional half-life (Mauger et al., 2019). Alternatively, Mauger et al. demonstrated that the incorporation of naturally occurring

modified uridines, such as the use of 1-methyl-pseudouridine (m1Ψ) instead of uridine, induces global changes in the secondary structure of mRNA which correlated with high protein expression. Importantly, the

introduction of these modified uridines inside the mRNA construct is currently the most efficient way to minimize the cellular recognition of mRNA by RNA-binding proteins that are involved in the innate immune reaction to foreign mRNA. This, in turn, enhances biological stability and translational capacity, while reducing the reactogenicity of mRNA vaccines. Moreover, there are also indications that m¹Ψ increases base stacking and the melting point of mRNA, thereby making mRNA more stable (Mauger et al., 2019; Zhao and He, 2015). This could mean that the incorporation of 1mΨ, as is done for the COVID-19 vaccines from Moderna and BioNTech/Pfizer, also affects the stability of mRNA before administration. CureVac followed a different path, as outlined by Thess et al. (Thess et al., 2015). An interesting analysis of the choices CureVac made in engineering the CVnCoV mRNA was recently published (Hubert, 2021). However, even when these structural elements are optimized, IM injection of naked mRNA through a syringe does not lead to a robust immune response, probably because of the poor cell transfection capacity of naked mRNA and the susceptibility to RNase (Pardi et al., 2015). Importantly, this illustrates that optimization of only the mRNA structure is not sufficient for creating effective mRNA vaccines: additional protection and delivery systems are needed (Kauffman et al., 2016; Sahin et al., 2014).

The other type of mRNA vaccines, SAMs, do not only encode the target antigen but also RNA polymerase encoding 'self-amplifying' factors derived from Alphavirus. Typically, they consist of 9 kb mRNA nucleotides compared to 2–4 kb for non-replicating mRNA vaccines. The SAM vaccine candidates were developed with the intent of forgoing the typical 'prime-boost' regimen of a two-dose strategy and instead focusing on a single injection per recipient. Because of their replication competence, the injected dose for SAM vaccines is lower than for conventional mRNA vaccines and one dose might be sufficient for protection (Erasmus et al., 2020; Vogel et al., 2018). When SAMs are translated in the host cell, an RNA replicase synthesizes negative-sense RNA intermediates complementary to the coding mRNA template (Fig. 1). These are in turn transcribed to many coding mRNA molecules, leading to prolonged and enhanced antigen expression (Bloom et al., 2020). Both SAM vaccines encode the full S protein and the highest dose for these vaccines in clinical trials was more than tenfold lower than the typical doses used for the conventional mRNA vaccines (Ward and McCormack, 2021). The two SAM vaccines in clinical development are nCoVsaRNA by the Imperial College London and ARCT-021 by Arcturus/Duke-NUS (both as mRNA-LNP).

2.2. LNPs as delivery system

To overcome these transfection problems with naked mRNA, protecting delivery systems have been developed. Currently, the leading mRNA COVID-19 vaccines (Table 1) are all utilizing LNP technology. This illustrates the successes achieved with this type of nanoparticle to stabilize mRNA and successfully deliver it into cells (Pardi et al., 2015). The LNPs in mRNA COVID-19 vaccines consist of four main components (cf. Table 1): a neutral phospholipid, cholesterol, a polyethylene-glycol (PEG)-lipid, and an ionizable cationic lipid. The latter contains positively charged ionizable amine groups (at low pH) to interact with the anionic mRNA during particle formation and also facilitate membrane fusion during internalization (Evers et al., 2018; Reichmuth et al., 2016). In addition, PEG-lipid is used to control the particle size and act as a steric barrier to prevent aggregation during storage. Together with the mRNA, these components form particles of about 60–100 nm in size by using a rapid mixing production technique (Evers et al., 2018). The SARS-CoV-2 vaccine candidates nCoVsaRNA and ARCoV, for example, have average particle sizes of 75 nm and 89 nm, respectively (McKay et al., 2020; N.-N. Zhang et al., 2020).

A key aspect of LNPs and the characteristic that makes them different from liposomes (spherical vesicles with at least one lipid bilayer and an aqueous core) is the presence of lipids in the core, although data from several studies indicate that water is also present to some extent (Arteta

et al., 2018; Kulkarni et al., 2018; Brader et al., 2021). This would mean that the mRNA could be exposed to an aqueous environment, even when it is encapsulated. This type of core structure has been previously found in both unloaded and siRNA (small interfering RNA) containing LNPs, as demonstrated by cryogenic transmission electron microscopy (cryo-TEM) (Kulkarni et al., 2019, 2018). Similarly, studies of mRNA-LNPs have shown electron dense cores (Fig. 2) (Arteta et al., 2018; Eygeris et al., 2020; Leung et al., 2015; Patel et al., 2020; Tanaka et al., 2020). Thionine was used for cryo-TEM contrast enhancement (Brader et al., 2021).

Although their lipid core is a common feature of mRNA-LNPs, characteristics of the exact structure of this core and its dependence on lipid ingredients (molar ratios) and the localization of the mRNA are still under debate (see Fig. 3). mRNA is certainly located inside the LNPs, as determined by the RiboGreen assay. RiboGreen is a dye that exhibits fluorescence when bound to single stranded mRNA, but cannot enter the LNPs. In mRNA-LNP formulations, such as those used in mRNA vaccines, the fraction of accessible mRNA is very low (Arteta et al., 2018; Patel et al., 2020) and thus, encapsulation efficiencies, derived from RiboGreen assays, are typically > 90%. Taken together, the cryo-TEM (Fig. 2) and encapsulation evidence shows that the mRNA-LNPs form nanoparticles with encapsulated mRNA that is protected from the external medium. There are 3 models proposed for the structure of mRNA encapsulated by LNPs; these mainly originate from siRNA-LNPs analysis (Fig. 3).

The dawn of mRNA vacca limitation of this is that the encapsulated cargo affects the structure of LNPs: siRNA is very different from mRNA in structure and size (Table 2) and the molar N/P (ionizable cationic lipid over phosphate) molar ratios differ, 3 versus 6, respectively (Table 1). mRNA is at least 100-fold larger than siRNA and this affects the structure of the LNPs. Besides, there are indications that mRNA is located in the core of the LNPs and siRNA more towards the surface and mRNA can form 'blebs' (Fig. 2) (Viger-Gravel et al., 2018). The composition of the bleb part of the LNP is a matter of debate (Leung et al., 2015; Brader et al., 2021). The latter state: "mRNA can dissociate from the charged lipid to reside within a solvent-filled bleb compartment."

The multilamellar vesicle model for mRNA-LNPs (Fig. 3A) is unlikely to be correct. It does not correspond to the electron dense cores found by TEM of the mRNA-LNPs. Currently, most researchers hold the view that

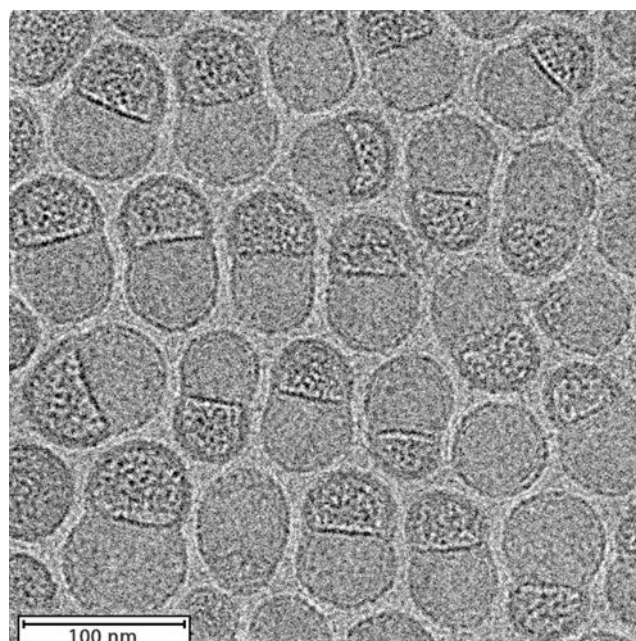


Fig. 2. Cryo-TEM image of mRNA-LNP showing 'bleb' structures with distinctly different electron density. Adapted from Brader et al. (2021) with permission.

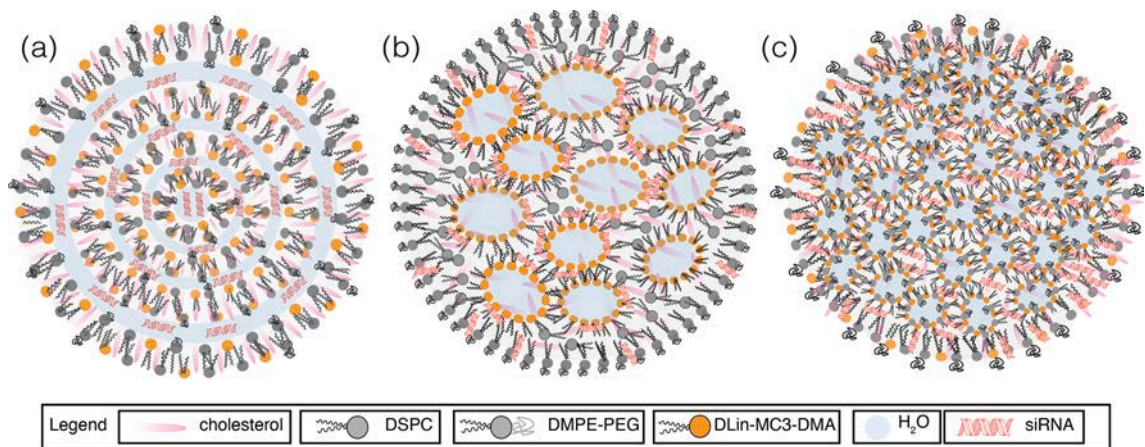


Fig. 3. Schematic representation of the proposed models for siRNA-LNP and mRNA-LNP structure. A: multilamellar vesicles; B: nanostructure core; C: homogeneous core shell as discussed by Viger-Gravel et al. (2018). Courtesy of the authors.

Table 2
Differences between mRNA and siRNA molecules.

	mRNA	siRNA
Molecular weight (g/mol)	$\geq 10^6$	10^4
Molecular conformation	Single stranded	Double stranded
5' end	5' cap	Phosphorylated 5' end
3' end	Poly-A tail	Hydroxylated 3' end

mRNA-LNPs are best described by the core-shell model (Fig. 3B & C). This means that the nanoparticles have a surface layer and an amorphous, isotropic core. Viger-Gravel et al. used NMR spectroscopy to elucidate an LNP structure and they make the case that two types of core are possible (Viger-Gravel et al., 2018). They describe the model of an amorphous core containing water pores surrounded by inverted cationic lipids (Fig. 3B). They also postulate that the lipids in the core could be homogeneously dispersed with small water pockets in between (Fig. 3C). The latter corresponds more to the experimental results for their siRNA-LNPs and mRNA-LNPs.

Arteta et al. based their mRNA-LNP structure-model on cryo-TEM, small-angle X-ray scattering (SAXS) and small-angle neutron scattering (SANS) measurements. They found that 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and PEG-lipid as well as part of the ionizable cationic lipid and cholesterol are located on the surface of the LNPs. Inside the core, the main part of the ionizable cationic lipid, cholesterol (dependent on its concentration), water and mRNA are present. Interestingly, their research indicates that the isotropic LNP core consists for 24% (volume fraction) of water. They propose that mRNA is located inside water cylinders, which are surrounded by cationic lipids (Fig. 4). This would mean that the mRNA is –at least partly– exposed to water inside the LNPs, which likely contributes to its instability upon storage under non-frozen conditions (Arteta et al., 2018). Comparable results were reported by Sebastiani et al. (2021).

It would, therefore, be interesting to study how mRNA interacts with water and ionizable cationic lipids in the LNP. mRNA is hydrophilic; it can interact electrostatically and through hydrogen bonds with ionizable cationic lipids (apparent $pK_a < 6.5$) (Buschmann et al., 2021). This depends on the pH inside the LNP. If the LNP shells are permeable to protons –which is likely, as ionized dyes such as 2-(p-toluidino)-6-naphthalene sulfonic acid (TNS) and thionine can enter the LNP core (Jayaraman et al., 2012; Brader et al., 2021)– the pH would be similar to the rest of the formulation, around 7 to 8, meaning that most of the ionizable cationic lipids would be uncharged. However, as the ionizable cationic lipids are stacked in the core, they may show polyelectrolyte behavior, leading to deviations of the Henderson-Hasselbalch equation, i.e., ‘smearing out’ of the titration curve (Pierrat and Lebeau, 2015).

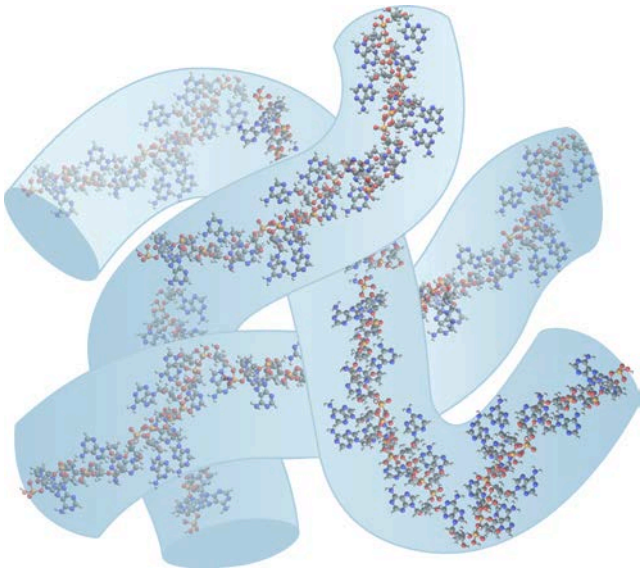


Fig. 4. Schematic representation of the mRNA-water cylinders in the core of mRNA-LNPs (Arteta et al., 2018). Courtesy of the authors.

Moreover, interaction between the mRNA and the ionizable cationic lipids might affect the ionization behavior. For siRNA only weak electrostatic interactions were found with the ionizable cationic lipid, indicating that at least for siRNA-LNP formulations the pH inside approaches or equals the pH outside (Viger-Gravel et al., 2018). For mRNA-LNPs, no such experimental studies have been performed yet. A molecular dynamics simulation study of the complexation of mRNA and a cationic lipid demonstrated lipid-lipid cluster formation and lipid-mRNA cluster formation. Both electrostatic and hydrogen bonds were driving the cationic lipid and mRNA interactions (Rissanou et al., 2020).

Another interesting finding by Arteta et al. is that the shell of their mRNA-LNPs is a monolayer (Arteta et al., 2018; Verbeke et al., 2019). Other researchers propose that the outer shell of mRNA-LNPs consists of one or multiple bilayers, based on cryo-TEM analysis (Fig. 2) (Patel et al., 2020; Tanaka et al., 2020) or SANS (Sebastiani et al., 2021). These findings indicate that assessment of the nature of the mRNA-LNP shell with these techniques is difficult and/or that multiple types of mRNA-LNP structures may exist, dependent on, e.g., the nature of the lipids and the preparation protocol for the mRNA-LNPs. This, in turn, could have implications for the stability of different formulations. In conclusion, questions remain around the structure of mRNA-LNPs and the

interactions between the encapsulated mRNA and the various lipid components.

Analysis of the components of the various mRNA-COVID-19 vaccines has shown that there are common features, but also significant differences (Table 1). The LNP formulation, the use of modified-nucleosides, the GC content and the differences in length between the conventional mRNA and SAM vaccines might influence the physical and chemical stability of these mRNA-COVID-19 vaccines during storage.

3. In vitro stability of mRNA vaccines

As mentioned in the introduction, one of the main obstacles for the distribution of the currently approved mRNA-COVID-19 vaccines is that they have to be stored in frozen form (cf. Crommelin et al., 2021). At refrigerator temperatures, 2–8 °C, the Pfizer/BioNTech and Moderna vaccines are stable for 5 and 30 days, respectively. Both companies provide detailed handling instructions for the end-user (EMA, 2020b, 2021). Interestingly, the vaccine candidate by CureVac is reported to be stable for 3 months at refrigerator temperatures and at –60 °C (CureVac, 2020). These are the only manufacturers who have released their long-term storage conditions at present. Such temperature requirements severely impact the logistics of the storage, transport, and distribution of these vaccines. However, to date little information on optimization of the stability of mRNA vaccines can be found in the public domain. This section aims to give an overview of the factors that influence the stability of the components of mRNA-LNP vaccines and discuss the methods to analyze this stability.

3.1. mRNA stability

One factor that strongly influences the required storage conditions is the stability of the mRNA. As discussed above under Section 2.1, the structure of the mRNA molecule is specifically designed to increase the translation of the target antigen *in vivo*. A special feature of mRNA is that even one change (strand break, or oxidation of the bases) in the long mRNA strand (typically between 1000 and 5000 nucleotides long) can stop translation (Klauer and van Hoof, 2012). This makes mRNA vaccines quite different from other vaccines in which small changes of the antigens do not necessarily have a measurable effect on their efficacy. Consequently, for mRNA vaccines, it is critical to monitor the integrity of the full molecule.

There are several ways in which mRNA degradation can occur; one can discern chemical and physical degradation. Chemical degradation encompasses the modifications of bonds in the mRNA molecule. Physical instability includes denaturation (loss of secondary and tertiary structure), which has different –likely less significant– consequences for the activity of mRNA than denaturation has for the activity of protein biologics. However, denaturation also comprises processes such as aggregation and precipitation, which negatively affect mRNA translation. In a review on the stability of nucleic acids Pogocki and Schöneich state

that chemical degradation plays a larger role in the degradation of small nucleic acids than physical instability and that is probably even more true for large structures such as mRNA (Pogocki and Schöneich, 2000).

Chemical degradation of mRNA *in vitro* mainly occurs through hydrolysis and oxidation. Hydrolysis predominantly occurs via the phosphodiester bonds that form the backbone of the mRNA molecule (Fig. 5). The 2' OH group on the ribose plays a crucial role as the transesterification reaction leading to a mRNA strand break starts by a nucleophilic attack by the 2'OH group on the phosphate ester bond leading to a break at the P-O5' ester bond (Fig. 5). This process requires water and can be catalyzed by nucleases, but also by the mRNA molecule itself and other exogenous factors like Brønsted acids and bases (Houseley and Tollervey, 2009; Pogocki and Schöneich, 2000). In two publications on mRNA hydrolysis the authors state that the base sequence and secondary structure of mRNA influence the rate of hydrolysis (Kaukinen et al., 2002; Mikkola et al., 2001). Specifically, base-stacking may decrease the cleavage rate of phosphodiester bonds. The 'average unpaired probability' of an mRNA molecule can be minimized. Specially designed algorithms that select nucleotide sequences for single stranded mRNA with maximum double stranded regions are available. *In vitro* stability is claimed to be significantly improved following this approach (Wayment-Steele et al., 2020). A difference between the CureVac, Pfizer/BioNTech and Moderna vaccines is that the latter two have single nucleoside incorporations of 1-methyl-pseudouridine. A previous study has shown that this modification improves RNA secondary structure stability (Mauger et al., 2019). CureVac uses GC-enrichment, which should have a similar effect (Hubert, 2021; Zhang et al., 2011).

Oxidation, in contrast, affects the nucleobases and to a lesser extent the sugar groups of the mRNA's ribose units. Oxidation can lead to the cleavage of bases, strand break and the alteration of the secondary structure of the mRNA (Pogocki and Schöneich, 2000). However, as stated before, hydrolysis appears to be accepted as the main factor driving mRNA degradation (Fabre et al., 2014).

3.2. Analyzing mRNA stability

As the integrity and purity of the mRNA are essential to safeguard efficacy and safety of mRNA vaccines, it is important to have tools to monitor these aspects. There are various attributes of the mRNA molecules that collectively determine whether the product can be used. The review by Poveda *et al.* highlights these attributes and briefly touches upon approaches that are used in general to measure and monitor them (Poveda et al., 2019).

Table 3 provides a comprehensive list of analytical methods to determine and monitor quality attributes and stability of mRNA vaccine bulk drug substance and final drug product. Quality specifications for the presently accepted mRNA-LNP COVID-19 products are still not available in the public domain. Leaked documents (through a cyber-attack of the EMA, just before the approval date in the UK and the

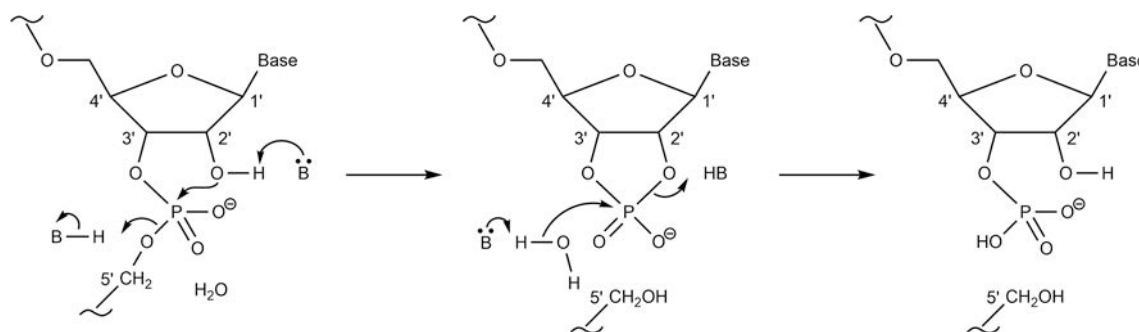


Fig. 5. Base-catalyzed intramolecular hydrolysis of the phosphodiester bond in RNA by way of a 2',3'-cyclic phosphate. B denotes a Brønsted base. Redrawn from Pogocki and Schöneich (2000).

Table 3

Assays to determine and monitor mRNA drug substance and mRNA-LNP drug product quality attributes and stability.¹⁾

Assay ²⁾	Attribute
Characterizing DNA templates and RNA transcripts	
DNA template sequencing/mRNA sequencing	Identification of mRNA
UV spectroscopy (A260 nm, A260/A280, A260/A230)	Quantification - purity dependent
Fluorescence-based assays (e.g., residual DNA)	Quantification - purity dependent
Agarose/acrylamide electrophoresis	Molecular mass, RNA integrity and quantification
Reverse transcriptase qPCR	Identification and quantification of mRNA
Western blot for dsRNA	Quality assessment
mRNA capping analysis	Quality assessment
mRNA polyadenylated tail analysis	Quality assessment
Chromatographic assays: RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC	Quantity and quality assessment
Characterizing mRNA-encoded translation products	
In vitro translation - cell free medium	Translation into target protein
Messenger RNA evaluation using various cell-based systems	Translation product analysis and potential toxicity assay
Characterizing mRNA-lipid complexes	
DLS	Particle size (distribution)
Laser Doppler electrophoresis	Zeta potential
NTA/TRPS	Particle size (distribution)
SE-HPLC(MALS)	Particle size distribution; assessing bound/unbound mRNA
Microscopy (cryo TEM, ESEM, AFM)	Nanoparticle morphology, particle size (distribution)
Gel or capillary electrophoresis	Assessing bound/unbound mRNA and surface charge
Chromatographic assays: RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC / mass spectrometry	Quantification and integrity of lipids and/or mRNA; for some: assessing bound/unbound mRNA and molar mass
Fluorescent dyes	Encapsulation efficiency
General pharmaceutical tests	
	Appearance, pH, osmolality, endotoxin concentration, sterility

¹⁾ Adapted from Poveda et al., 2019; Muralidhara et al., 2016; Fan et al., 2021; Crommelin et al., 2021.

²⁾ Abbreviations: AF4, asymmetrical flow field-flow fractionation; AFM, atomic force microscopy; dsDNA, double stranded DNA; DLS, dynamic light scattering; ESEM, environmental scanning electron microscopy; IEX-HPLC, ion-exchange high performance liquid chromatography; IP-HPLC, ion-pair high performance liquid chromatography; MALS, multi-angle light scattering; NTA, nanoparticle tracking analysis; qPCR, quantitative polymerase chain reaction; RP-HPLC, reversed-phase high performance liquid chromatography; SE-HPLC, size-exclusion high performance liquid chromatography; TEM, transmission electron microscopy; TRPS, tunable resistive pulse sensing.

USA), which contain classified information on the quality of Comirnaty, mention percentages of mRNA integrity between 70 and 75% (Tinari, 2021) and the assessment report from the EMA reads: 'the quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable.'

Here we elaborate on the techniques that are applicable for studying the integrity of mRNA and used for quality control (QC). An overview of quality documentation required by EU authorities for an Investigational Medicinal Products Dossier (IMPD) with a focus on mRNA vaccines is given by Schmidt and the interested reader is referred to that informative document for details (Schmid, 2017). Because many of the described methods are intended for assaying naked mRNA, whereas mRNA vaccines for COVID-19 are encapsulated in LNPs, for some assays the mRNA first needs to be released and isolated from the LNP. Potential effects of this isolation process can be taken into account by including proper controls.

Gel electrophoresis is a frequently used technique that can give information on the size and the integrity of the mRNA. When mRNA degrades and strand breaks occur, the mRNA strand becomes shorter. As a result, the intensity of the band at the expected mRNA length will decrease or the band will broaden, while new bands may appear. Using this approach Démoulin et al. analyzed the quality of SAM under RNase free conditions (Démoulin et al., 2017). Based on the gel electrophoresis data, they were able to determine whether the mRNA is of acceptable quality and stable. Commercial electrophoresis equipment is now available for high-throughput analysis of mRNA (Pocernich et al., 2019).

Recently, Zhang et al. showed that fluorescence correlation spectroscopy (FCS) can be used to monitor changes in mRNA size (H. Zhang et al., 2020). The Brownian motion of fluorescent mRNA gives an indication of its molecular weight. This technique, however, needs a fluorescent label, is not more accurate than gel electrophoresis and only detects mRNA degradation involving substantial changes in molecular weight, e.g., strand breaks.

Throughout the (bio)pharmaceutical industry chromatographic techniques form a powerful platform to monitor purity and stability of active pharmaceutical ingredients and drug products. However, the development of HPLC techniques for establishing purity and stability of mRNA molecules has been slow so far. Successful protocols for analyzing large mRNA molecules can be found in the patent literature as well as in publications where RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC methods are described (Issa and Packer, 2019; Kanavarioti, 2019; Spivak et al., 2014). Some of these techniques can also be used for mRNA purification purposes (Kim et al., 2007; Levine et al., 2019). IEX-HPLC can be used for measuring free and LNP encapsulated mRNA. An orthogonal technique to establish the same parameter is the earlier mentioned RiboGreen technique. Different outcomes, however, were found for the same mRNA-LNP product; the IEX-HPLC outcome correlated better with the *in vivo* readout than the RiboGreen data. This illustrates that even established techniques like the RiboGreen assay should be carefully validated on a case-by-case basis (Schariter et al., 2019).

mRNA degradation can also be analyzed by using the reverse transcription quantitative polymerase chain reaction (RT-qPCR). This approach quantifies the total amount of mRNA that can be transcribed into intact cDNA targets for PCR. This means that all degradation that prevents this can be quantified indirectly. In their evaluation of this technique, Brisco and Morley argue that it gives reliable quantitative results (Brisco and Morley, 2012). Another advantage of this method is that all types of degradation that affect transcription are taken into account, whereas the previously discussed techniques only look at mRNA size. However, RT-qPCR sometimes is less reliable due to the error rate of the enzymes that are used (Schmid, 2017). Other disadvantages of this approach are that it is not widely used and the different types of degradation cannot be distinguished from each other.

mRNA expression *in vitro* (in cells) is also used to analyze the integrity of mRNA (Zhang et al., 2020b; Zhao et al., 2020). By using mRNA that encodes a fluorescent protein, the mRNA integrity can indirectly be determined by measuring the fluorescence signal. This approach can assist in providing guiding principles for bioactive mRNA-LNP design and formulation development studies. Alternatively, the translation efficacy of mRNA encoding non-fluorescent antigens can be determined using an enzyme-linked immunosorbent assay (ELISA), or western blotting techniques as has been used previously to analyze the stability of mRNA encoding the receptor-binding domain (RBD) of SARS-CoV-2 (Zhang et al., 2020b). Advantages of this approach are that it gives the sum of the overall integrity of the formulation and everything that can influence the transcription of the mRNA. Disadvantages of this method are that it is not very precise, unable to show the type of mRNA damage, and time-consuming.

3.3. LNP stability

Besides mRNA integrity, stability of LNPs is critical for the quality of mRNA-LNP vaccines. No information on LNP stability tests could be found for the present mRNA COVID-19 vaccines, but the siRNA-LNP formulation of Onpattro (patisiran) has a three-year shelf life when kept between 2° and 8 °C (EMA, 2018). There is a warning in this SMPC text that the dispersion should not be frozen. The composition of the Onpattro LNP system is: DLin-MC3-DMA, as ionizable cationic lipid; DSPC; cholesterol; PEG2000-C-DMG (see table 1) (mol-ratio 50:10:38.5:1.5 mol%); they are composition-wise similar to the LNPs in Comirnaty and mRNA-1273. A study on siRNA-LNPs composed of the lipidoid 306O₁₃ instead of DLin-MC3-DMA, showed that in aqueous conditions the formulation remained stable at 2 °C for 156 days at pH 7 (Ball et al., 2016). Particle size and siRNA encapsulation for this formulation did not significantly change. Complementary research by Suzuki et al. showed that siRNA-LNPs are stable over the experimental period, i.e. 1.5 years, at 4 °C (Suzuki et al., 2015). Altogether, these data strongly indicate that instability of the mRNA, rather than LNP instability, determines the storage conditions and shelf life of the current mRNA-LNP COVID-19 vaccines.

The stability and quality attributes of liposomes and LNPs have been reviewed by Fan et al. (Fan et al., 2021). LNPs can undergo chemical and physical instability. Chemical instability comprises the degradation of the lipids in the LNPs that are susceptible to hydrolysis and oxidation. Lipid oxidation can occur in unsaturated fatty acid moieties (not present in Comirnaty and mRNA-1273) and with cholesterol, potentially as a result of a hydroperoxide attack, an impurity present in the PEG-group of PEG2000-C-DMG (Jaeger et al., 1994; Wang et al., 2019). Oxidative impurities may also result in oxidation of encapsulated mRNA. The carboxylic ester bonds in lipids, such as DSPC and the ionizable cationic lipids, are susceptible to temperature- and pH-dependent hydrolysis (Fig. 6).

Another key aspect of LNP stability is physical degradation. There are three main types of physical instability that can occur: aggregation, fusion, and leakage of the encapsulated pharmaceutical ingredient. Aggregation of LNPs during storage and fusion of LNPs has been reported (Ayat et al., 2019; Ball et al., 2016). To increase stability on the shelf, LNPs are often formulated with PEG-lipids (Burke et al., 2013; Ryals et al., 2020). The PEG-molecules at the surface prevent the individual LNPs from aggregating. The other type of physical degradation –leakage of the mRNA– mainly affects the stability of the encapsulated product. Of note, encapsulation efficiencies are typically > 90% and release of the RNA payload from LNPs during storage has not been reported (as measured with the RiboGreen test). mRNA that is not encapsulated ('naked mRNA') is hardly taken up by cells; besides, it degrades rapidly and is, therefore, not available for translation.

Hypersensitivity reactions –rarely observed upon intramuscular

injection of the mRNA-LNP COVID-19 vaccines– may be related to the PEG-lipids. Therefore, alternative lipids to prevent aggregate formation have been investigated. Introduction of polysarcosine-modified lipids stabilized lipid-based systems against aggregation while reducing the immunostimulatory response (Nogueira et al., 2020). Additional testing is needed to establish whether such PEG-lipid alternatives improve the mRNA stability (e.g., owing to lack of peroxides).

3.4. Analyzing LNP stability

Analytical methods to monitor the stability of LNPs have been expertly reviewed in the previously mentioned article by Fan et al. and Kim et al. and we refer the interested reader to this literature source (Fan et al., 2021; Kim et al., 2021).

3.5. Which mRNA-LNP component is more unstable: The mRNA, the lipids, or the combination?

To date, several studies have investigated ways to stabilize mRNA and to stabilize LNPs during storage (Ball et al., 2016; Jones et al., 2007). It is, however, interesting to question which of these components is the bottleneck for stability. Is it the mRNA that degrades when the mRNA-LNP formulations are not frozen, are the LNPs causing the problem, or is it the combination of mRNA with the LNPs?

LNP systems entrapping chemically modified and highly stable siRNA molecules (e.g. Onpattro) have significantly longer shelf lives as compared to mRNA-LNP systems. This would suggest that not the LNP, but rather the mRNA is the current stability bottleneck.

To date, there is no research report available in the public domain on the integrity of both mRNA and LNPs in mRNA-LNP formulations. In the few studies in which the effect of storage is investigated, such as the research by Zhang et al. (N.-N. Zhang et al., 2020), long-term effects are not measured. Therefore, we will be looking first at the long-term stability of naked mRNA, with the caveat that this may be different from the stability of mRNA encapsulated in LNPs (see below).

In their review Pascolo et al. remark that aqueous solutions of naked mRNA can be stored at 4 °C for only a few days, provided that the mRNA is protected from degradation by contaminating ribonucleases by an RNase inhibitor (Pascolo, 2008). This seems to be in line with the current view of mRNA instability. The existing body of research on the long-term stability of naked mRNA suggests that mRNA needs to be frozen or dried in order to stay stable for longer periods of time.

In 2009, Roesler et al. show that the translation efficacy of mRNA encoding luciferase begins to decrease after 8 days or 16 days when stored –RNase free– at room temperature as a liquid or in a lyophilized form, respectively. No efforts were made to optimize the formulations in terms of excipients and freeze drying conditions (Fig. 7) (Roesler et al., 2009). Conclusions about the long-term stability at refrigerator

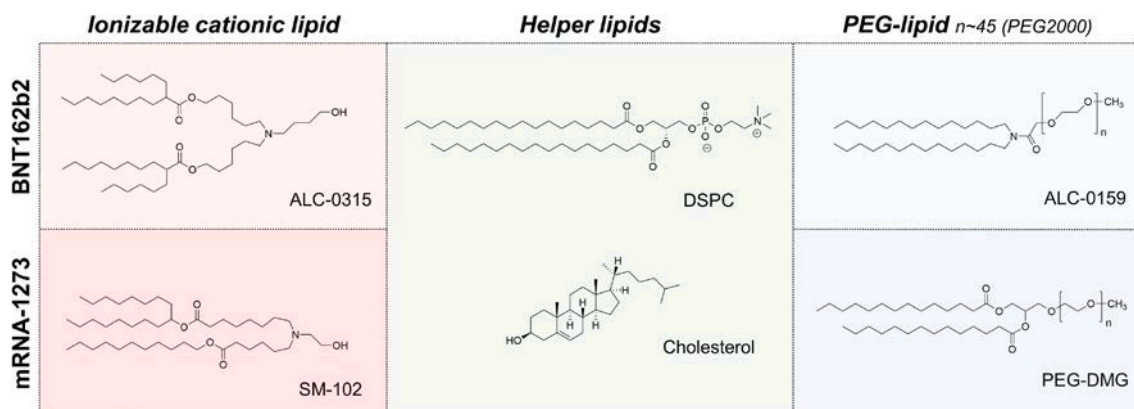


Fig. 6. Lipids used in the mRNA-LNP COVID-19 vaccines BNT162b2 (Comirnaty) and mRNA-1273.

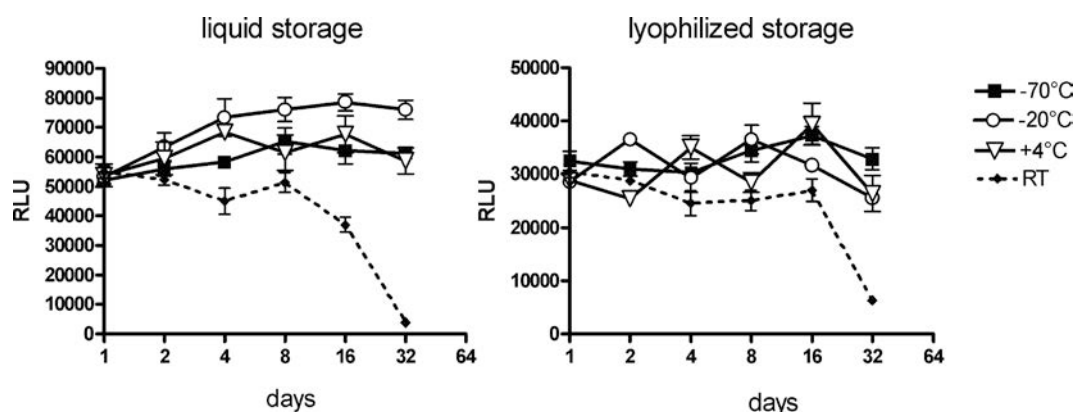


Fig. 7. Stability of mRNA in water analysed by luciferase expression in transfected BHK-21 cells. Courtesy of Roesler et al. (2009).

temperatures can not be drawn from this study, as the stability was only followed for 32 days. There is also information based on theoretical cleavage rate calculations. Wayment-Steele *et al.* predict that mRNA (4000 nt) will have a half-life of 941 days when it is stored at pH 7.4 and 5 °C (Wayment-Steele et al., 2020). They do note that longer mRNA sequences, such as SAMs, are more prone to hydrolysis. Because this is a theoretical calculation that is only based on hydrolytic degradation kinetics, it might underestimate mRNA degradation, e.g., when trace amounts of RNase are present. More research into the stability of mRNA would have to be done to find a definitive answer.

Together, these studies indicate that in an aqueous solution mRNA likely is less stable than LNPs. However, it should be reiterated that results on these two components in isolation could differ from the situation of mRNA encapsulated by LNPs. As discussed in previous sections, mRNA is located inside the LNP core together with an ionizable cationic lipid, cholesterol and water (cf. Fig. 4) (Arteta et al., 2018). This would mean that the mRNA is in an aqueous environment and therefore is susceptible to hydrolysis. The mechanisms of hydrolysis might then be similar to those for mRNA in solution (Brader et al., 2021). However, on the other hand, mRNA inside the LNPs may be coated by the ionizable lipid through hydrophobic, hydrogen-bond and/or electrostatic interactions. In that case the mRNA might be more stable than naked mRNA dissolved in an aqueous medium. Without further studies, it can only be concluded that mRNA instability dictates storage conditions and drives the search for improved, more stable formulations.

3.6. Reasons for different storage conditions

Another interesting aspect of the current mRNA vaccines is that the reported storage temperatures and corresponding 'shelf lives' vary widely: from -80 °C to 2–8 °C and from days to months (Crommelin et al., 2021). Is it possible to identify a difference in the formulation of the mRNA vaccines that could cause this variation? Or, could the difference in storage conditions be related to the limitations of the thermostability testing protocol or a more guarded approach (Schmid, 2017)? This information is important, as insights into the factors that positively affect the stability may be an interesting starting point for the future design of thermostable mRNA vaccines.

Tom Madden, the CEO of Acuitas Therapeutics, stated that the Moderna and Pfizer/BioNTech mRNA vaccines likely have the same stability (Dolgin, 2020). Is it possible that the latter use a more conservative approach to ensure stability? Still, it is quite likely that the Pfizer/BioNTech mRNA-LNP vaccine, that currently has to be stored between -60 to -80 °C was also tested at higher temperatures and under refrigerated conditions as done by CureVac scientists (Stitz et al., 2017). Moreover, the analysis techniques in the stability tests could differ in sensitivity as could the acceptance criteria. Publication of the stability study reports would provide the answers and it would be

interesting to run comparative studies.

4. Opportunities for improving shelf life & storage conditions

When freezing is needed to keep a vaccine stable, distribution, storage and handling by the end-user are highly protocolized and costs increase. For distribution purposes, vaccine stability at refrigerator temperatures, 2–8 °C, would be a desired improvement. In the following section we will focus on research to achieve such storage conditions, as these are seen as a considerable inconvenience for large scale use of mRNA vaccines, such as in the COVID-19 pandemic.

4.1. Excipients

The conclusion from the previous section on the stability of mRNA vaccines is that in order to create more stable mRNA-LNP vaccines, stabilizing the mRNA is the first target. Obviously, any excipient used for mRNA-based vaccines must be RNase free. A review by Muralidhara *et al.* captures a lot of information on the impact of excipients and formulation milieu (Muralidhara et al., 2016).

Some of the excipients proposed by Muralidhara *et al.* are already used in the mRNA vaccines by Moderna and Pfizer/BioNTech. Excipients in the formulations serve as buffers, osmolytes and cryoprotectant or have a dual effect. Moderna, for example, uses a Tris-HCl buffer that would have an additional stabilizing effect on nucleic acid macromolecules as it is also a hydroxyl radical scavenger (EMA, 2021). When selecting these excipients, one should keep in mind that the product may need to be stored at sub-zero temperatures and excipients affect that milieu. The choice of the buffering system and osmolyte is important as the pH may change upon freezing, as has been shown for sodium phosphate buffered systems; a 3.5 pH-units drop occurs upon freezing. Histidine buffers are more 'pH-resistant' upon freezing. But still, the pH may drop 0.5 unit when cooling from 0 °C to -30 °C (Kolhe et al., 2010). And, another example, NaCl (osmolyte)-solutions have a eutectic temperature of -21 °C. Other excipients that could be added are antioxidants, non-reducing free radical scavengers (e.g., ethanol) or metal chelators (Evans et al., 2000). However, the question remains to what extent they indeed ameliorate the stability of mRNA-LNP formulations during storage below or above 0 °C.

pH optimization is also important for mRNA vaccine stability, as the pH influences the hydrolysis rate of mRNA and also LNP stability. Generally, mRNA is most stable in a weakly basic environment. The pH of the Moderna and Pfizer/BioNTech vaccines is between 7 and 8. Wayment-Steele et al. make the point that the apparent pH at the surface of the cationic, fully charged lipids could be higher than in the immediate surrounding aqueous medium (Wayment-Steele et al., 2020).

4.2. Lyophilization

As the presence of water initiates degradation reactions in mRNA-LNPs, lyophilization would be a logical step to improve the long-term stability of mRNA-LNP formulations. The head of viral vaccines research at Pfizer, Philip Dormitzer, has already mentioned Pfizer's aspiration to use lyophilization for mRNA-LNP SARS-CoV-2 vaccines (Dolgin, 2020). Moreover, a lyophilized form of a mRNA-based cytomegalovirus vaccine (mRNA-1647) is used in a phase 2 clinical trial. It has a claimed shelf life at 5 °C of ≥ 18 months. However, no details on the formulation and production process can be found in the public domain (Moderna, 2021).

Freeze drying is widely used for live, attenuated virus vaccines (Hansen et al., 2015). It has also already been investigated for naked mRNA formulations, demonstrating its applicability and beneficial effect on mRNA stabilisation. Previous research by Jones *et al.* shows that freeze-dried mRNA formulated with trehalose is stable at 4 °C for up to 10 months (Jones et al., 2007). Lipid nanoparticles can be successfully freeze dried as well. During the freeze-drying process the structures are exposed to stress. Therefore, lyoprotectants that stabilize these colloidal particles should be included in the formulation. Sucrose or trehalose are used for that purpose (Abdelwahed et al., 2006). Thus, the studies with either mRNA or with LNPs suggest that lyophilization could be a possible way to increase the stability of the combination, mRNA-LNP, and could thereby allow for storage at higher temperatures than those currently required. However, lyophilization does have its downsides, as it requires reconstitution before administration and is a relatively expensive, energy- and time-consuming process. On the other hand, keeping the mRNA vaccines (deep)frozen also comes at a cost. Therefore, a logical next step is to investigate whether lyophilization is a viable option for mRNA-LNP formulations.

Shirane *et al.* freeze dried the ethanol-containing siRNA-LNP dispersion obtained immediately after LNP formation and found no difference between the gene knockdown efficiency of the freshly prepared (ethanol removed by ultrafiltration) and the reconstituted freeze-dried formulations *in vivo* (Shirane et al., 2018). These results show promise for the feasibility of lyophilization of mRNA-LNPs, while recognizing the structural differences between siRNA and mRNA.

There is little published data on the lyophilization of mRNA-LNPs, but there is one recent paper by Zhao *et al.* studying mRNA lipid-like nanoparticles (Zhao et al., 2020). They studied the effect of freeze-drying of these nanoparticles that contain an ionizable cationic lipid-like molecule. No details of the -freeze-drying process are provided. Contrary to the data on siRNA-LNPs obtained by Shirane *et al.*, they found that after lyophilization and reconstitution the *in vitro* test showed no loss of activity, but the *in vivo* efficiency was lost. Thus, freeze-drying of mRNA-LNPs might be a more difficult task than previous research suggests. It would be helpful to elucidate the mechanism behind this nullification of *in vivo* efficiency. It could, for example, be that the formulation was suboptimal for freeze-drying or that the lyophilization process itself was flawed. The authors speculate that an alteration in the nanostructure of the mRNA-LNPs may have caused the low *in vivo* efficacy, as such a change could affect properties like the binding to serum proteins, which are absent in the *in vitro* study. Therefore, further improvement of the formulation excipients and freeze-drying conditions might lead to successful lyophilization of mRNA-LNPs.

Another approach, in case lyophilization of the fully prepared mRNA-LNPs complex is problematic, is to lyophilize naked mRNA and combine it with the LNPs shortly before administration. Ball *et al.* successfully followed the opposite approach by reconstituting freeze dried LNPs with siRNA/ethanol solutions (Ball et al., 2016). They correctly pointed out that: 'Unfortunately, the addition of ethanol to reconstitution solutions is often neither convenient nor practical, as dialysis into aqueous buffer would be required before use in animals or in the clinic' If one wishes to avoid freeze drying or organic solvents for the generation of active mRNA-LNPs, one may mix an 'empty' LNP aqueous

suspension with 'fresh' mRNA and find that the mRNA is taken up and active (Leavitt et al., 2020).

Apart from challenges to preserve the integrity of mRNA-LNP through lyophilization, there are other hurdles such as the high energy consumption of the process and other costs, e.g., those related to the necessary, dramatic expansion of the lyophilization capacity worldwide in times of a pandemic. Therefore, it is worthwhile to consider alternative drying techniques. Only one publication could be found on spray drying of mRNA-LNPs where polymers (e.g., Eudragit) were needed as stabilizers for mRNA-LNPs to secure translation efficiency *in vivo* (Karve et al., 2020). Supercritical drying techniques would be another alternative for freeze-drying; they have been shown to be feasible –with their pros and cons– for other macromolecular biotech products, such as proteins (Jovanović et al., 2004).

5. Conclusions and prospects

This review outlines how different aspects of the current mRNA vaccine formulations influence their stability during storage. We conclude that exposure of mRNA to water likely is the main factor for mRNA vaccine instability. An implication of this is that decreasing the exposure to water would be a promising approach for improving mRNA vaccine stability.

The studies on mRNA-LNP structures indicate that the mRNA is located in the core of LNPs together with ionizable cationic lipid and water. This raises important questions about the possible shielding of the mRNA from water. It is, for example, unknown if and how the ionizable cationic lipids in the LNP interact with the mRNA. More work needs to be done to confirm the proposed structure and to understand the consequences. For instance, the pH inside the LNPs has been identified as an important characteristic to study in relation to stability. Another object of study would be to specifically analyze the type(s) of degradation that mRNA molecules undergo in their final formulation and whether sequence adjustment could help to maintain strand integrity. This could then also be coupled to characterization and optimization of the secondary and tertiary structure of mRNA, as there are indications that some folded structures are more stable.

This report is the first comprehensive survey of the factors behind mRNA-LNP vaccine instability. It also points towards solutions to address this instability and thereby may be of assistance to the development of more thermostable mRNA-LNP vaccines, alleviating a major barrier for the distribution of these vaccines.

CRedit authorship contribution statement

Linde Schoenmaker: Conceptualization, Writing - review & editing. **Dominik Witzigmann:** Writing - review & editing. **Jayesh A. Kul-karni:** Writing - review & editing. **Rein Verbeke:** Writing - review & editing. **Gideon Kersten:** Writing - review & editing. **Wim Jiskoot:** Conceptualization, Writing - review & editing. **Daan Crommelin:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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