

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALNYLAM
PHARMACEUTICALS, INC.,

Plaintiff,

v.

PFIZER, INC., PHARMACIA &
UPJOHN CO. LLC, BIONTECH
SE, and BIONTECH
MANUFACTURING GMBH,

Defendants.

Civil Action No. 22-336-CFC
(consolidated)

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REVISED MEMORANDUM OPINION¹

September 9, 2024
Wilmington, Delaware

¹ This Revised Memorandum Opinion replaces the Memorandum Opinion issued on August 12, 2024 (D.I. 241) pursuant to the Memorandum Order issued on September 9, 2024 (D.I. 245).



COLM F. CONNOLLY
CHIEF JUDGE

In these consolidated actions, Plaintiff Alnylam Pharmaceuticals, Inc. alleges that COVID-19 vaccines manufactured by Defendants Pfizer, Inc, Pharmacia & Upjohn Co. LLC, BioNTech SE, and BioNTech Manufacturing GmbH infringe claims of six Alnylam patents: U.S. Patent Nos. 11,246,933 (the #933 patent), 11,328,979 (the #979 patent), 11,590,229 (the #229 patent), 11,612,657 (the #657 patent), 11,633,479 (the #479 patent), and 11,633,480 (the #480 patent). Pending before me is the parties' dispute about the construction of the term "head group," a term that appears in all the asserted claims of the #933 and #979 patents, and in asserted claims 27 and 28 of the #229 patent, claims 4–6, 15–19, 22, 23, 26, 28, and 29 of the #657 patent, claims 10–12 of the #479 patent, and claims 1–4, 11–15, and 17–19 of the #480 patent.

The asserted patents are in the same patent family and have the same title: "Biodegradable Lipids for the Delivery of Active Agents." The patents also share the same written description and priority date (December 2011). According to the patents' Abstract, their claimed invention "relates to a cationic lipid" that has "one or more biodegradable groups located in a lipidic moiety (e.g., a hydrophobic chain)" and that "may be incorporated into a lipid particle for delivering an active agent, such as a nucleic acid." #933 patent, Abstract. Based on the parties'

agreement, I construed “cationic lipid” to mean “a lipid that is positively charged or that may be protonated at physiological pH.” D.I. 109 at 1; *see also* D.I. 86 at 15 (Alnylam stating that “[t]here is no dispute between the parties that a cationic lipid is a lipid that may be protonated at physiological pH.”); D.I. 86 at 21 (Defendants stating that “the parties agree that a cationic lipid, as the term is used in the Patents-in-Suit, must have at least one protonatable group, and thus, be protonatable.”). Protonate means to add a proton to a molecule—that is, to positively charge the molecule.

The asserted patents each claim a cationic lipid with three parts:

(a) “hydrophobic tails,” (b) a “linker” or “central moiety,” and (c) a “head group.”

D.I. 124-1 ¶ 15; D.I. 125 ¶ 32. The crux of the dispute before me is whether the patents’ claimed head group must be either permanently positively charged or protonatable. Defendants say yes to this question. Alnylam says that the head group need not be permanently positively charged or protonatable and that the positive charge of the claimed cationic lipid can reside in either the head group or the central moiety.

I. PROCEDURAL HISTORY

I held a claim construction hearing for the #933 and #979 patents on August 9, 2023. I heard argument that day on numerous terms, including “head group.” The parties’ arguments were extremely technical, and I therefore invited the parties

to present expert testimony about the meaning “head group” would have to an artisan of ordinary skill in 2011. *See* D.I. 104 at 85:11–20; 88:10–20. The parties submitted expert declarations and additional briefing in October 2023. *See* D.I. 123; D.I. 124; D.I. 125. I heard testimony from Alnylam’s expert, Dr. Alexander Kros, and Defendants’ expert, Dr. Kathryn Whitehead, at a hearing in January 2024.

A claim construction hearing for the #229, #657, #479, and #480 patents was originally scheduled for April 2024. That hearing was postponed and ultimately held on July 12, 2024 to accommodate the schedules of Drs. Kros and Whitehead so that they could testify further about the meaning of the term “head group.”

II. LEGAL STANDARDS

“It is a ‘bedrock principle’ of patent law that ‘the claims of a patent define the invention to which the patentee is entitled the right to exclude.’” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). A patent’s claims, however, “do not stand alone.” *Id.* A patent is “a fully integrated written instrument,” *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996), that “consist[s] principally of a specification that concludes with the claims,” *Phillips*, 415 F.3d at 1315.

“[T]he construction of a patent, including terms of art within its claim[s], is exclusively within the province of the court.” *Markman*, 517 U.S. at 372. In

performing this function, the court is “required” to follow “the standard construction rule that terms can be defined only in a way that comports with *the instrument as a whole*.” *Id.* (emphasis added) (citation omitted).

The Federal Circuit has “frequently stated that the words of a claim ‘are generally given their ordinary and customary meaning.’” *Phillips*, 415 F.3d at 1312–13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (emphasis added)). The court has also “made clear . . . that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Id.* “Th[is] inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation.” *Id.* But consistent with the “standard construction rule” announced by the Supreme Court in *Markman*, the court clarified in *Phillips* that “the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but [also] in the context of the entire patent, including the specification.” *Id.* at 1313. In the court’s words:

[C]laims must be read in view of the specification, of which they are a part. . . . [T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.

Id. (internal quotation marks and citations omitted).

As the court noted in *Phillips*, in some cases, the ordinary meaning of claim language as understood by a person of skill in the art “is readily apparent even to lay judges.” *Id.* at 1314. In such cases, claim construction “involves little more than the application of the widely accepted meaning of commonly understood words.” *Id.* But “[i]n many cases that give rise to litigation, . . . determining the ordinary and customary meaning of the claim requires examination of terms that have a particular meaning in a field of art.” *Id.* In these latter cases,

[b]ecause the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent, and because patentees frequently use terms idiosyncratically, the court looks to those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean. Those sources include the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.

Id. (internal quotation marks and citation omitted).

In considering evidence beyond the patent and prosecution history, however, a court must always be mindful that “[e]xtrinsic evidence is to be used for the court’s understanding of the patent, not for the purpose of varying or contradicting the terms of the claims.” *Markman*, 52 F.3d at 981.

“Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (citing *Markman*, 517 U.S. at 389). “The construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.” *Id.*

III. DISCUSSION

Alnylam argues that I should construe “head group” to mean “a portion of the lipid molecule that is less hydrophobic than the hydrophobic tails.” D.I. 86 at 38; D.I. 184 at 8. Defendants do not dispute that a lipid’s head group is less hydrophobic than the lipid’s tails, but they say that this definition is incomplete and ignores what artisans of ordinary skill in 2011 understood the primary function a head group in a *cationic* lipid to be—i.e., to bring a positive charge to that lipid. *See* D.I. 184 at 40–42. Defendants ask me to construe “head group” to mean “a group that must be either permanently positively charged or protonatable.”¹ In my

¹ On July 31, 2024, I issued an Oral Order proposing to change Defendants’ original proposed construction—“a group that may be protonated”—to what I think is a more precise formulation—“a group that must be either permanently positively charged or protonatable.” On August 2, 2024, Defendants agreed to this construction. D.I. 237. Under binding Federal Circuit law, “the trial judge has an independent obligation to determine the meaning of the claims, notwithstanding

view, Defendants' proposed construction of "head group" most naturally aligns with the patents' description of the invention. I am also persuaded by the extrinsic evidence adduced by the parties that an artisan of ordinary skill would have understood "head group" in the context of the asserted patents to mean a group that must be either permanently positively charged or protonatable.

A. The Asserted Independent Claims

The parties treated claim 18 of the #933 patent as representative of the asserted independent claims in the #933 and #979 patents. It reads:

A cationic lipid comprising a primary group and two biodegradable hydrophobic tails, wherein

the primary group comprises (i) a head group that optionally comprises a primary, secondary, or tertiary amine, and (ii) a central moiety to which the head group and the two biodegradable hydrophobic tails are directly bonded;

the central moiety is a central carbon or nitrogen atom;

each biodegradable hydrophobic tail independently has the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain), wherein the biodegradable group is —OC(O)— or —C(O)O—;

for at least one biodegradable hydrophobic tail, the terminal hydrophobic chain in the biodegradable hydrophobic tail is a branched alkyl, where the branching occurs at the α -position relative to the biodegradable group and the biodegradable hydrophobic tail has the

the views asserted by the adversary parties." *Exxon Chem. Pats., Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1555 (Fed. Cir. 1995).

formula $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$, where R^{12} is a $\text{C}_4\text{—C}_{14}$ alkylene or $\text{C}_4\text{—C}_{14}$ alkenylene, M^1 is the biodegradable group, R^{13} is a branched $\text{C}_{10}\text{—C}_{20}$ alkyl, and the total carbon atom content of the tail $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ is 21 to 26;

in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms; and

the lipid has a pK_a in the range of about 4 to about 11 and a $\log P$ of at least 10.1.

#933 Patent, 538:13–38.

The parties treated claim 27 of the #229 patent as representative of the asserted independent claims in the #229, #657, #479, and #480 patents. It reads:

A vaccine comprising a lipid particle and a pharmaceutically acceptable diluent, excipient, or carrier, wherein the lipid particle comprises:

- (i) a nucleic acid, wherein the nucleic acid comprises RNA,
- (ii) 36-65 mol % of a protonatable lipid compound,
- (iii) 3-12 mol % distearoylphosphatidylcholine (DSPC),
- (iv) 15-45 mol % cholesterol, and
- (v) 0.5-10 mol % of a PEG-modified lipid,

wherein the mol % is based on 100% total moles of lipids in the lipid particle,

wherein the protonatable lipid compound comprises a head group, hydrophobic tails, and a central moiety to which the head group and the hydrophobic tails are directly bonded, wherein:

the central moiety is a nitrogen atom;

the hydrophobic tails consist of two hydrophobic tails;
each of the two hydrophobic tails has the formula $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$, wherein:

R^{12} is a $\text{C}_4\text{—C}_{14}$ alkyl group, M^1 is —OC(O)— , and R^{13} is a $\text{C}_{10}\text{—C}_{20}$ branched alkyl, wherein R^{13} is branched at the alpha position relative to the —OC(O)— group;

the chain length of formula $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ is 17 atoms;
and

the total carbon atom content of each hydrophobic tail is
21 to 26 carbon atoms.

#229 patent at 497:18–498:19.

There are two noteworthy differences between the two representative claims. First, claim 18 of the #933 patent allows for the central moiety to be either a carbon or a nitrogen atom, whereas Claim 27 of the #229 patent requires the central moiety to be a nitrogen atom. Second, claim 18 of the #933 patent explicitly claims a “primary group,” defined by the claims as “a head group and a central moiety” #933 patent at 535:40–41. It is the only independent claim in the asserted patents that claims a primary group. Neither claim 27 of the #229 patent nor any other independent claim in the remaining patents claims a primary group. This difference, however, is of no moment, because the parties agree that, consistent with the claims of the #933 patent, the shared written description of all the asserted patents defines “primary group” as including both a head group and a central moiety. *See* D.I. 184 at 42 n.25, *id.* at 51; #933 patent at 16:53–55.

As an initial matter, the language of the asserted independent claims confirms the inadequacy of Alnylam’s proposed construction. It is undisputed that the primary group—a group that is comprised in part of, and distinct from, the head group—is less hydrophobic than the hydrophobic tails. *See* D.I. 163 at 102:9–15 (Alnylam’s expert, Dr. Kros, agreeing that “the entire primary group, as that term is used in the patents, is less hydrophobic than the tails”). Thus, Alnylam’s proposed construction does not ascribe to the claimed head group a meaning that differentiates it from the primary group as that term is used in all the asserted patents and claimed in the #933 patent. For that reason, Alnylam’s proposed construction is overinclusive and thus inadequate. *See CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co.*, 224 F.3d 1308, 1317 (Fed. Cir. 2000) (“In the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings.”); *Bd. of Regents of the Univ. of Texas Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008) (“Different claim terms are presumed to have different meanings.”).

With respect to Defendants’ proposed construction, nothing in the asserted independent claims of the patents makes clear whether the claimed head group must be permanently positively charged or protonatable. Defendants argue that “the plain language of the claims is consistent with [their] construction because it recites ‘a head group that optionally comprises a primary, secondary, and tertiary

amine,’ which are protonatable groups.” D.I. 86 at 50. But this language is not inconsistent with Alnylam’s position that the claimed cationic lipid’s protonatable group can reside in either the head group or the central moiety. “Optionally” means “may or may not,” and thus the claim language cited by Defendants does not *require* that the head group be a protonatable group.

Alnylam similarly overreaches when it says that Defendants’ construction of head group is “contrary” to the “plain claim language” of the asserted patents. D.I. 184 at 10. Alnylam is correct that all the asserted patents claim a lipid that is either permanently positively charged or protonatable and that “the independent claim language *never* expressly states the requirement that the head group be protonatable.” D.I. 184 at 10 (emphasis in the original). It is also correct that the central moiety claimed in the #933 and #979 patents can be protonatable (i.e., “a central carbon *or* nitrogen atom”) and that the claimed moiety in the #229, #657, #479, and #480 patents must be protonatable (i.e., be a nitrogen). But as a matter of logic, it does not follow from any of these premises that the head group cannot be permanently positively charged or protonatable. A lipid that has a permanently positively charged or protonatable head group will be permanently positively charged or protonatable. And a cationic lipid can have *both* a protonatable central moiety and a protonatable head group. D.I. 163 at 106:8–10. Thus, the claim

language cited by Alnylam is not inconsistent with Defendants' proposed construction.

To sum up: The language of the asserted independent claims is incompatible with Alnylam's proposed construction. The language is compatible with Defendants' proposed construction but does not require that construction.

B. The Patents' Written Description

Although it cannot be gleaned solely from the language of the claims whether the patents' head group must be permanently positively charged or protonatable, the remainder of the patents' shared written description makes clear that the claimed head group must be so. The patents' shared written description spans more than 250 pages and contains 1,021 drawn embodiments of complete cationic lipids. #933 patent at 76:24–395:25; D.I. 104 at 75:18–19. Without exception, the head group of each drawn embodiment is either permanently positively charged or protonatable. D.I. 125 ¶ 45.

The written description contains nine general formulas for cationic lipids (Formulas I, II, III, IIIA, IV, V, VIB, and VIII). #933 patent at 2:7–15:67. Each formula contains variables, and for each variable, the patent identifies structures that an artisan of ordinary skill could choose in designing a cationic lipid that accords with the patents' teachings. *See generally id.* Without exception, the head

groups used in all nine formulas are either permanently positively charged or protonatable. D.I. 125 ¶ 41.

Tables 1A, 2A, and 2B in the patents' shared written description also disclose head groups. Table 1A lists head groups that the patent describes as "suitable." #933 patent at 37:25–26. Table 1B of the patents' written description lists primary groups (combined head groups and linkers) that are "suitable." *Id.* at 42:51–52. Table 2A lists "representative" head groups that can be combined with linkers and representative hydrophobic chains to make cationic lipids in accordance with the teachings of the written description. #933 patent at 61:22–30. Without exception, every head group identified in Tables 1A, 2A, and 2B is permanently positively charged or protonatable. D.I. 125 ¶¶ 42–44.

The written description also discloses that the patents' inventors ran tests on certain identified cationic lipids. *Id.* ¶¶ 47–48. The lipids selected for testing and the results of the tests are reported in Examples 36 and 37 of the written description. #933 patent at 521:13–534:20. Without exception, the head group in each cationic lipid selected for testing in Examples 36 and 37 was either permanently positively charged or protonatable. D.I. 125 ¶¶ 47–48.

In sum, none of the thousands of head groups disclosed in the patents' voluminous written description is both not permanently positively charged and not

protonatable. Every disclosed head group is either permanently positively charged or protonatable.

Alnylam insists otherwise, but its assertions to the contrary do not bear up to scrutiny. Alnylam says in its most recent brief, for example, that the patents' written description discloses "specific examples of non-protonatable head groups at physiological pH, including hydroxyl and methoxy groups, as well as pyridine and imidazole," . . . [and] zwitterionic head groups." D.I. 184 at 51–52 (citing #229 patent at 32:57–33:4). It cites in support of this assertion the following paragraph from the written description found in column 32 of the #933 patent:

The head group can include an amine; for example an amine having a desired pK_a . The pK_a can be influenced by the structure of the lipid, particularly the nature of [the] head group; e.g. the presence, absence, and location of functional groups such as anionic functional groups, hydrogen bond donor functional groups, hydrogen bond acceptor groups, hydrophobic groups (e.g. aliphatic groups), hydrophilic groups (e.g. hydroxyl or methoxy), or aryl groups. The head group amine can be a cationic amine; a primary, secondary, or tertiary amine; the head group can include one amine group (monoamine), two amine groups (diamine), three amine groups (triamine), or a larger number of amine groups, as in an oligoamine or polyamine. The head group can include a functional group that is less strongly basic than an amine, such as, for example, an imidazole, a pyridine, or a guanidinium group. The head group can be zwitterionic. Other head groups are suitable as well.

#933 Patent at 32: 45–64.²

As an initial matter, the paragraph does not teach that the claimed head group can be only a hydroxyl group, methoxy group, pyridine group, or imidazole group. The paragraph instead discloses a head group that has an amine and may also have “functional groups” that could influence the pK_a of that amine. The paragraph identifies hydroxyl, methoxy, pyridine, and imidazole groups as examples of such functional groups. It is undisputed, however, that the existence of an amine in the head group makes the head group protonatable. *See* D.I. 124-1 ¶ 66 (Dr. Kros acknowledging that amines are protonatable at physiological pH); D.I. 163 at 67:15 (Dr. Kros acknowledging that an amine is a protonatable group at physiological pH); D.I. 125 ¶ 33 (“The nitrogen atom in the protonatable cationic lipid example from the Patents-in-Suit is bound to three non-hydrogen atoms, not four atoms like the quaternary amines of the original [permanently positively charged] cationic lipids. This makes this amine group a tertiary amine. The practical result is that this cationic lipid is protonatable, i.e., capable of being positively charged, at certain pH values, instead of being permanently positively charged.”). Accordingly, an artisan of ordinary skill would not understand the

² The exact location of certain paragraphs or figures in the patents’ shared written description may be slightly different from patent to patent based upon formatting and the material on the cover page.

above-quoted paragraph to disclose a non-protonatable head group that has a hydroxyl, methoxy, pyridine, or imidazole group on its own.

The paragraph does state that the head group can be zwitterionic, and it does not limit its reference to zwitterionic head groups to zwitterionic head groups with amines. But it is undisputed that a zwitterionic compound has a positively charged section. D.I. 163 at 126:10–16 (“Q: Well, a zwitterionic head group has a positive charge, right? A: [Dr. Kros] Which is balanced out by an equal number of negative charges. So if you have one positive charge, then you will have next to it one -- sorry. If you have one positive charge, then you have one negative charge.”); D.I. 125 ¶ 62 (Dr. Whitehead explaining “zwitterionic head groups do have at least one positively charged/protonatable group.”). A zwitterion is a compound with both positively and negatively charged sections that does not have an aggregate electrical charge. D.I. 236 at 65:6–7 (“[A] zwitterion has positive charge and a negative charge. So the sum is 0.”). Thus, a head group that consisted solely of a zwitterionic group would fall within Defendant’s proposed construction of head group. (At the initial claim construction hearing, Alnylam took the position that “[z]witterionic means that [a compound] can be, in certain circumstances, either positively or negatively charged” and said that “neither party is suggesting that zwitterionic is relevant to the construction of the particular claims at issue,” D.I. 104 at 29:18–20.)

Alnylam also points to the disclosure in Table 2A of the patents’ written description of pyridine and imidazole head groups without amines. Alnylam argues that these head groups “are not protonatable at physiological pH.” D.I. 184 at 52. That may be true, but it is irrelevant. Defendants’ proposed construction does not require that the head group be protonatable at physiological pH, and Alnylam does not dispute that the pyridine and imidazole groups are protonatable at some pH level. *See* D.I. 184 at 37. *See also* D.I. 236 at 118:24–119:24; D.I. 163 at 124:15–25.

Alnylam also argues that Defendants’ proposed construction is inconsistent with two sentences in the written description that disclose a protonatable central moiety. *See* D.I. 184 at 51 (citing #229 patent at 17:16–17); D.I. 184 at 16 (citing #229 patent at 33:6–7). But neither sentence discloses a protonatable central moiety to the *exclusion* of a permanently positively charged or protonatable head group. The sentences in question merely allow for the possibility of a protonatable moiety. They say nothing about the composition of the head group. Moreover, the two specific examples of cationic lipids with a nitrogen central moiety disclosed in the specifications both have head groups that contain protonatable amines. *See* D.I. 125 ¶ 66; D.I. 163 at 105:10–106:10.

Finally, Alnylam argues that the statement in the patents’ written description that “[o]ther head groups are suitable as well” “highlights the error” of Defendants’

proposed construction. D.I. 86 at 40. The sentence in question is the last sentence in the paragraph from column 32 of the #933 patent quoted above. As discussed above, every head group discussed in that paragraph is permanently positively charged or protonatable. But even more important, as also discussed above, the patents’ written description discloses thousands of cationic lipids, not one of which has a head group that is both not permanently positively charged and not protonatable. As Dr. Kros admitted at the January 4, 2024 claim construction hearing, the asserted patents’ written description “never says an uncharged head group is suitable for the claimed cationic lipids.” D.I. 104 at 127:9–11. Thus, reading the sentence, as I must under *Markman*, in the context of the specification as a whole, it is clear that this catch-all sentence refers only to head groups of the same type as the thousands of examples drawn and described in the patents’ written description—that is, groups that must be either permanently positively charged or protonatable.

C. Extrinsic Evidence

The extrinsic evidence brought to my attention by the parties confirms that “head group” should be construed to mean a group that must be permanently positively charged or protonatable.

Dr. Kros repeatedly testified that an artisan of ordinary skill would have understood in 2011 that, for the purpose of encapsulating RNA, it does not matter

where the positive charge is within the cationic lipid. *See, e.g.*, D.I. 163 at 61:21–23 (“you really need a cationic charge, but it doesn’t matter where it is located on the molecule, as long as somewhere in the molecule, there’s a positive charge so it can bind to the RNA”); 62:3–6 (“Q: Does the RNA care where in the cationic lipid the protonation takes place? A. No. It should be cationic lipids and exact location doesn’t matter for the RNA”); 102:5–8 (“the patents teach me that somewhere in the primary group, I need to have the positive charge, but it doesn’t tell me whether it is in the head group or in central moiety. I can choose, and RNA doesn’t care”).

Dr. Whitehead offered a more nuanced take, testifying that a person of ordinary skill in 2011 had a different understanding. According to Dr. Whitehead, although artisans of ordinary skill *now* know that the location of the charge is not critical, this knowledge “is something that has developed over time.” D.I. 163 at 161:13–

15. In Dr. Whitehead’s words:

So at that time, you know, as I mentioned, that positive charge was almost always, as far as possible, towards the end of the head group because if you put it . . . in what we’re calling here the central moiety, folks thought that it’s not going to be able to -- like the lipid, like the head group would almost have to bend backwards a little bit to kind of thrust, for lack of a better word, to reveal that positive . . . group in order to maximize interactions. And so it was a matter of steric hindrance. Of course – you know, of course we were ultimately wrong, and we see now that we can have something in the central moiety that has the same function. But at that time, it was not considered possible. Somebody would not have done that.

Id. at 161:16–162:6.

I find Dr. Whitehead’s perspective credible, and as a general matter, based on her demeanor, I found her to be a credible witness. Dr. Whitehead was the lead author of numerous peer-reviewed articles published around the time of the asserted patents’ priority date that focus on the operation and efficacy of lipids or lipid-like compounds for nucleic acid delivery. *See, e.g.*, Kathryn A. Whitehead et al., *Knocking Down Barriers: Advances in siRNA Delivery*, 8 NATURE REVIEWS | DRUG DELIVERY 129 (Feb. 2009) (discussed in D.I. 125); Kathryn A. Whitehead et al., *Synergistic Silencing: Combinations of Lipid-like Materials for Efficacious siRNA Delivery*, 19 MOLECULAR THERAPY: THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY 1688 (2011) (D.I. 184, Ex. 59) (discussed in D.I. 184 Exs. 53; 64) (referred to by the parties as “Whitehead (2011)”). Her firsthand experience working with lipids and lipid-like compounds in this time frame is instructive as to what an artisan of ordinary skill would think was possible and preferred in cationic lipid design.

The extrinsic references introduced by both parties support Defendants’ construction of “head group.” Defendants introduced references that consistently use the term “head group” to refer to permanently positively charged or protonatable structures. The references introduced by Alnylam either use “head group” consistently with Defendants’ references or are not probative.

I begin with Defendants' references. Defendants introduced multiple articles published during the 1999–2012 time frame that all described cationic lipids as having permanently positively charged or protonatable head groups. I found these references compelling. These articles supported Dr. Whitehead's testimony that artisans of ordinary skill twenty years ago understood cationic lipids to have permanently positively charged head groups. D.I. 163 at 165:9–19; *see also* D.I. 125 ¶ 28 (citing Tang & Hughes, *Synthesis of a Single-Tailed Cationic Lipid and Investigation of its Transfection*, 62 J. CONTROLLED RELEASE 345, 345–46 (1999) (“[a]ll cationic lipid molecules contain three functional domains: a positively charged head group, a hydrophobic region, and a linker that tethers the cationic group and hydrophobic groups.”). *See also* Chesnoy and Huang, *Structure and Function of Lipid-DNA Complexes for Gene Delivery*, 29 ANNUAL REV. OF BIOPHYSICS AND BIOMOLECULAR STRUCTURE 27, 28 (2000). “Over time . . . [c]ationic lipids with a permanently positive charge in the head group were used less than cationic lipids with a protonatable head group” because lipids with a permanent charge were “consistently less effective” than lipids with protonatable head groups. D.I. 125 ¶ 31 (quoting Jayaraman et al., *Maximizing the Potency of siRNA Lipid Nanoparticles for Hepatic Gene Silencing In Vivo*, 51 ANGEW. CHEM. INT. ED. 8529 (2012)).

Two articles discussed by Dr. Kros use the term “head group” in a way that is consistent with Defendants’ construction. The first is from 2005: Martin, *The design of cationic lipids for gene delivery*, 11 CURRENT PHARM. DESIGN, 375 (2005) (hereafter, “Martin (2005)”). As Dr. Kros notes, Martin (2005) identifies drawn examples of lipids with head groups that are not protonatable and that contain a nitrogen central moiety. D.I. 184-6, Ex. 53 at PageID 14934. But Martin (2005) also consistently describes the head group as “cationic,” and describes a cationic lipid for drug delivery as containing “three fundamental constituent parts: the cationic head group, hydrophobic domain, and connecting linker.” D.I. 184-6, Ex. 55 at PageID 14972. *See also id.* at PageID 14975 (“A cationic lipid is a positively charged amphiphile, which generally contains the three following structural domains: i) a hydrophilic headgroup which is positively charged. . . .”). Thus, the reference supports Defendants’ articulation of how an artisan used the term “head group” in the context of cationic lipids.

Dr. Kros also relied on a 2002 article by Srilakshmi et al. D.I. 184-6, Ex. 53 at PageID 14931 (citing Srilakshmi et al., *Anchor-dependent lipofection with non-glycerol based cytofectins containing single 2-hydroxyethyl head groups*, 1559(2) BIOCHIMICA ET BIOPHYSICA ACTA - BIOMEMBRANES, 87 (2002)) (hereafter “Srilakshmi (2002)”). Like Martin (2005), Srilakshmi (2002) has figures that Dr. Kros contends depict cationic lipids with non-protonatable head groups.

D.I. 184-6, Ex. 53 at PageID 14931–32 (citing D.I. 184-6, Ex. 54 at PageID 14959). But like Martin (2005), the text of Srilakshmi (2002) consistently uses the term “head group” to refer to the portion of the compounds identified by Dr. Kros that are permanently positively charged. D.I. 236 at 94:16–18; 95:14–96:11.

The remainder of the references Alnylam relies on are not probative as to meaning of “head group” in 2011 in the context of cationic lipids. The first reference cited by Alnylam and Dr. Kros is a 2023 article in *Encyclopedia Britannica*, D.I. 124-1 ¶¶ 37–42. Dr. Kros also cited a passage from the textbook *Molecular Biology of the Cell*. D.I. 124-1 ¶¶ 37, 38, 40. Putting aside the date of the *Encyclopedia Britannica* article, these general references discuss only naturally occurring lipids at a very high level of generality. Neither source offers guidance as to whether an artisan of ordinary skill in 2011 would have understood the term “head group” to mean a positively charged structure in the context of engineered, cationic lipids.

Dr. Kros also relied on a published patent application and a 2008 article from the journal *Nature Biotechnology*. The patent application, WO 2006/138380 (the #380 Application) lists Dr. Daniel Anderson as the lead inventor and is cited as prior art on the face of the asserted patents. D.I. 124-1 ¶ 58 n.14. The *Nature Biotechnology* article (referred to by the parties as “Anderson (2008)”) lists Dr. Anderson, as well as some inventors of the asserted patents and others, as authors,

and includes a description of compounds disclosed in the earlier #380 Application. D.I. 184-6 at PageID 14939. Dr. Kros identified six specific compounds—LD31, LF31, LF93, LF94, LG93 and ND28—that are disclosed in the two references and that he contends are cationic lipids with protonatable central moieties and non-protonatable head groups. *Id.* at PageID 14937–38.

Like the article in *Encyclopedia Britannica* and *Molecular Biology of the Cell*, the #380 Application and Anderson (2008) are not helpful. First and foremost, the #380 Application and Anderson (2008) never once use the term “head group.” D.I. 184 at 49. Second, for reasons explained more fully below, the #380 Application and Anderson (2008) disclose examples of a distinct class of materials called *lipidoids*, not lipids. Although the six compounds identified by Dr. Kros were called “lipids” in the #380 patent application in 2006, by the time the article describing the compounds’ structure was published in *Nature Biotechnology* two years later, the compounds were called “lipidoids.” D.I. 236 at 24:4–8. Dr. Kros argued that an artisan of ordinary skill would consider the compounds cationic lipids based on their structure, *id.* at 23:22–24:1, and he speculated that the authors came up with the name “lipidoids” because they “want[ed] to distinguish [the subject matter of the article] from lipids, especially biological lipids, that are already there [] [a]nd . . . give [the subject matter of the

article] an air of novelty in order to get—to increase the chances that your work is being published in a highly respected journal like Nature Biotech,” *id.* at 24:17–22.

Dr. Whitehead, who “found the time to work on [Anderson (2008)] during [her] post-doctoral research,” disagreed with Dr. Kros. *Id.* at 149:18–21.

According to Dr. Whitehead, Anderson (2008) introduced lipidoids as a new class of materials. *Id.* at 149:12–16. She testified that experts in the field pushed back against calling the compounds disclosed in Anderson (2008) lipids and “felt that [] these needed to be named something else because they were distinct from classical cationic lipids.” *Id.* at 150:1–5; 9–11. She testified that the compounds “were not named for – just for the purpose of having a paper published in a fancy journal like Nature Biotech.” *Id.* at 130:6–7.

Again, I find Dr. Whitehead’s testimony to be credible. Dr. Whitehead was involved in the work underlying the Anderson (2008) paper and the industry discussions surrounding the introduction of lipidoids as a class of RNA delivery materials. Moreover, I question the notion that the editors and peer reviewers at a prestigious journal like *Nature Biotechnology* would fall for the type of gamesmanship suggested by Dr. Kros. I therefore find that these references, which discuss neither cationic lipids nor head groups, are not useful in helping me understand how an artisan of ordinary skill understood the term “head group” in the context of cationic lipids.

Alnylam also introduced Dr. Whitehead's own paper from 2011. *See* Whitehead (2011) *supra* p.19. But like Anderson (2008), this paper only discusses lipidoids from the #380 Application. *See* D.I. 236 at 151: 3–9 (Dr. Whitehead explaining that in her article “we were interested in understanding more about lipid-like materials or lipidoids, and we were interested in taking that paper from Anderson in 2008 and examining some of the materials that did not work well . . .”). Accordingly, Whitehead (2011) is also unhelpful to the issue at hand.

In sum, although there may have been isolated instances in the prior art of lipid-like compounds or even traditional lipids that did not have protonatable head groups in the parties' extrinsic references, the record shows that artisans of ordinary skill overwhelmingly used the term “head group” to refer to the protonatable or permanently positively charged portion of a cationic lipid. I find Dr. Whitehead's explanation of the development of the field since 2011 credible and find that the extrinsic evidence favors Defendants' construction of “head group.”

D. Dependent Claims

Lastly, Alnylam argues that I should reject Defendants' proposed construction of “head group” because it “directly contradict[s]” certain dependent claims of the #229, #657, #479, and #480 patents that “require that the head group contain only groups that are not protonatable at physiological pH.” D.I. 124 at 11

(italics removed). It is undisputed that these claims—claims 10, 16, 25, and 28 of the #229 patent, claims 19 and 23 of the #657 patent, claims 8, 12, and 19 of the #479 patent, and claims 10 and 11 of the #480 patent—require that the claimed cationic lipid contain a protonatable central moiety or primary group with a head group that “consists of a saturated aliphatic group and a hydroxyl group.” It is also undisputed that an artisan of ordinary skill would not consider a head group consisting of a saturated aliphatic group and a hydroxyl group to be protonatable in a biological context. *See* D.I. 163 at 192:5–21; D.I. 124-1 ¶¶ 18 n.4; 58 n.16; 66 n.19. Thus, my adoption of Defendants’ construction of “head group” would effectively nullify these dependent claims. But that consequence, even though generally disfavored, is a fair result under the circumstances present here.

As an initial matter, the dependent claims in question offer no assistance in determining the ordinary and customary meaning of the term “head group” to an artisan of ordinary skill in 2011. Alnylam submitted the claims that led to the issuance of each of the six asserted patents in 2021 or later—i.e., *ten years* after Alnylam filed the provisional application to which the asserted patents claim priority. D.I. 86 at 6–7. Moreover, Alnylam did not file the patent applications leading to the six asserted patents until *after* information about the lipids used in the Pfizer/BioNTech accused mRNA vaccines was publicly disclosed. D.I. 236 at 60:24–25. (“All of the claims of all six patents were filed for after the product

was made.”); D.I. 86 at 7 n.7 (“Defendants’ lipid structure was published on April 9, 2021.”). The applications leading to the asserted patents were filed between April 21, 2021 and February 14, 2022.

Although there is a presumption against construing a patent claim’s term in a way that eliminates other claims, that presumption is not an unbreakable rule and can be overcome. *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350 (2016). In *Multilayer*, the asserted patent had an independent claim directed to a “multi-layer, thermoplastic stretch wrap film,” with “two identifiable outer layers” and “five identifiable inner layers.” 831 F.3d at 1353. The five inner layers were to be “selected from the group consisting of” four different types of plastic resins: LLDPE, VLDPE, ULDPE, and mLLDPE. *Id.* at 1355. The claim used the transitional phrase “consisting of,” and was structured as a “Markush” group, i.e. a claim that contains a limitation allowing for the selection of alternate structures from an enumerated list. *Id.* at 1357. The district court therefore construed the limitation to require each inner layer to be composed of a single plastic resin from the list. *Id.* at 1355. The district court’s construction did not encompass any inner layer made from a blend of more than one resin or a resin other than the four listed in the claim. *Id.* at 1356.

The asserted patent had “dependent claims that describe inner layers containing” a fifth type of plastic resin, “LDPE.” *Id.* at 1360. Under the district

court's construction, the dependent claims were fundamentally inconsistent with their parent claim. Despite the inconsistency, the Federal Circuit upheld the portion of the district court's claim construction limiting the independent claim to four alternative resins, because "[t]he language of a dependent claim cannot change the scope of an independent claim whose meaning is clear on its face." *Id.*

Although nonprecedential, the Federal Circuit's recent decision in *Barrday, Inc. v. Lincoln Fabrics Inc.*, 2023 WL 7871688 (Fed. Cir. Nov. 16, 2023) is especially instructive. In *Barrday*, the two asserted patents described multi-layer, woven ballistic fabrics. 2023 WL 7871688, at * 1. The representative independent claim of both patents described "a multi-layer ballistic woven fabric" comprising at least two layers, an "upper woven layer" and a "lower woven layer." *Id.* The independent claim required that the upper and lower layers had "warp yarns" (yarns that run with the grain of the fabric), "weft yarns" (yarns that run across the grain of the fabric), and that the fabric had "securing yarns" that interwove with the warp and weft yarns of both layers to secure the layers together. *Id.*

Barrday asserted one of its patents against defendant Lincoln Fabrics in February 2015. *Id.* at *2. Lincoln informed Barrday that its products did not infringe because "the accused Lincoln fabrics interweave the upper (or first) and lower (or second) layers without using securing yarns." *Id.* Less than a month later, Barrday amended the claims of its then-pending second asserted patent to add

five dependent claims that each claim upper and lower layers connected by some permutation of the upper or lower warp or weft yarns *acting* as the securing yarn.

Id. The second patent issued after this amendment and Barrday added it to the case against Lincoln. *Id.*

“The crux of the parties’ dispute [wa]s whether the securing yarns claim term can include yarns from the upper and lower woven layers when such yarns are serving the securing function.” *Id.* at 3. The panel majority held that the plain language of the independent claim separated securing yarns from the claimed layers, and that the written description and figures “exclusively refer[red] to securing yarns as structures that are separate and distinct from warp and weft yarns of the upper and lower layers.” *Id.* at 4. The specification also criticized the practice of interweaving yarns from multiple layers as the practice creates crimps and weak points. *Id.* at 4. In the face of Lincoln’s overwhelming specification evidence, Barrday identified only a short excerpt of the written description and the aforementioned dependent claims in its later-issued asserted patent as support for its construction. *Id.* at 5–6.

Barrday made the exact argument Alnylam makes here—the patents’ dependent claims must inform the construction of the claim terms—and it cited many of the same cases Alnylam cites in its portion of the Joint Claim

Construction Brief (D.I. 184). The panel majority did “not find [that] argument persuasive.” *Id.* at 7. In the court’s words:

“While it is true that dependent claims can aid in interpreting the scope of claims from which they depend, they are only an aid to interpretation and are not conclusive.” *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1360 (Fed. Cir. 2016) (citations omitted). “[C]laim differentiation is a rebuttable presumption that may be overcome by a contrary construction dictated by the written description or prosecution history.” *Howmedica [Osteonics Corp. v. Zimmer, Inc.]*, 822 F.3d[, 1312] 1323 [Fed. Cir. (2016)] (citation omitted). This court has adopted a construction rendering dependent claims meaningless when that construction was supported by either the specification or the prosecution history. *See Marine Polymer Techs., Inc. v. HemCon, Inc.*, 672 F.3d 1350, 1358–59 (Fed. Cir. 2012) (en banc) (construction supported by specification); *Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1371–76 (Fed. Cir. 2008) (construction supported by prosecution history); *Enzo Biochem Inc. v. Applera Corp.*, 780 F.3d 1149, 1154–57 (Fed. Cir. 2015) (construction supported by specification); *Multilayer Stretch*, 831 F.3d at 1358–62 (construction supported by specification). Similarly, we do so here where the claim language, specification, and figures all support a securing yarns construction that excludes yarns from the upper and lower layers.

The lack of weight afforded to the dependent claims is particularly appropriate here because such claims were added after the filing of the original patent application and because the motive for adding such claims appears to be litigation-driven.

Id. (footnote omitted).

As discussed above, in this case, an artisan of ordinary skill reading the specifications as a whole would understand that the claimed head group must be either permanently positively charged or protonatable. This ordinary and customary meaning of the term is bolstered by the peer-reviewed articles published before and around the priority date of the asserted patents and Dr. Whitehead's credible testimony about the state of the art in 2011. The language of the issued independent claims in all the asserted patents must be read in harmony with the ordinary and customary meaning of "head group." The specifications and independent claims are sufficiently clear. Accordingly, I will not change the ordinary and customary meaning of the term "head group" because of dependent claims in the later-issued patents. That conclusion is especially warranted here, as the timing of Alnylam's patent applications as well as the content of the dependent claims in the later-issued patents are strong indications that Alnylam's continued prosecution of this patent family was conducted with the specific intent to ensnare Defendants' mRNA vaccine products.

IV. CONCLUSION

For the foregoing reasons, I will construe "head group" to mean "a group that must be either permanently positively charged or protonatable."

The Court will enter an Order consistent with this Memorandum Opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALNYLAM
PHARMACEUTICALS, INC.,

Plaintiff,

v.

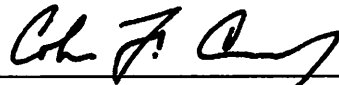
PFIZER, INC., PHARMACIA &
UPJOHN CO. LLC, BIONTECH
SE, and BIONTECH
MANUFACTURING GMBH,

Defendants.

Civil Action No. 22-336-CFC
(consolidated)

ORDER

At Wilmington on this Ninth day of September in 2024, it is **HEREBY ORDERED** that the term “head group” in the asserted claims of U.S. Patent Nos. 11,246,933, 11,328,979, 11,590,229, 11,612,657, 11,633,479, and 11,633,480 is construed to mean “a group that must be either permanently positively charged or protonatable.”



CHIEF JUDGE