

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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ALNYLAM PHARMACEUTICALS, INC.  
Petitioner,

v.

SILENCE THERAPEUTICS GMBH  
Patent Owner.

Case No. PGR2018-00089

Patent No. 9,790,501

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**PATENT OWNER'S PRELIMINARY RESPONSE**

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**Exhibit List for Post Grant Review of U.S. Patent No. 9,790,501**

Exhibit Description	Exhibit #
Defendants' Skeleton Argument for the CMC (UK litigation)	2001

Patent Owner Silence Therapeutics GMBH submits this preliminary response to Petitioner Alnylam Pharmaceuticals, Inc.’s (“Alnylam”) petition for post grant review of claims 1-30 of U.S. Patent No. 9,790,501 (“the ’501 patent” (Ex. 1001)) in accordance with 37 C.F.R. § 42.207(a).

## **I. INTRODUCTION**

The ’501 patent claims the benefit of nine priority applications, seven of them filed before the America Invents Act (“AIA”) effective date of March 16, 2013. Therefore, to show that the challenged claims are eligible for post grant review, Alnylam bears the burden of demonstrating that the claims lack the benefit of all the pre-AIA priority applications. Alnylam has failed to meet that burden, for several reasons.

First, on October 10, 2018, the Patent Trial and Appeal Board (the “Board”) denied Petitioner’s request to institute post grant review of a related a patent, U.S. Patent No. 9,695,423 (the ’423 patent), finding that (1) the ’423 patent’s provisional applications claiming a priority date prior to March 16, 2013 “provide[d] disclosure for each of the claim limitations argued by Petitioner sufficient to satisfy the written-description requirement under [35 U.S.C.] § 112” (*Alnylam Pharm., Inc. v. Silence Therapeutics GMBH*, PGR2018-00059 (PTAB Oct. 10, 2018) (Paper 9 at 17) (“Alnylam ’423 Decision”)); and (2) at least two of the ’423 patent’s provisional applications claiming a priority date prior to March

16, 2013 “provide sufficient guidance and ample disclosure to enable each of the challenged claims, including all of the claimed structural modifications and functional limitations, and that undue experimentation would not be required to practice the claims.” (*Id.* at 24.) Those same provisional applications on which the Board based its decision in the Alnylam ’423 Decision are at issue in the present case. Moreover, the claims at issue here and Alnylam’s arguments in support of this petition closely mirror its arguments in the IPR found insufficient by the Board. The same result should apply here.

Second, as in the previous IPR, Alnylam relies extensively on a declaration from its expert witness, but the declaration is based in large part on art published after the earliest priority applications were filed. This post-filing evidence does not and cannot show that one of skill in the art, as of the effective filing date of the priority applications, would have concluded that the inventors possessed the claimed invention. Nor can it show that as of the priority date the priority applications failed to teach one of skill in the art how to practice the claimed invention.

In addition, as in the previous IPR, Alnylam argues that some of the claims encompass non-functional siRNA molecules with double-stranded regions 17 nucleotides long. But Alnylam fails to establish that the claims encompass such

non-functional molecules. Alnylam's petition fails as a matter of law, and the post grant review should not be instituted.

## **II. SUMMARY OF THE INVENTION**

siRNAs are short double-stranded RNA molecules that reduce (i.e., “silence”) expression of target genes having complementary nucleotide sequences. In 2002, when the earliest priority application that gave rise to the '501 patent was filed, scientists appreciated that there were major challenges impeding the usefulness of siRNAs as a potential therapy. In particular, siRNAs were known to rapidly degrade in the serum and cells to which they had been introduced. ('501 patent, Ex. 1001 at 2:20-23.) The inventors of the '501 patent found that certain types of modified siRNAs exhibit increased stability while still being effective at inhibiting the target gene.

The claims at issue in this post grant review all claim modified double-stranded siRNAs in which (a) the first stretch and the second stretch each comprises contiguous alternating 2'-O-alkyl ribonucleotides, wherein the 2'-O-alkyl ribonucleotides alternate with unmodified or differently modified ribonucleotides; (b) the 2'-O-alkyl ribonucleotides of the first strand are shifted by one ribonucleotide relative to the 2'-O-alkyl ribonucleotides of the second strand; and (c) each of the first stretch and the second stretch consists of at least 17 and fewer than 30 ribonucleotides. The '501 patent and its priority applications

include disclosure of this claimed concept. EP 2017601.2 (Ex. 1006) states, for example:

In a fourth aspect the problem underlying the present invention is solved by a ribonucleic acid comprising a double stranded structure, whereby the double- stranded structure comprises a first strand and a second strand, whereby the first strand comprises a first stretch of contiguous nucleotides and whereby said first stretch is at least partially complementary to a target nucleic acid, and the second strand comprises a second stretch of contiguous nucleotides and whereby said second stretch is at least partially identical to a target nucleic acid, whereby said first strand and/or said second strand comprises a plurality of groups of modified nucleotides having a modification at the 2'-position whereby within the strand each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides whereby the flanking nucleotides forming the flanking group of nucleotides is either an unmodified nucleotide or a nucleotide having a modification different from the modification of the modified nucleotides. ...

In another embodiment of the ribonucleic acid according to the fourth aspect of the present invention the pattern of modified nucleotides of said first strand is the same as the pattern of modified nucleotides of said second strand. ... In an alternative embodiment of the ribonucleic acid according to



the fourth aspect of the present invention the pattern of said first strand is shifted by one or more nucleotides relative to the pattern of the second strand...In an embodiment of the ribonucleic acid according to the fourth aspect of the present invention the modification is ... alkyl.

(Ex. 1006 at 4-6.) The specification further states:

The length of the first stretch and second stretch, respectively, is typically about 15 to about 23, preferably 17 to 21 ... bases. In connection with this it is to be noted that a length of less than 30 nucleotides ... does not cause any biological system which is basically capable of showing RNA interference and also interferon response, to develop an interferon response.

(Ex. 1006 at 18.) The specification further provides examples of a double-stranded siRNA molecules wherein the first stretch and the second stretch each comprise contiguous alternating 2'-O-alkyl ribonucleotides, wherein the 2'-O-alkyl ribonucleotides alternate with unmodified or differently modified ribonucleotides. For example, Example 9 discloses the double-stranded siRNA molecule 94A1/94B2 which is described as being "modified with 2'-O-methyl groups alternating with unmodified nucleotides" and as having "the same pattern of modified and unmodified nucleotides" with "a phase shift such that the modified nucleotide forms base pairing with an unmodified nucleotide." (Ex. 1006, Example 9 at 36-37 and Fig. 11B.) The '501 patent contains the same disclosure. (*See e.g.*,

'501 patent, Ex. 1001 at 4:1-56, 18:35-41, 29:3-25 and Figure 12B), and Alnylam acknowledges that the patent and priority applications are “substantially similar.” (Petition at 17, 19.) In the Alnylam '423 Decision, the Board found that all of the priority applications at issue here are “substantially identical.” (Alnylam '423 Decision, Paper 9 at 17.)

Alnylam concedes that the priority applications “provide a[n] . . . embodiment which may encompass siRNA molecules with contiguous alternating 2'-O-alkyl modified ribonucleotides and different modified ribonucleotides and siRNA molecules with contiguous alternating 2'-O-alkyl modified ribonucleotides and a mixed motif of unmodified and differently modified ribonucleotides” (Petition at 14.) Alnylam nonetheless contends that the prior applications fail to describe or enable the challenged claims. As shown below, Alnylam has failed to meet its burden of proof.

### **III. ALNYLAM'S PETITION FAILS TO SHOW THAT ANY OF THE CLAIMS ARE ELIGIBLE FOR POST GRANT REVIEW**

Alnylam bears the burden of demonstrating that the challenged claims are eligible for post grant review. As the board held in *U.S. Endodontics v. Gold Standard Instr.*, a petition seeking post grant review must show that the challenged patent is “eligible for post-grant review. . . . Among the requirements for post-grant review eligibility is that the patent is subject to the first-inventor-to-file provisions of the AIA. *See* AIA §§ 3(n)(1), 6(f)(2)(A). Thus, as part of [the]

showing that it is entitled to the requested relief of post-grant review, the petitioner has the burden to show that the patent is subject to the first-inventor-to-file provisions of the AIA.” *US Endodontics, LLC v. Gold Standard Instrs. LLC*, PGR2015-00019 (PTAB. Jan. 29, 2016) (Paper 17 at 11-12).

To meet its burden, Alnylam must therefore prove that the challenged claims have an effective date on or after March 16, 2013. Here, the patent at issue claims the benefit of seven patent applications filed before March 16, 2013. (*See* Exs. 1006-1012.) Alnylam therefore bears the burden of proving that *each* of these pre-AIA priority applications fails to support the challenged claims. Alnylam has failed to meet that burden.

**A. Alnylam’s Petition Fails Because it Relies on Arguments the Board Has Already Rejected**

The ’423 patent and the ’501 patent rely on the same seven pre-AIA priority applications. In support of its claims that the ’501 patent’s priority applications fail to sufficiently describe or enable the present invention, Alnylam makes many of the same arguments as it did in its petition for post grant review of the ’423 patent (“the ’423 petition”). The Board rejected those arguments previously, and should reject them for the same reasons here. (*See, e.g.*, Alnylam ’423 Decision, Paper 9 at 17 (“we determine that the priority applications actually do provide disclosure for each of the claim limitations argued by Petitioner sufficient to satisfy the written-description requirement under § 112”); *id.* at 24 (“[f]or principally the

same reasons we previously discussed above with respect to written description, we determine that the priority applications provide enabling disclosure sufficient to support each of the claim limitations . . . .”).)

For example, Alnylam argues in this petition that the ’501 patent’s priority applications do not sufficiently describe or enable an siRNA molecule that “comprises modified ribonucleotides that alternate with differently modified ribonucleotides or a mixed motif of differently modified and unmodified ribonucleotides . . . .” (Petition at 49 (emphases omitted).) The Board has already rejected a similar argument where Alnylam alleged that the priority applications fail to provide written description support for the modification at the 2’-position of the flanking nucleotide being different from the modification at the 2’ position of the modified nucleotide. The Board stated that the priority applications adequately described and enabled “the modification at the 2’-position of the flanking nucleotide being different from the modification at the 2’-position of the modified nucleotide” because both the “EP1 application and the ’541 provisional each describes: modified nucleotides with an amino, fluoro, alkoxy, or alkyl modification at the 2’ position; nucleotides flanking the modified nucleotides with an amino, fluoro, alkoxy, or alkyl modification at the 2’ position; and where the modification at the 2’ position of the flanking nucleotides is different from the modification at the 2’ position of the modified nucleotides.” (Alnylam ’423

Decision, Paper 9 at 17-18.) The priority applications also provide support for a mixed motif of differently modified and unmodified ribonucleotides. (*See* Ex. 1006 at 4-6.)

Alynlam also argues now that the '501 patent's priority applications do not sufficiently describe or enable "any siRNA molecule with a double-stranded length greater than 21 ribonucleotides . . . ." (Petition at 49 (emphasis omitted).) The Board rejected Alynlam's nearly-identical argument in its petition for post grant review of the '423 patent and stated that "the EP1 application and the '541 provisional each explicitly discloses that the 'length of the first stretch and second stretch, respectively, is typically about 15 to about 23, preferably 17 to 21, and more preferably 18 or 19 bases.'" (Alynlam '423 Decision, Paper 9 at 18.)

As in its petition for post grant review of the '423 patent, Alynlam argues here that siRNA molecules with a length of 17 nucleotides are not adequately described or enabled by the priority applications. The Board rejected that argument, stating that the "EP1 application and the '541 provisional also each describes an embodiment wherein a '17 nucleotide long siRNA' molecule showed 'decreased activity,' as compared to certain other siRNA molecules 18 nucleotides or longer in length." (Alynlam '423 Decision, Paper 9 at 19.) The Board found that "the disclosure would have informed one of ordinary skill in the art that the molecule exhibits decreased RNA activity" and the priority applications "would

have reasonably conveyed to one of ordinary skill in the art that the inventor had possession of the claimed invention as of the filing date, sufficient to satisfy the written description requirement of § 112.” (*Id.* at 19.)

The remaining arguments that Alynlam relies on to allege that the claims of the ’501 patent are not adequately described or enabled should be rejected for similar reasons. As with the arguments the Board has already considered, the priority applications sufficiently describe and enable the challenged limitations of the ’501 patent claims.

**B. Alynlam Fails to Meet Its Burden By Improperly Relying on Post-Filing Evidence**

Alynlam argues that claims 1-30 of the ’501 patent are neither described nor enabled by the priority applications. In support of its argument, Alynlam relies on a declaration from its expert witness, Dr. Jonathan Watts, who offers various opinions relevant to the question of the priority applications’ enablement and written description of the challenged claims. (*See* Ex. 1002.) Significantly, the majority of publications referenced by Dr. Watt post-date the 2002 filing of the earliest priority application here.

In providing what he describes as a “Scientific and Technological Tutorial” (Ex. 1002 ¶¶ 39-56), Dr. Watts relies heavily on a 2009 article by Deleavey. (Ex. 1035 ¶¶ 50, 52-56.) Dr. Watts cites Deleavey as showing that “a number of significant obstacles” impede the use of siRNAs, as well as establishing that “a

wide variety of chemical modifications to the siRNA strands have been proposed.” (Ex. 1002 ¶ 53.) Dr. Watts also cites Deleavey as providing that “a great number of factors” need to be considered in order to develop an effective siRNA. (*Id.* ¶ 54.) He further relies on Deleavey as showing that “a number of different architectures” for siRNA molecules are possible. (*Id.* ¶ 55.) Dr. Watts does not opine that any of these concepts disclosed in the Deleavey 2009 article were known to those of skill in the art as of 2002.

Dr. Watts also relies on post-filing evidence purporting to show the scope of the claims. Dr. Watts points to a 2010 article by Gaglione (Ex. 1032) to support his opinion that “the claimed siRNA molecules could include any type of nucleotide base modifications . . . .” (Ex. 1002 ¶ 196), “any type of nucleotide sugar modifications . . . .” (*id.* ¶ 197), and “any type of siRNA backbone modifications . . . .” (*Id.* ¶ 198.) He also relies on a 2006 article (Ex. 1033) as support for his opinion that “the claims would also encompass siRNA molecules having various structural (or duplex) architectures . . . .” (Ex. 1002 ¶ 200.) He relies again on the 2010 Gaglione article to opine that the claims cover siRNA molecules “with any type of end modifications . . . .” (*Id.* ¶ 201.) All of these post-filing articles are the basis for his ultimate opinion that “the number of siRNA molecules encompassed by the claimed genus would be vast or potentially unlimited.” (*Id.* ¶ 202.) Significantly, however, Dr. Watts makes no effort to show that any of the siRNA

modifications disclosed in these post-filing date articles actually fall within the scope of the '501 patent claims, properly construed.

Dr. Watts further relies on post-filing evidence to support his opinion that “different [siRNA molecules] interact in different ways.” (Ex. 1002 ¶ 228.) Dr. Watts uses as 2006 study by Kraynack and Baker (Ex. 1060) to opine that “the activity of modified siRNAs . . . was dependent on construct design . . . .” (Ex. 1002 ¶ 229.) He finds that “[t]his study highlighted the interplay between duplex architecture, sequence, and chemical architecture, and their impact on functionality of chemically modified siRNAs.” (*Id.*) He similarly relies on the Deleavey article from 2009 (Ex. 1035), an article by Bramsen from 2012 (Ex. 1036), an article by Haringsma from 2012 (Ex. 1037), an article by Collingwood from 2008 (Ex. 1038), an article from Behlke from 2008 (Ex. 1039), and an article from Watts from 2008 (Ex. 1027) to support his opinions that “[f]rom outside the RNAi field, it may look deceptively simply to find active sequences and designs . . . ,” but that “there is a complex interplay of sequence, chemical modifications, various possible oligonucleotide lengths, duplex or single-stranded architecture, targeting ligand or delivery vehicle etc.” (Ex. 1002 ¶ 235.) He uses all of these articles to support his opinion that “there are numerous obstacles that need to be addressed when developing an RNAi molecule . . . .” (*Id.*) He offers no opinion that these



“obstacles” were known to exist at the time of the filing of the priority applications.

Alnylam improperly relies on this post-filing evidence to support its argument that the ’501 patent and its priority applications lack written description support. In *Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017), the Court held that post-priority-date evidence may be relevant only in limited circumstances. In particular, “post-priority-date evidence proffered to illuminate the post-priority-date state of the art . . . is *improper*.” 872 F.3d at 1374 (emphasis added). In contrast, post-priority-date evidence that shows “a patent fails to disclose a representative number of species” is proper. *Id.* at 1375.

Here, Alnylam’s evidence does not meet the *Amgen* standard. Much of the post-filing-date evidence discussed by Dr. Watts is aimed to show the general present day state of the art, and the purported unpredictability of the art based on present day knowledge. (See Ex. 1002 ¶¶ 39-56, 228-235.) Such evidence is squarely prohibited by *Amgen*. Additional opinions by Dr. Watts about the purported scope of the claim (see *id.* ¶¶ 200-204) are simply improper. In *Amgen*, the Court authorized post-filing-date evidence of recently discovered embodiments that met the claim requirements. In this case, by contrast, Dr. Watts and Alnylam make no showing that any of the supposed “unlimited” modified siRNAs discussed by Dr. Watts fall within the scope of the properly construed claims. Absent such a

showing, Alnylam's evidence does nothing more than show present day unpredictability. That is precisely what *Amgen* precludes.

Alnylam's reliance on this evidence to show lack of enablement is equally deficient. Post-filing evidence showing "lengthy and potentially undue experimentation" to arrive at an infringing product may be relevant to enablement, *Amgen*, 872 F.3d at 1375, but Alnylam offers no such evidence here. Nor has Alnylam made any showing that its post-filing-date articles consist of "later reports as evidence of the state of the art" as of the filing date. *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003). Rather, Alnylam has put forward post-filing-date evidence in an attempt to divert attention to what is known now, rather than meet its burden of showing the relevant state of the art. *U.S. Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251-52 (Fed. Cir. 1989) ("The central flaw in defendants' evidence . . . is that it was directed solely to a later state of the art.").

**C. Alnylam's Separate Argument that Claims 1-30 Are Not Functional Fails**

Alnylam makes an additional argument about claims 1-30. Alnylam argues that these claims "encompass siRNA molecules comprising a double-stranded region of 17 ribonucleotides in length . . ." (*See, e.g.*, Petition at 56.) According to Alnylam, these claims are not adequately described or enabled by the priority applications because (1) they encompass molecules having 17 double stranded

nucleotides; and (2) such molecules are not functional. (Petition at 56.) Alnylam fails to meet its burden as to both points.

First, Alnylam ignores the fact that Claim 9 explicitly is limited to a molecule that “consists of at least 18 nucleotides.” (’501 patent, Ex. 1001, Claim 9.) Alnylam’s argument thus, fails at the outset as to Claim 9. For the rest of the claims, Alnylam fails to show that a siRNA molecule with a double-stranded region 17 nucleotides long is necessarily non-functional. Alnylam points to statements in the patent specification describing 18 nucleotides as necessary for functionality, but ignores other statements in the specification suggesting that proposition may not be correct in all cases. For example, the specification reports experiments in which a 17 nucleotide long siRNA showed “reduced” activity when compared to longer molecules. (Ex. 1001 at 24:65-25:2.) The inventors concluded from that experiment that “a minimum base pairing of 18” nucleotides “*may* be obligatory.” (*Id.* at 25:4-6 (emphasis added).) Elsewhere the specification states that “[t]he length of the first stretch and second stretch [of the double stranded siRNA] is typically about 15 to about 23, preferably 17 to 21, and more preferably 18 or 19 bases.” (*Id.* at 18:35-37.) Alnylam does not contend with any of this evidence.

Significantly, Alnylam offers no evidence that such molecules are not functional; Alnylam’s expert instead simply cites to the patent specification as

purported evidence about what the inventors thought. (*See, e.g.*, Ex. 1002 ¶¶ 215-220 (reporting on what the inventors stated in the patent, without offering an opinion as to the functionality of siRNA molecules with a double-stranded region of 17 nucleotides).) Alnylam’s expert apparently was unable to offer the opinion that a siRNA molecule with a double stranded region of 17 nucleotides would be non-functional in all cases. Nor did Alnylam offer any other evidence to support its contention that a siRNA molecule with a double-stranded region 17 nucleotides long would necessarily be non-functional. In pending litigation over a counterpart Silence European patent, Alnylam informed the High Court of Justice in the UK that “in the course of R&D work [it had] made and tested many different modified potential RNAi products, in the course of which testing [it has] encountered many difficulties, failures and dead end potential products.” (Ex. 2001 ¶ 23.) Alnylam further told the UK Court that it “intend[s] to adduce fact evidence at trial about this.” (*Id.* ¶ 24.) Yet Alnylam introduced none of this evidence to the Board.

Finally, even if Alnylam could show that certain non-functional molecules were within the scope of the challenged claims, that would still not establish a failure of written description or enablement. The law is clear that the presence of inoperative embodiments does not render claims invalid under section 112. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *see also* M.P.E.P. § 2164.08(b) (“[t]he presence of inoperative

embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art”); *Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380 (Fed. Cir. 2002) (“although claims may read on some inoperative embodiments, this does not necessarily invalidate the claim if the necessary information to limit the claims to operative embodiments is known to a person of ordinary skill in the art.” (citing *Atlas Powder Co.*, 750 F.2d at 1576)).

#### **IV. CONCLUSION**

Alnylam has failed to meet its burden of demonstrating that the ’501 patent claims are eligible for post grant review. Post grant review should not be instituted in this case.

Dated: October 24, 2018

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**Certification of Word Count (37 C.F.R. § 42.24)**

I hereby certify that this Patent Owner's Preliminary Response has 3,901 words (as counted by the "Word Count" feature of the Microsoft Word™ word-processing system), exclusive of "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

Dated: October 24, 2018

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**CERTIFICATE OF SERVICE**

I hereby certify that the attached Patent Owner's Preliminary Response was served as of the below date via electronic mail by agreement on the Petitioner at the following correspondence address:

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