

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.,
Petitioner,

v.

NIPPON SHINYAKU CO., LTD. and
NATIONAL CENTER OF NEUROLOGY AND PSYCHIATRY,
Patent Owner.

IPR2021-01138
Patent 10,647,741 B2

Before ULRIKE W. JENKS, SHERIDAN K. SNEDDEN, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background and Summary

Sarepta Therapeutics, Inc. (“Petitioner”) filed a Petition for *inter partes* review of claims 1–12 of U.S. Patent No. 10,647,741 B2 (“the ’741 patent,” Ex. 1001). Paper 1 (“Pet.”). Nippon Shinyaku Co., Ltd. (“Patent Owner”) filed a Preliminary Response. Paper 11 (“Prelim. Res.”). Petitioner filed an authorized Reply to the Preliminary Response (Paper 14, “Reply”), and Patent Owner filed a corresponding Sur-reply (Paper 16, “Sur-reply”).

To institute an *inter partes* review, we must determine that the information presented in the Petition shows “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the evidence and arguments presented in the Petition, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least 1 claim of the ’741 patent is unpatentable. Accordingly, an *inter partes* review of all of the claims and all of the grounds presented in the Petition is hereby instituted.

This Decision is not a final decision as to the patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the record as fully developed during trial.

B. Real Parties in Interest

Petitioner identifies itself, Sarepta Therapeutics, Inc., as the real party-in-interest. Pet. 64. Patent Owner, identifies itself, Nippon Shinyaku Co.

Ltd. and National Center of Neurology and Psychiatry as real parties-in-interest. Paper 3, 1.

C. Related Matters

The '741 patent is at issue in *Nippon Shinyaku Co. v. Sarepta Therapeutics, Inc.*, Case No. 1-21-cv-01015 (D. Del. filed July 13, 2021). Paper 3, 1; Paper 5, 1.

In addition to the '741 patent challenged here, Petitioner has filed Petitions for *inter partes* review of related U.S. patents as follows: U.S. Patent No. 9,708,361 B2 ("the '361 patent") in IPR2021-01134; U.S. Patent No. 10,385,092 B2 ("the '092 patent") in IPR2021-01135; U.S. Patent No. 10,407,461 B2 ("the '461 patent") in IPR2021-01136; U.S. Patent No. 10,487,106 B2 ("the '106 patent") in IPR2021-01137; U.S. Patent No. 10,662,217 B2 ("the '217 patent") in IPR2021-01139; and U.S. Patent No. 10,683,322 B2 ("the '322 patent") in IPR2021-01140. Paper 5, 1; Paper 7, 1. Patent Owner further lists two pending applications in the same family, U.S. App. Serial Nos. 17/126,366 and 17/133,677. Paper 7, 1.

The '741 patent issued from U.S. Application No. 16/449,537, which claims priority through a series of continuations to PCT/JP2011/070318 (Ex. 1002), filed August 31, 2011, and Japanese Provisional Application No. 2010-196032 (Ex. 1003), filed on September 1, 2010. Ex. 1001, codes (21), (30), (63). Petitioner contends that claimed antisense oligomer complimentary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in human dystrophin pre-mRNA was first disclosed as H53_36–60 in Table 7 of PCT/JP2011/070318, and, as such, the claims are entitled to an earliest priority date of August 31, 2011. Pet. 10–12. Patent Owner does not argue otherwise. *See generally* Prelim. Resp.

D. The '741 Patent (Ex. 1001)

1. Background and Specification

The '741 patent discloses an antisense oligomer ("AO") that induces skipping of exon 53 in the human dystrophin gene during translation. Ex. 1001, Abstract, 3:10–13. The '741 patent discloses that exon skipping is expected to serve as a method for treating Duchenne muscular dystrophy ("DMD"). *Id.* at 2:14–15. DMD is caused by a mutation in the dystrophin gene that shifts the amino acid reading frame, thereby preventing the production of functional dystrophin protein. *Id.* at 1:46–47, 2:7–10. Skipping the mutation during translation may restore the amino acid reading frame of dystrophin mRNA, resulting in a dystrophin protein with partial functionality and milder disease symptoms. *Id.* at 2:14–26. The Specification discloses that

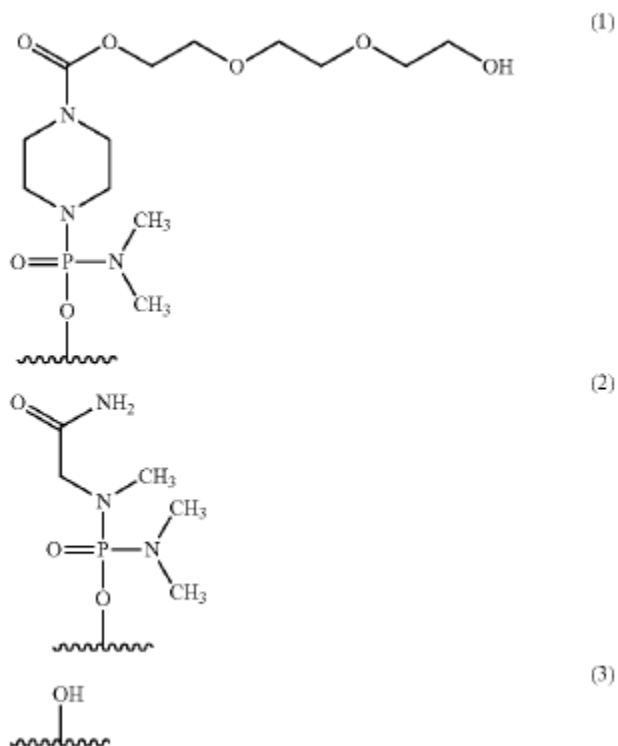
approximately 8% of all DMD patients may be treated by skipping the 53rd exon (hereinafter referred to as "exon 53"). In recent years, a plurality of research organizations reported on the studies where exon 53 in the dystrophin gene was targeted for exon skipping. . . . However, a [high efficiency] technique for skipping exon 53 has not been yet established.

Id. at 2:49–57.

Against this background the '741 patent discloses antisense oligomers that skip exon 53 with high efficiency by targeting specific nucleotide sequences in the mRNA precursor ("pre-mRNA"). *Id.* at 3:14–20. The Specification discloses that successful skipping of exon 53 can be confirmed by introducing the oligomer into a dystrophin expression cell, amplifying the region surrounding exon 53 of mRNA of the human dystrophin gene from the total RNA of the dystrophin expression cell by RT-PCR, and performing

nested PCR or sequence analysis on the PCR amplified product. *Id.* at 11:14–21.

The Specification discloses that the antisense oligomers may include oligonucleotides, morpholino oligomers, or peptide nucleic acids. *Id.* at 11:31–35. Oligonucleotides include modified nucleotides having fully or partly modified nucleobases, sugar moieties and/or phosphate-binding regions, which constitute the ribonucleotide or deoxyribonucleotide. *Id.* at 11:42–45. Preferred morpholino oligomers include phosphorodiamidate morpholino oligomers (“PMO”) where the nucleotide-ribose is replaced with a morpholino ring and the nucleotide phosphate-binding region is replaced with phosphorodiamidate. *See id.* at 13:64–14:19. The 5' end of the oligomer may include the structures reproduced below:



Structures 1–3 illustrate triethylene glycol (1), amide (2), and (3)-hydroxyl (3) substitutions. *Id.* at 24:65–25:27.

The Specification describes *in vitro* assays performed using antisense oligomers of 2'-O-methoxy-phosphorothioates (2'-OMe-S-RNA), including H53_36–60, SEQ. ID NO: 57. *Id.* at 40:40–58, 41:7.

The nucleotide sequence of exon 53 in the human wild type dystrophin gene is represented by SEQ ID NO: 1. *Id.* at 6:48–49.

SEQ ID NO: 124 is identical to the pre-mRNA corresponding to the 36th to 60th nucleotides of exon 53 of the human dystrophin gene. *Id.* at 85:18–25.

2. Illustrative Claims

Claims 1, 4, 7 and 10 are the independent claims, reproduced below, and are illustrative of the claimed subject matter of the '741:

1. A method comprising

administering to a patient with DMD an antisense phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer oligomer that is 100% complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in a human dystrophin pre-mRNA,

wherein the 53rd exon in said human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1,

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing, and

wherein skipping of the 53rd exon is induced in said patient.

4. A method of inducing exon 53 skipping in a patient with DMD comprising

administering to said patient an antisense phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer oligomer that is 100%

complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in a human dystrophin pre-mRNA,

wherein the 53rd exon in said human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1, and

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing.

7. A method comprising

administering to a patient with DMD an antisense phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer oligomer that is 100% complementary to the target sequence 5'-GAACACCUUCAGAACCGGAGGCAAC-3' (SEQ ID NO: 124),

wherein the 53rd exon in a human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1,

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing, and

wherein skipping of the 53rd exon is induced in said patient.

10. A method of inducing exon 53 skipping in a patient with DMD comprising

administering to said patient an antisense phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer oligomer that is 100% complementary to the target sequence 5'-GAACACCUUCAGAACCGGAGGCAAC-3' (SEQ ID NO: 124),

wherein the 53rd exon in a human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1, and

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing.

Id. at 85:26–90:22.

3. *Relevant Prosecution History*

The '741 patent was filed with two preliminary amendments dated June 24, 2019 and July 3, 2019. *See* Ex. 1015, 12–26. The second Preliminary Amendment cancelled the original claims and added new claims 15–25, which issued as claims 1–12 of the '741 patent. *See id.* at 20–24. In the Remarks accompanying the amendment, the Applicant “submit[ted] that newly added SEQ ID NO: 124 is at least inherently supported by SEQ ID NOS: 1 and 57 of the Specification.” *Id.* at 25. The application was allowed after the Applicant filed terminal disclaimers obviating provisional double patenting rejections over the claims of Application Nos. 16/712,686 and 16/717,274. *See id.* 31–38.

During the prosecution of the '741 patent's grandparent application (Application No. 14/615,504, now the '361 patent), the Examiner rejected the claims as obvious over Popplewell '212¹ and Sazani '591². *See* Ex. 1011, 31–36 (Non-Final Act. dated March 25, 2016); 53–61 (Final Act. dated October 27, 2016); Ex. 2007; Ex. 2009.³ Specifically, the Examiner found that Popplewell '212 teaches that “the same region targeted by the instantly claimed oligomers is superior to other regions of exon.” Ex. 1011, 57. The Examiner further found that the sequences recited by the then pending claims—oligomers consisting of the nucleotide sequences of SEQ

¹ US 2010/0168212 A1, published July 1, 2010 to Popplewell et al. (Ex. 1023).

² US 2010/80130591 A1, published May 27, 2010 to Sazani et al. (Ex. 1024).

³ The relevant prosecution history is included in the record as Exhibits 1011 and 2005–2012. We cite Exhibit 1011, unless otherwise specified.

ID NO: 11 and SEQ ID NO: 57 (Ex. 1011, 43)—“fall squarely within SEQ ID NOS:10–12 and 24 which has been taught by Popplewell [’212] to be a ‘superior’ target region of exon 53.” *Id.* (citing Ex. 1023, Ex. 2, cls. 1–12). The Examiner found that Sazani ’591 similarly taught antisense oligomers for inducing exon 53 skipping in the human dystrophin gene. *Id.* at 57–58.

The Examiner found that, although the prior art did not teach the identical claimed sequences, “[i]t would have been well within the skill of the artisan to test various sizes of oligomers in an optimization of antisense compounds targeting a known superior target region.” *Id.* at 58. The Examiner acknowledged that the Applicant argued the claimed compounds have unexpected properties, but found “[t]he fact that applicant screened for more oligonucleotides in a region that has been taught to be superior utilizing size ranges and modifications known in the art is not unexpected.” *Id.* at 61.

The Applicant then amended the claims by deleting SEQ ID NO: 11 and claiming only SEQ ID NO: 57. *See* Ex. 1011, 65 (After-final amendment dated February 27, 2017). The Applicant argued that Popplewell ’212 “teaches that the oligomer corresponding to positions 30–59 of exon 53 provides the highest activity” and that “Popplewell’s top performer is different from the presently recited ones.” *Id.* at 69–70 (citing Ex. 1023 ¶ 74, Fig. 8). The Applicant further argued that SEQ ID NO: 57 offered superior skipping effects as compared to the oligomers of Popplewell ’212 and Sazani ’591. *See id.* Specifically, the Applicant argued that the Specification shows that the oligomer with SEQ ID NO: 57 (H53_36_60) displays greater skipping activity than the oligomer with SEQ ID NO: 11 (H53_32_56), which in turn displays greater skipping activity than that of PMO Nos. 12 and 15 corresponding to Popplewell’s sequence

targeting H53_30_59. *Id.* at 70 (citing Ex. 1001 Figs. 2–4, 16–19, Table 2). Following the amendment, the claims were allowed without further comment by the Examiner. *See id.* at 72–76.

E. Evidence

Petitioner relies upon information that includes the following.

Ex. 1021, Popplewell et al., *Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials*, 20 NEUROMUSCULAR DISORDERS 102–110 (2010) (“Popplewell”).

Ex. 1022, Sazani et al., *Safety Pharmacology and Genotoxicity Evaluation of AVI-4658*, 29 INTL. J. TOXICOLOGY 2:143–156 (2010) (“Sazani”).

Petitioner also relies on the declaration of David R. Corey, Ph.D (Ex. 1099) to support its contentions.

F. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–12 would have been unpatentable on the following ground:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–12	103	Popplewell and Sazani

II. ANALYSIS

A. Legal Standards

“In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See*

Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Claims 1 and 7 recite “[a] method comprising administering to a patient with DMD . . . wherein skipping of the 53rd exon is induced in said patient.” Ex. 1001, 85:26–36, 87:54–64. Claims 4 and 10 recite “[a] method of inducing exon 53 skipping in a patient with DMD comprising administering to said patient an antisense phosphorodiamidate morpholino oligomer” *Id.* at 86:54–64, 88:56–67. Petitioner argues that claims 1 and 7 do not require treatment of DMD, nor inducement of a particular level of exon skipping. Pet. 6–9. Petitioner argues that claims 4 and 10 do not require treatment of DMD, contain no efficacy limitations, and do not require that the recited PMOs induce skipping of exon 53. *Id.* Petitioner, however, does not propose an express claim construction for any claim term. *See generally* Pet.

Patent Owner does not address claim construction in its preliminary response. *See generally* Prelim. Resp.

Having considered the parties’ positions and evidence of record, we determine that no express construction of any claim term is necessary to determine whether to institute *inter partes* review. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v.*

Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999))). To the extent further discussion of the meaning of any claim term is necessary to our decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

C. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art would have had “a Ph.D. in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience with AOs for inducing exon skipping” and would “have familiarity with methods for making and testing the safety and efficacy of such AOs, both *in vitro* and *in vivo*, and the use of AOs for inducing exon skipping in the context of medical conditions, such as DMD, that may be treated by administering such AOs.” Pet. 31–32 (citing Ex. 1099 ¶ 98). Petitioner also proposes that a person of ordinary skill in the art “would have knowledge of and experience with chemical modifications that may be incorporated into AOs, such as modifications to the backbone and/or nucleobases of the AOs, and the potential impact of those modifications on the utility of the AOs.” *Id.* at 32 (citing Ex. 1099 ¶ 99).

Patent Owner states, “[s]olely for purposes of this IPR, Patent Owner does not dispute Petitioner’s definition of a POSA. To the extent the Board decides to institute this Petition, Patent Owner reserves the right to present a different definition post-institution.” Prelim. Resp. 14.

Because Petitioner’s proposed definition is unopposed at this stage of the proceeding and appears consistent with the Specification and art of record, we apply it here.

D. Summary of Cited Prior Art

1. Overview of Popplewell (Ex. 1021)

Popplewell explores antisense oligonucleotide sequences targeting exon 53 of the human DMD gene. Ex. 1021, 102. Specifically, Popplewell used a DMD patient primary myoblast culture system to test twenty-four previously known AOs designed to target exon 53 to confirm which AOs would have the potential as a treatment for patients with an eligible deletion. *Id.* at Abstract, 103–104. All of the tested AOs were synthesized as phosphorodiamidate morpholino oligomers (PMOs). *Id.* at 103. Popplewell discloses that, of 13 PMOs whose target sites are within the sequence +29 to +74 of exon 53, “PMOs -G, -H and -A were the most efficient, producing a mean of 73% ($\pm 4.10\%$), 68% ($\pm 4.77\%$) and 68% ($\pm 4.14\%$) exon skipping respectively (classified as Type 1)^[4] (Fig. 1).” *Id.* at 104. The 13 PMOs in this region, PMOs A–M, are listed in Table 1, along with their start and end positions relative to exon 53. *Id.* at 105.

⁴ Popplewell classified antisense oligonucleotides according to skipping efficacy: “PMOs that produced over 50 % exon skipping were designated as Type I, those that produced between 25% and 50% exon skipping were described as Type 2, while those that produced less than 25% as Type 3.” *Id.*

Popplewell's Figure 1b is reproduced below.

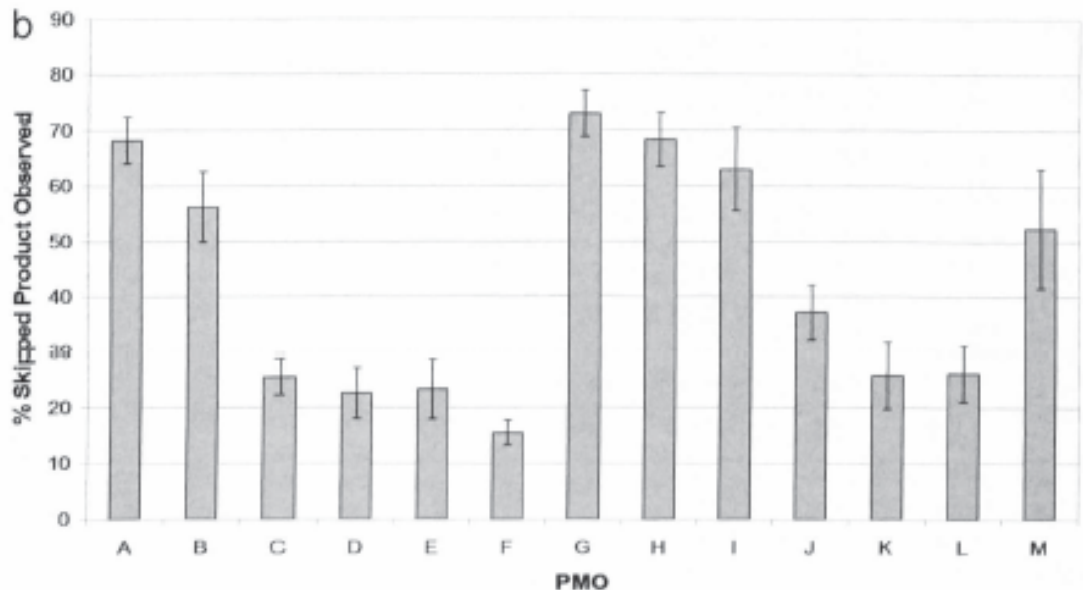


Figure 1b is a bar graph showing the percentage of exon skipping achieved for each PMO A–M. *Id.* at 106. Popplewell found no statistical difference between results for the numerically highest PMO, PMO-G and PMOs -A, -B, -H, -I, and -M. *Id.* at 106, Fig. 1C. Popplewell selected the six most effective PMOs (i.e. Type 1) (-A, -B, -G, -H, -I and -M)⁵ for dose-response, time-course, and in vivo experiments on the assumption that “more efficacious PMOs should produce sustained and pronounced exon skipping when applied at lower concentrations.” *Id.*

In the dose-dependent experiments, Popplewell discloses that PMO-G and PMO-H were more efficient at low concentration than PMOs -A, -B, and -M. *Id.* More particularly, Popplewell states:

When the concentration dependence of exon skipping was examined for the most efficient PMOs, skipping levels approaching 30 % were evident for the Type 1 PMOs -G

⁵ As noted by Dr. Corey, “[o]f the Type 1 PMOs, two were 25-mers (PMO-A and -B), three were 30-mers (PMO-G, -H, and -I), and one was a 31-mer (PMO-M).” Ex. 1099 ¶ 114.

and -H at concentrations as low as 25 nM (Fig. 2a, b). The other PMOs classified as Type 1 (PMOs -A, -B, -I and -M) did not induce such levels of exon skipping when used at lower concentrations. Similar levels of skipping (30%) were only achieved by PMO -A, PMO -B and PMO -M at 100 nM, while PMO-1 needed to be present at 200 nM to produce over 30% exon skipping (Fig. 2a,b).

Id. Accordingly, Popplewell concludes, “concentration dependence of exon skipping is a valuable tool in ascertaining the most efficient AO(s).” *Id.*

In discussing the time-course experiments, Popplewell states that “exon skipping produced by the six Type 1 PMOs was shown to be persistent, lasting for up to 10 days after transfection, with over 60% exon skipping observed for the lifetime of the cultures for PMOs -A, PMO-G and PMO-H (Fig. 3a, b).” *Id.* In addition, Western blot analysis showed that “[d]e novo expression of dystrophin protein was evident with all six PMOs but was most pronounced with PMOs -H, -I, -G and -A, producing 50%, 45%, 33% and 26% dystrophin expression, respectively.” *Id.* at 105.

With respect to in vivo experiments, Popplewell states: “The Type 1 PMOs (-A, -G, -H, -I and -M) (20 pg) were injected into the gastrocnemius muscle of hDMD mice in duplo. RNA extracted from the muscles was analysed for exon 53 skipping by RT-PCR (Fig. 5b).” *Id.* at 107.

Skipping of exon 53 was evident for each of the PMOs tested: average skipping seen in both legs was 8% for PMO-A, 7.6% for PMO- I. 7.2% for PMO-G, but a slightly lower level of 4.8% for PMO-H. PMO-M produced exon skipping levels of less than 1%, which is the detection threshold for the system used.

Id.

According to Popplewell, “[w]hen considering the data presented previously . . . and here as a whole, the superiority of the PMOs targeting the

sequence +30+65 (i.e. PMOs -A, -B, -G and -H) is strongly indicated.” *Id.* at 109. Moreover, “PMOs targeting within the sequence +30+65 of exon 53 (namely PMO -A, -G and -H) produce levels of exon skipping that may be considered effective (over 50% exon skipping).” *Id.* at 108. Accordingly, Popplewell recommends the PMOs targeting the +30+65 region “worthy of consideration for any upcoming clinical trial. *Id.* at 109.

Of the individual Type 1 PMOs identified, Popplewell suggests

PMO-G as a potential clinical trial reagent of choice for the targeted skipping of exon 53 of the DMD gene relative to the other Type 1 PMOs . . . based primarily on its more persistent longevity of action . . . with PMOs -A and -H providing viable alternatives if required.

Id. at 109. Popplewell concludes, however, “that stepped base-by-base screening of AOs across the entirety of exon 53 . . . might reveal an AO with a better dose-response and longevity of action profile.” *Id.* at 108.

2. Overview of Sazani (Ex. 1022)

Sazani describes the safety pharmacology and genotoxicity evaluations of AVI-4658, a PMO under clinical evaluation for treating DMD. Ex. 1022, 143. Specifically, AVI-4658 is a PMO designed to skip exon 51 of human dystrophin and thus restore dystrophin expression in DMD patients. *Id.* at 144. Sazani illustrates AVI-4658 as a PMO with a triethylene glycol moiety at its 5'-end. *See id.* at 145, Fig. 1. Figure 1 is reproduced below.

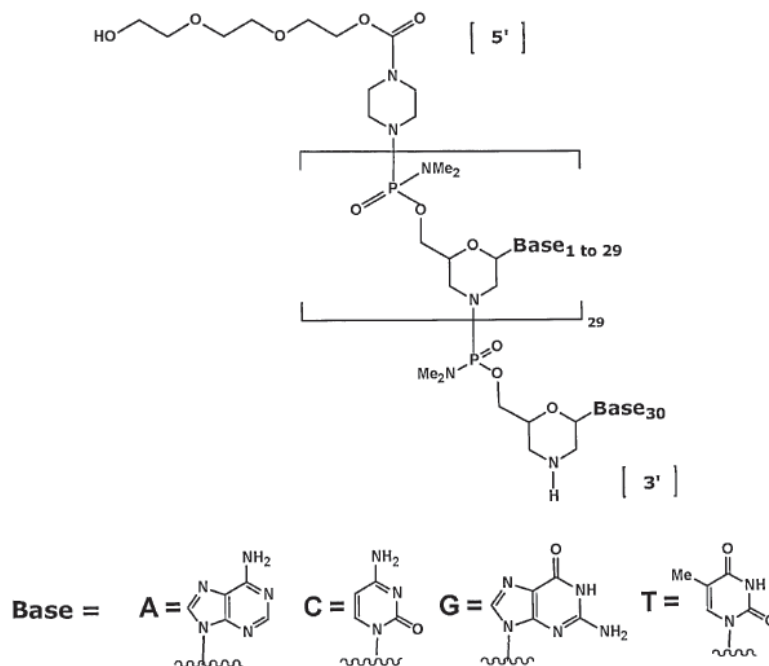


Figure 1 illustrates a PMO subunit, substituted with bases including adenine, cytosine, guanine, and thymine.

Sazani discloses that, based on positive safety and genotoxicity data, a proof-of-concept clinical trial was performed to evaluate the safety and efficacy of AVI-4658. *Id.* at 154. The study demonstrated specific dose-dependent exon skipping and strong dystrophin production in treated muscles of DMD boys. *Id.*

E. Obviousness of Claims 1–12 over the Combination of Popplewell and Sazani

1. Analysis of Independent Claims 1, 4, 7, and 10

Petitioner contends that claims 1, 4, 7 and 10 are invalid for obviousness over Popplewell and Sazani. Pet. 32–50. Claim 7 is identical to claim 1, except that claim 7 recites the target sequence corresponding to the 36th to the 60th nucleotides from the 5' end of the 53rd exon. Ex. 1001, 85:26–36, 87:54–64. Claim 10 is likewise identical to claim 4, except that

claim 10 recites the target sequence corresponding to the 36th to the 60th nucleotides from the 5' end of the 53rd exon. *Id.* at 86:54–64, 88:56–67.

Popplewell discloses a phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer antisense oligomer that is 100% complementary to the 35th to the 59th nucleotides from the 5' end of the 53rd exon in a human dystrophin pre-mRNA. *See* Ex. 1021, 102, 105 (Table 1, PMO-A). Popplewell discloses that the PMO hybridizes to human dystrophin pre-mRNA with Watson-Crick base pairing thereby inducing skipping of the 53rd exon. *See id.* Popplewell does not disclose a 25-mer antisense oligomer that is 100% complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon. *See id.* at 105. Accordingly, the issue before us is whether the prior art would have suggested those of ordinary skill in the art to modify Popplewell in view of Sazani to make the claimed oligomer with a reasonable expectation of success. To that point, we note that Sazani discloses PMO monomer subunits having the formula of claim 1 wherein each of R² and R³ represents a methyl, wherein the Base is cytosine, thymine, adenine, and guanine, and wherein the 5' end of the PMO includes a triethylene glycol moiety. *See* Ex. 1022, 145, Fig. 1b.

a) Motivation to Modify PMO-A of Popplewell

(1) Petitioner's Contentions

Petitioner argues that Popplewell recommends PMOs targeting sequence +30+65 of exon 53 of the DMD gene for clinical trials to identify treatments for DMD. Pet. 36 (citing Ex. 1021, 102–103, 109). Petitioner argues that Popplewell teaches two 25-mers that target the +30+65 sequence of exon 53, of which PMO-A (+35+59) was the most effective. *Id.* at 38 (citing Ex. 1021, 109 (“When considering the data presented previously and

here as a whole, the superiority of the PMOs targeting the sequence +30+65 (i.e., PMOs -A, -B, -G and -H) is strongly indicated.”); Ex. 1099 ¶¶ 76, 115, 117, 123, 129). Petitioner argues that “[a] POSA would have been motivated to further optimize the target sequence of the most effective 25-mer, PMO-A (+35+59), by using the same routine AO screening techniques employed by Popplewell (and others) to identify additional effective AOs.” *Id.* at 38–39 (citing Ex. 1099 ¶ 118). Petitioner argues that Popplewell’s routine screening techniques includes stepped base-by-base screenings of AOs. *Id.* at 39 (citing Ex. 1021, 108).

Petitioner contends that “[u]sing the AO screening approach discussed above, a person of ordinary skill in the art, starting from the AOs identified in Popplewell as most promising, including PMO-A would have quickly landed on a PMO with a sequence that is 100% complementary to the +36+60 nucleotides of exon 53 as recited in claims 1, 4, 7, and 10.” *Id.* at 40 (citing Ex. 1099 ¶ 119). Petitioner compares the sequences as illustrated below.

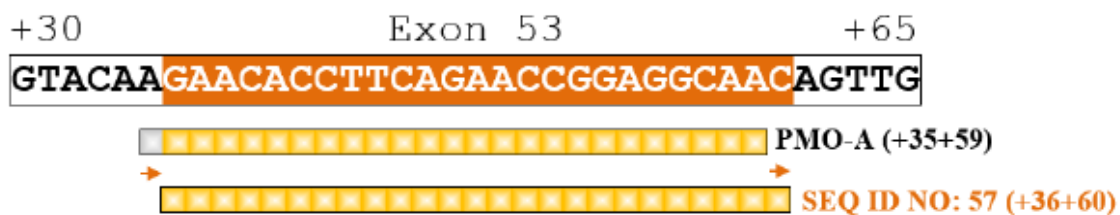


Illustration of Exon 53 including nucleic acids +30+65 with nucleic acids +36+60 highlighted in orange, followed below by PMO-A (+35+59), followed below by SEQ ID NO: 57 (+36+60) with arrows advancing one nucleotide in the 3' direction. *Id.* at 41 (citing Ex. 1099 ¶ 119).

Petitioner argues that a person of ordinary skill in the art would have been motivated to administer an AO with a PMO backbone to induce exon 53 skipping to a DMD patient. *Id.* at 41 (citing Ex. 1099 ¶¶ 131). Petitioner

argues that Sazani provides additional teachings as to administering PMOs to DMD patients. *See id.* at 41–43. Specifically, Petitioner argues that Sazani teaches a pre-clinical study of administering a PMO, AVI-4658, that induces skipping of exon 51 in DMD patients. *Id.* at 41–42 (citing Ex. 1022, 144, 154; Ex. 1099 ¶¶ 134–135). Petitioner argues that favorable safety and efficacy results for AVI-4658 supported a progression to clinical testing, and that “Sazani would have provided a POSA with guidance regarding dosages and modes of administration of a PMO to a patient with DMD further supporting a reasonable expectation of success.” *Id.* at 42–43 (citing Ex. 1022, Abstract; Ex. 1099 ¶ 138).

Petitioner acknowledges that Popplewell teaches 30-mers, e.g., PMO-G, as preferred embodiments, but argues that it is well settled that preferred embodiments do not constitute a teaching away from somewhat less preferred embodiments. *Id.* at 46–48 (citing *In re Susi*, 440 F.2d 442, 446, n.3 (CCPA 1971); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989)). Petitioner argues that Popplewell expressly describes 25-mers as “viable alternative[s]” to PMO-G, and that “the 25-mer PMO-A performed better than several of the 30-mer AOs tested in Popplewell and had the highest *in vivo* efficacy of *any* PMO tested by Popplewell in the humanized DMD mouse.” *Id.* at 46 (citing Ex. 1021, 109; Ex. 1099 ¶ 123). Petitioner argues that there would have been additional considerations for a person of ordinary skill “to use 25-mers, including limiting off-target effects, relative ease of synthesis, and reduced manufacturing costs associated with shorter AOs.” *See id.* at 47 (citing Ex. 1099 ¶¶ 42–43, 46, 121).

(2) *Patent Owner's Contentions*

Patent Owner responds by arguing that Petitioner does not provide “any reasoned explanation or rationale as to why a POSA would select PMO-A (1) from among the many AOs in the prior art *as a whole*, (2) over the AOs that Popplewell discloses, (3) over Popplewell’s undisputed best performing AO—PMO-G, or (4) over Popplewell’s other strong performing AOs.” Prelim. Resp. 46–47.

First, Patent Owner argues that Petitioner presents a “lead compound analysis” without identifying Popplewell’s PMO-A as a “lead sequence” for modification. *See id.* at 47–55. Specifically, Patent Owner argues that Petitioner’s references to PMO-A as the “most promising” sequence and a “starting point” for modification implies a lead compound analysis. *See id.* at 47–48 (citing Pet. 39–40; Ex. 1099 ¶¶ 119, 123). Patent Owner argues that Petitioner’s argument—choosing of PMO-A as a “lead sequence” out of numerous AOs that skip exon 53—relies on impermissible hindsight in view of Popplewell’s teaching that 30-mer AOs were preferred. *See id.* at 48–52 (citing Pet. 16; Ex. 1021, 108). Patent Owner further argues that Petitioner has presented contrary arguments applying a “lead compound analysis” in the prosecution of Petitioner’s own unrelated patent applications claiming similar AOs targeting exon 53 of the DMD gene. *See id.* at 52–55 (citing Ex. 2017, 10–13, 23, 27; Ex. 2019, 24; Ex. 2049, 13).

Second, Patent Owner argues that Petitioner failed to show a motivation to modify PMO-A. Prelim. Resp. 56–58. Patent Owner argues that Petitioner has “repeatedly argued during the prosecution of its own patent applications,” that Popplewell describes empirical testing of AOs according to a trial and error procedure with unpredictable results. *See id.* at 53–54 (citing Ex. 2017, 13, 26–27; Ex. 2020, 18). Patent Owner further

argues that “Popplewell leads a POSA in a direction divergent from that proposed by Petitioner” because “PMO-A had a poor efficiency of only 12.7%,” and the efficiency decreased when shifting the sequences in the 3’ direction. *See id.* at 57 (citing Ex. 1021, Table 1). Patent Owner argues that “[i]n view of these results, a POSA would have expected that shifting the target sequence in the 3’ direction would result in considerably less skipping activity.” *Id.* at 58.

(3) Discussion

As Patent Owner admits, Petitioner does expressly rely on a lead compound analysis, nor is it clear that the entirety of the lead compound analysis applies to the selection of nucleotide sequences at issue here. *See* Prelim. Resp. 46–50. Rather, in arguing that one of ordinary skill in the art would have sought to “optimize the target sequence of the most effective 25-mer, PMO-A (+35+59),” Petitioner appears to focus on the portion of exon 53 that binds PMO-A and its surrounds, rather than PMO-A itself. *See* Pet. 38. Whether this is a distinction with a difference remains to be determined. Nevertheless, for the purpose of this section, we refer to PMO-A as a proxy for any nuance intended by Petitioner.

Because the antisense oligonucleotides encompassed by the challenged claims encompass a genus of chemical compounds, we consider first, whether Petitioner has established sufficiently that one of ordinary skill in the art would have selected PMO-A as a starting point for further analysis. In this regard, the “lead compound” approach set forth by the Federal Circuit may well be relevant to the obviousness analysis in this case. *See Eisai Co. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (stating that even “post-*KSR*, a *prima facie* case of obviousness for a chemical compound

still, in general, begins with the reasoned identification of a lead compound”).

With respect to the selection of PMO-A as a starting point, we note Patent Owner’s argument that Petitioner does not provide “any reasoned explanation or rationale as to why a POSA would select PMO-A (1) from among the many AOs in the prior art *as a whole*, (2) over the AOs that Popplewell discloses, (3) over Popplewell’s undisputed best performing AO—PMO-G, or (4) over Popplewell’s other strong performing AOs.” Prelim. Resp. 46–47. That argument, however, rests on the assumption that in any given endeavor, there is one, and only one, lead compound. *See e.g., id.* (quoting *Otsuka Pharm.*, 678 F.3d at 1291). The Federal Circuit, however, makes clear that “the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound,” but consider whether “one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art.” *Daiichi Sankyo Co. v. Matrix Lab’ys, Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). We, therefore, address Patent Owner’s arguments with the understanding that our case law does not demand the identification of a single, best lead compound.

As noted in section II.D.1, above, beginning with an initial cohort of twenty-four antisense oligomers targeting exon 53, Popplewell concludes that “the superiority of the PMOs targeting the sequence +30+65 (i.e. PMOs -A, -B, -G and -H) is strongly indicated.” Ex. 1021, 109. Although PMO-A showed the highest level of exon skipping in a human DMD mouse model, Popplewell identified “PMO-G as a potential clinical trial reagent of choice . . . based primarily on its more persistent longevity of action.” *Id.* at 107, 109. Popplewell, nevertheless, characterized PMO-A and PMO-H as

“viable alternatives.” *Id.* at 109. Considering the possibility of further improvement,” Popplewell suggests “that stepped base-by-base screening of AOs across the entirety of exon 53 . . . might reveal an AO with a better dose-response and longevity of action profile.” *Id.* at 108.

Standing alone, the above facts would appear to identify PMO-A as a suitable target for further development. Patent Owner, however, argues that Petitioner’s focus on PMO-A amounts to impermissible hindsight and is contrary to Popplewell’s teaching that 30-mer oligos (e.g., PMO-G and PMO-H) were more bioactive than 25-mers such as PMO-A. *See* Prelim. Resp. 50–52. In particular, Popplewell states:

that the 30 mer PMOs (-G, -H) were more bioactive than 25 mer PMO counterpart (-A) targeted to the same open/accessible sites on the exon, would suggest that strength of binding of PMO to the target site may be the most important factor in determining PMO bioactivity. The influence of AO length on bioactivity has been reported elsewhere, and is further confirmed in the present study; all 30mers tested were more bioactive relative to their 25 mer counterpart.

Ex. 1021, 108 (internal footnote numbers omitted). Popplewell further notes that its best PMOs achieved greater skipping efficacy than shown by another research group using 2’OMe AOs, which might reflect the length of their nucleotide sequences and/or other factors. *Id.* at 109. Popplewell notes, however, that “[n]o direct comparison was made” between the two sets of AOs and, moreover, a “direct comparison would in fact be difficult as 2’Ome AOs are generally only 20 nucleotides long, whereas the PMOs used here were 25 and 30mers.” *Id.*

Patent Owner’s argument that one of ordinary skill in the art would not select PMO-A for further development because it was a 25-

mer thus finds some support in Popplewell. Such disclosure, however, is seemingly contradicted by Popplewell's in vivo results showing that the 25-mer PMO-A resulted in higher levels of exon skipping than five different 30-mers— including PMO-G, and PMO-H. *See* Ex. 1021, 107, Table 1. We also consider Petitioner's argument regarding the supposed practice and benefits of using shorter oligonucleotides. Pet. 15, 38–39 (citing Ex. 1040, 495; Ex. 1099 ¶¶ 43, 124). As such, the evidence for and against the selection of a PMO-A as a starting point is mixed and will benefit from further development at trial.

Patent Owner further contends that the Petition is deficient for failure to consider known exon skipping AOs beyond those disclosed in Popplewell, “let alone provide ‘a reason to select [PMO-A] from the panoply of compounds in the prior art.’” Prelim. Resp. 49 (quoting *Otsuka Pharm.*, 678 F.3d at 1292). Patent Owner's argument is unavailing on the present record. As an initial matter, Figure 9 of Dr. Corey's Declaration “summarizes select AOs that were reported to effectively induce skipping of exon 53 as of August 31, 2011.” Ex. 1099 ¶ 64. Dr. Corey further testifies that, as of the critical date, the art had “identified the (+30+65) region as a hotspot for AOs that could induce efficient exon skipping,” such that “[i]t would have been obvious that this hotspot target region would have been the starting point for testing AOs to ensure that no AO of greater promise was missed.” *Id.*

And although Patent Owner identifies “***several additional effective AOs targeting exon 53***,” it points to no information on their relative efficacy as compared to Popplewell's sequences. *See* Prelim.

Resp. 49.⁶ Moreover, to the extent the references cited by Patent Owner contain efficacy data, Popplewell teaches that numerous factors could account for apparent differences between laboratories and even direct comparisons can be “difficult.” *See* Ex. 2021, 109. Under these circumstances, that numerous groups had reported “effective” skipping of exon 53, merely underscores the court’s admonition to not “rigidly focus on the selection of a single, best lead compound.” *Daiichi*, 619 F.3d at 1354.

Patent Owner further argues that Petitioner has presented contrary arguments applying a “lead compound analysis” in the prosecution of Petitioner’s own unrelated patent applications claiming similar AOs targeting exon 53 of the DMD gene. *See id.* at 52–55 (citing Ex. 2018, 11; Ex. 2013, 8; Ex. 2014, 8; Ex. 2015, 7; Ex. 2017, 10–13, 27; Ex. 2019, 24). While the Patent Owner’s argument underscores that the determinations before us are a close call, we decline to give preclusive effect to arguments made on a different record in an unrelated application. It also appears that Petitioner’s prior arguments did not persuade the Examiner and it eventually abandoned the application. Pet. 47 (citing Ex. 1063, 1–2).⁷

⁶ We note that 5 of the 6 AOs specifically identified by Patent Owner in this section appear to be 18-mers. *See id.* at 42–43 (identifying h53AON1 (+45+62), AO65 (+21+38), AO95 (+30+47), AO66 (+39+56), and AO67 (+57+74)). Patent Owner’s suggestion that Petitioner should have considered 18 nucleotide AOs as lead compounds undercuts its argument disparaging the 25 nucleotide PMO-A based on its length.

⁷ Given that we give little weight to statements made in Petitioner’s unrelated, abandoned application, we decline Patent Owner’s invitation to deny the Petition because “Petitioner withheld its August 28, 2017 and

On balance, Petitioner has established sufficiently that one of ordinary skill in the art would have selected PMO-A for further development.⁸

b) Reasonable Expectation of Success

(1) Petitioner's Contentions

Petitioner argues that a person of ordinary skill in the art would have had reasonable expectation of success of administering a 25-mer PMO targeting a sequence within the 30th to 65th hotspot region of exon 53 to a patient with DMD to induce exon 53 skipping. Pet. 38 (citing Ex. 1099 ¶¶ 125–139). Specifically, Petitioner argues that Popplewell discloses multiple PMOs complementary to a region that encompasses SEQ ID NO: 57 (hotspot +30+65), as well as methods for evaluating whether the PMOs induce exons skipping. *See id.* at 38–40 (citing Ex. 1021, 103, 109; Ex. 1099 ¶¶ 118–122).

Petitioner also advances substantial evidence that methods of making PMOs were known, as were methods of evaluating the ability of a PMO to

December 14, 2018 Responses.” *See* Prelim. Resp. 47 (citing Ex. 2019, Ex. 2017) (emphasis removed).

⁸ Petitioner cites *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) for the proposition that the “[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation” to discover optimal conditions within a known range.” Pet. 38–39. In their post-institution briefing, the parties are requested to address the applicability of the presumption of obviousness and the analytical framework associated with overlapping ranges to the situation presented here, where there is an overlap of nucleotide sequences between the claimed AO and the prior art PMO-A. *See E.I. Dupont De Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018); *cf. Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) (holding that ordinary motivation to optimize did not apply where disclosure was 68,000 protein variants including 2,332 amino acids).

induce exon 53 skipping. *Id.* (citing Ex. 1001, 13:15–19; 14:16–19, 14:49–50, 31:11–12; Ex. 1021, 103; Ex. 1024, ¶ 97; Ex. 1035, 1294–1295; Ex. 1049, 26; Ex. 1050, 35; Ex. 1054, 33; Ex. 1065, 584; Ex. 1099 ¶ 120). We further note Dr. Corey’s testimony that, “[t]he numerous effective prior art AOs (including those identified in Popplewell) with target regions throughout the hotspot target region of exon 53 (+30+65) would have provided a reasonable expectation that an AO 100% complementary to the (+36+60) sequence of exon 53 would be similarly effective in causing skipping of exon 53.” Ex. 1099 ¶ 16.

(2) Patent Owner’s Contentions

Patent Owner argues that Petitioner failed to establish a reasonable expectation of success in a highly unpredictable art. Prelim. Resp. 59. Patent Owner argues that identifying potent AOs requires empirical testing of multiple AOs, with a typical strategy of stepped base-by-base screening across the entirety of a target exon. *Id.* at 59–60 (citing Ex. 1099 ¶¶ 43, 118). Patent Owner further argues that Petitioner made similar arguments of unpredictability while prosecuting its own patent applications before the Office. *See id.* at 57–59 (citing Ex. 2017, 14–18; Ex. 2013, 13–14; Ex. 2014, 13–14; Ex. 2015, 11–12; Ex. 2016, 12–13).

Patent Owner argues that Petitioner merely suggests that “the only way to find a possibly more active AO would be to empirically test overlapping AOs *across the entire exon.*” *Id.* at 62. Patent Owner further argues that “Petitioner provides no evidence that a POSA would have had a reasonable expectation of successfully inducing exon skipping in a DMD patient by administering the claimed AO based on the disclosures of Popplewell and Sazani.” Prelim. Resp. 68. Patent Owner argues that

Sazani's teachings that AVI-4658 induces exon skipping in DMD patients are inapplicable because AVI-4658 is a 30-mer targeting exon 51, not exon 53. *Id.* at 67 (citing Ex. 1022, 144).

(3) Discussion

On the present record, Petitioner has the better argument. As noted by Petitioner, the '741 Specification acknowledges that "PMOs could be produced in accordance from known methods or even ordered from a company." Pet. 40. Popplewell discloses several methods for testing exon-skipping activity, as well as numerous AOs in the region (+30+65) of exon 53—all of which appear to show some level of activity. Patent Owner does not argue testing for exon-skipping entails undue experimentation. To the extent one of ordinary skill in the art was motivated to conduct a screen for active 25-mer PMOs in the (+30+65) target region in the manner Petitioner urges, Petitioner has sufficiently established that the skilled artisan would have had a reasonable expectation of success of identifying active PMOs. Given the finite and limited number of possible 25-mers in the (+30+65) target region—and particularly in the region of PMO-A—Petitioner has sufficiently established that one of those tested would correspond to SEQ ID NO: 57. SEQ ID NO: 124, recited in the claims, corresponds to the 36th to 60th nucleotides of SEQ ID NO: 1, and is complementary to SEQ ID NO: 57. Pet. 12; Ex. 1099 ¶¶ 101–139.

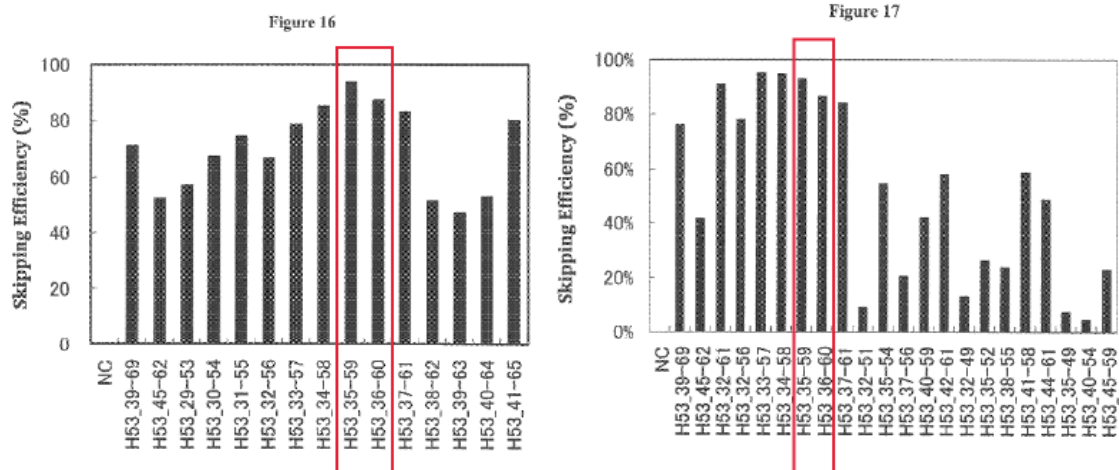
c) Parties Contentions Concerning Objective Evidence of Nonobviousness

(1) Petitioner's Contentions

Petitioner contends that during prosecution of the grandparent application, Patent Owner argued "that a 2'-OMePS targeting the +36+60

sequence of exon 53, referred to as H53_36-60, had unexpected superiority over the ‘top performer’ disclosed in [Poplewell ’212] (PMO-G, (+30+59)).” Pet. 53 (citing Ex. 1011, 70). Petitioner contends, however, that the evidence of unexpected results was based on an indirect comparison, which did not directly compare the claimed oligomer to the closest prior art. *See id.* at 53–55 (citing Ex. 1011, 69–71; Ex. 1099 ¶¶ 150–154). Petitioner argues that the indirect comparison is unreliable as the experiment differed in significant aspects, the Patent Owner failed to evaluate multiple concentrations, and the studies lacked error bars. *Id.* at 54–55 (citing Ex. 1099 ¶ 153).

Petitioner contends further that the Examiner overlooked a direct comparison between an oligomer having the same sequence as Poplewell’s PMO-A (+35+39) and the claimed oligomer of SEQ ID NO: 57 (+36+60). *Id.* at 55 (citing Ex. 1001, Figs. 16 and 17; Ex. 1099 ¶¶ 155–156). Petitioner argues that the direct comparison is illustrated in Figures 16 and 17, reproduced below.



Figures 16 and 17 include bar graphs illustrating skipping efficiency percentage with Petitioner’s annotations highlighting two results, those of H53_35–59 and H53_36–60. *See* Pet. 55–56. Both H53_35–59 and

H53_36–60 displayed greater than 80% skipping efficiency, with H53_35–59 showing greater skipping efficiency than H53_36–60, although the bar graphs do not include error bars. *See id.* Petitioner argues that the data “reveals that AOs having the same target sequence as the challenged claims perform no better than, and perhaps less well than, an AO with the same target sequence as the closest prior art.” *Id.* at 56 (citing Ex. 1099 ¶¶ 155–156). Petitioner further argues that “some degree of increased efficacy for an AO targeting +36+60 as compared to the PMOs disclosed in Popplewell” would not have been unexpected and would not undercut a reasonable expectation of success. *Id.* at 57 (citing Ex. 1099 ¶ 164).

(2) Patent Owner’s Contentions

Patent Owner argues that Petitioner’s assertions of unexpected results for an AO targeting the +36+60 sequence in exon 53 in its later-filed Application No. 14/776,533 (“the ’533 application”).⁹ Prelim. Resp. 69–70 (citing Ex. 2019, 31, 33–34, 37). Patent Owner argues that Petitioner filed a declaration stating that an AO targeting the +36+60 sequence in exon 53 showed a profound and unexpected improvement over the closest prior art. *Id.* (citing Ex. 2052 ¶¶ 7, 8). Patent Owner argues that “[t]here is no reason why Petitioner’s assertions of unexpected properties for the AO targeting the +36+60 sequence in exon 53 claimed in its later-filed ’533 application should not also apply to the challenged patent’s claimed AO targeting the exact same sequence.” *Id.* at 70.

⁹ Petitioner notes that it has abandoned the ’533 application “and the arguments made therein.” Pet. 47 (citing Ex. 1062, 15–17; Ex. 1063, 1–2).

(3) *Discussion*

As we read the Preliminary Response, we do not understand Patent Owner to rely on secondary considerations, including the evidence of unexpected results. Patent Owner is, nevertheless, welcome to timely introduce evidence of secondary considerations at trial.

d) *Parties Contentions Concerning Near-Simultaneous Development*

(1) *Petitioner's Contentions*

Petitioner separately argues that “the near-simultaneous development by others of a method of inducing exon 53 skipping in a patient with DMD with a 25-mer PMO targeting the +36+60 sequence of exon 53 is objective evidence of obviousness.” Pet. 58 (citing *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376, 1389 (Fed. Cir. 2000); *Geo. M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010)). Specifically, Petitioner argues that that other researchers (Prosensa) filed an application within five months after the PCT application describing an AO that is 100% complementary to the +36+60 sequence of exon 53, sharing the same target sequence as the PMOs of claims 1–12 of the ’741 patent. *See id.* at 52–53 (citing Ex. 1066, 1, 9–11, 58; Ex. 1099 ¶¶ 165–166, 169).

(2) *Patent Owner's Contentions*

Patent Owner responds that “Petitioner does not allege that Prosensa’s provisional application discloses every limitation of the challenged claims, namely an AO with a TEG at its 5’ end. Therefore, the Prosensa provisional application cannot be used as evidence of ‘simultaneous invention.’” Prelim. Resp. 71 (citing *Endo Pharms. Inc. v. Actavis Pharm., LLC*, 922 F.3d 1365, 1378 n.14 (Fed. Cir. 2019)). Patent Owner further argues that a

single instance of simultaneous invention alone is not objective evidence of obviousness. *See id.*

(3) Discussion

That Prosensa disclosed substantially the same invention in this time frame is suggestive of motivation, and weighs somewhat in favor of obviousness. *See Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (“Independently made, simultaneous inventions, made ‘within a comparatively short space of time,’ are persuasive evidence that the claimed apparatus ‘was the product only of ordinary mechanical or engineering skill.’”) (citation omitted).

e) Conclusion

In view of the above, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1, 4, 7 and 10 as obvious over the combination of Popplewell and Sazani. Specifically, on the present record, Petitioner has shown sufficiently that a person of ordinary skill in the art would have been motivated with a reasonable expectation of success to administer to a DMD patient a PMO 100% complementary to the +36+60 sequence of exon 53 and would have had a reasonable expectation that such administration would induce skipping of exon 53. Our final determination, however, is expected to address a fuller record.

2. Analysis of Dependent Claims 2, 5, 8, and 11

Claims 2, 5, 8, and 11 depend from claims 1, 4, 7, and 10, respectively, and additionally specify the structure of the PMO monomer (N,N-dimethyl phosphorodiamidate) and further recite that the “Base” of each monomer is uracil, cytosine, thymine, adenine, or guanine.

Petitioner contends that claims 2, 5, 8, and 11 would have been obvious over the combination of Popplewell and Sazani. Pet. 50–51. In support of its contention, Petitioner provides a detailed discussion explaining how the combination of Popplewell and Sazani discloses the elements of claims 2, 5, 8, and 11 and why a person of ordinary skill in the art would have been motivated to combine the teachings of those references with a reasonable expectation of success. *Id.* In particular, Petitioner contends,

a [person of ordinary skill in the art] would have been motivated, with a reasonable expectation of success, to make and administer to DMD patients a 25-mer PMO 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing) using the claimed PMO monomer subunit of the '741 patent. (EX1099, ¶¶141–143.) The PMO monomer subunit recited in claims 2, 5, 8, and 11 of the '741 patent was routinely used in constructing PMOs as of August 31, 2011. (EX1044, 536, Fig. 2; EX1040, 496, Fig. 1; EX1099, ¶141.) For example, Sazani discloses that the same PMO monomer subunit containing cytosine, thymine, adenine, or guanine was present in AVI-4658, one of the two exon 51-targeting AO candidates undergoing clinical studies as of August 31, 2011. (EX1022, 145, Fig. 1; EX1099, ¶141.)

Id.

Patent Owner does not address Petitioner's arguments with respect to claims 2, 5, 8, and 11, apart from its arguments discussed above with respect to independent claims 1, 4, 7, and 10. *See generally* Prelim. Resp.

Upon review of the parties' arguments and supporting evidence, we determine that Petitioner demonstrates a reasonable likelihood that claims 4 and 5 would have been obvious over Popplewell and Sazani.

3. *Analysis of Dependent Claims 3, 6, 9, and 12*

Claims 3, 6, 9, and 12 depend from claims 2, 5, 8, and 11, respectively, and additionally specify that the 25-mer PMO has attached at its 5' end a group selected from: (1) a triethylene glycol moiety, (2) an amide moiety, or (3) a hydroxyl group.

Petitioner contends that claims 3, 6, 9, and 12 would have been obvious over the combination of Popplewell and Sazani. Pet. 51–52. In support of its contention, Petitioner provides a detailed discussion explaining how the combination of Popplewell and Sazani discloses the elements of claims 3, 6, 9, and 12 and why a person of ordinary skill in the art would have been motivated to combine the teachings of those references with a reasonable expectation of success. *Id.* Specifically, Petitioner contends that a person of ordinary skill in the art would have been motivated to modify a PMO targeting the +36+60 sequence of exon 53 by adding at the 5' end the triethylene glycol modification taught by Sazani because

Conjugation of a triethylene glycol moiety to the 5' end of a PMO was a routine modification and was recognized in the art as potentially improving solubility. (EX1047, ¶¶[0049], [0156]; EX1075, ¶[0044]; EX1076, ¶[0338]; EX1077, 12:9–11; EX1099, ¶146.) The same 5' triethylene glycol moiety recited in claims 3, 6, 9, and 12 of the '741 patent was present in AVI-4658, one of the two exon 51-targeting AO candidates undergoing clinical studies as of August 31, 2011. (EX1022, 145, Fig. 1; EX1099, ¶146.)

Id. at 52.

Patent Owner contends that Petitioner has not established a motivation to modify the claimed AO sequence to include a 5' TEG moiety. Prelim.

Resp. 63–66. Patent Owner notes that Summerton,¹⁰ relied on by Petitioner “states that ‘**longer** morpholino polymers may have solubilities only in the submicromolar range’ and that ‘it may be advantageous to enhance polymer solubility by addition of one or more hydrophilic moieties.’” *Id.* at 65 (citing Ex. 1077, 12:7–11). Patent Owner points out that although Sanzani added a 5’ TEG moiety to a 30 nucleotide oligonucleotide, SEQ ID NO: 57 is only a 25-mer. *Id.* at 65. In this respect, Patent Owner argues that “the Petition is silent as to whether any alleged improvement in solubility conferred by TEG modification to Sanzani’s 30-mer would also result from the modification of a 25-mer as claimed.” *Id.*

We do not find Patent Owner’s argument availing on this record. Summerton suggests that it may be advantageous to enhance the solubility of “longer morpholino polymers” by the addition of hydrophilic moieties such as polyethylene glycol—which we understand to encompass triethylene glycol or TEG. Ex. 1077, 12:7–11. As an indication of what Summerton may have meant by “longer” we note that the reference discloses sequences of 3–7 nucleotides known in the art (*id.* at 17:27–34); references “[e]xperiments performed in support of the instant invention” involving oligomers of 3-5 nucleotides (*id.* at 17:35–50); “details the assembly of a 4-subunit polymer (*id.* at 10:25–26); and describes a series of tetramers as “short oligomers” (*id.* at 28:4–7). As such, we would infer that “longer” might involve something more than at least seven nucleotides.

We also consider that Summerton’s use of “longer” in a narrower context. The cited text appears in a section titled: “E. Polymer Processing

¹⁰ Summerton et al., U.S. Patent No. 5,185,444, issued Feb. 9, 1993 (Ex. 1077).

and Purification.” *Id.* at 11:6–12:41. The section begins with a discussion of Examples 12 and 14, which appear to involve polymers of 4 and 6 nucleotides, respectively. *See, e.g., id.* at 10:25–26, 11:8–27, 12:67–13:7, 13:37–48, 32:1–6. Thus, taken this in context, we understand Summerton’s reference to “longer” polymers as meaning at least more than 6 nucleotides.

We further note that Summerton appears to characterize polymers of 10 to 20 nucleotides as “of moderate size.” *See id.* at 12:44–47. As such, both Sanzani’s 30-mer and the claimed 25-mer would appear to qualify as “longer” polymers, which may benefit from the addition of the hydrophobic moieties as taught by Summerton. *See Ex. 1077, 12:7–11.*

Accordingly, and as we presently understand the record before us, Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to modify the claimed PMO sequence to include a 5’ TEG moiety as required by claims 3, 6, 9, and 12.

F. Discretion Under 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise our discretion under 325(d) to deny institution because, the same or substantially the same prior art or arguments previously were presented to the Office. Prelim. Resp. 20–45; Sur-Reply 1–8.

1. Legal Framework

We have discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In that respect, section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. *Advanced Bionics, LLC v.*

Med-El Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating the exercise of discretion to deny institution under § 325(d), the Board applies a two-part framework: (1) first, we determine whether the same or substantially the same art previously was presented to the Office, or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, we examine whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”). “If, after review of factors (a), (b), and

(d), it is determined that the same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.”

Advanced Bionics, 10.

a) Same or Substantially the Same Art or Arguments

Patent Owner argues that Popplewell was submitted in an information disclosure statement (“IDS”) during prosecution of the ’361 patent and is listed on the face of the ’741 patent. Prelim. Resp. 21–22 (citing Ex. 2007, 15; Ex. 1001, 2). Patent Owner further argues that the Examiner allowed the claims over a similar disclosure in Popplewell ’212. *Id.* at 24–29.

Accordingly, Patent Owner argues that Popplewell is cumulative of Popplewell ’212, with a detailed comparison of the references. *Id.* at 29–31.

Petitioner responds that there are material differences between Popplewell and Popplewell ’212. Pet. 59–62. Petitioner argues that Popplewell contains “disclosures not found in [Popplewell ’212] regarding PMO-A (+35+59), the closest prior art AO to the claimed AOs targeting the +36+60 sequence of exon 53.” *Id.* at 61. Specifically, Petitioner argues that Popplewell describes PMO-A as a viable alternative to PMO-G, in contrast to Popplewell ’212 which discloses a preference for PMO-G only. *See id.*

Patent Owner also argues that Sazani is cumulative of Sazani ’591. Prelim. Resp. 32–35. Specifically, Patent Owner argues that the Examiner relied on the same disclosure in Sazani ’591 during prosecution, specifically conjugating triethylene glycol to the 5’ end of an antisense oligomer (AVI-4658) to improve solubility. *Id.* at 33. Patent Owner further argues that there is no material difference between Sazani and Sazani ’591, particularly with respect to the triethylene glycol 5’ end moiety, the AVI-4658 sequence,

or the PMO structure. *Id.* Finally, Patent Owner argues that Sazani's teachings of animal safety data are cumulative to the safety results reported in Popplewell '212. *See id.* at 34–35 (citing Ex. 1023 ¶¶ 4, 30).

Petitioner responds that Sazani was not considered during prosecution and is not cumulative of Sazani '591 and Popplewell '212. *See* Pet. 62–63; Reply 1. Specifically, Petitioner argues that “Sazani discloses the complete structure of AVI-4658 . . . including the TEG moiety conjugated at the 5'-end of the PMO” and animal safety data that were crucial in demonstrating the safety of AVI-4658 and the PMO class of compounds. *Id.* at 62 (citing Ex. 1022, 145, 154).

We determine that the Popplewell article relied upon by Petitioner in this proceeding is the same or substantially the same as the art previously presented to the Office. As noted by Patent Owner, Popplewell was cited in an IDS and indicated as being considered by the Examiner during prosecution. Prelim. Resp. 1, 21–22; Ex. 2012, 2; Ex. 2007, 15. Moreover, Popplewell is discussed in the Specification of the '741 patent as prior art in which “a technique for skipping exon 53 with a high efficiency has not yet been established.” Ex. 1001, 2:55–56, 3:5–6. This is sufficient under the under the first part of the *Advanced Bionics* framework. As explained in *Advanced Bionics*, “[p]reviously presented art includes art made of record . . . such as on an [IDS].” *Advanced Bionics* at 7-8. We further note that the Popplewell '212 reference that formed the basis of the Examiner's rejection during prosecution appears to include substantially similar disclosures as Popplewell, including with regard to the 25-mer PMO-A, which form the primary basis for Petitioner's unpatentability arguments in this proceeding. *See, e.g.*, Ex. 1023, ¶ 87 (“When tested and compared directly at 300 nM doses by nucleofection, PMO-G, PMO-H and PMO-A were most active

producing in the order of 60% exon skipping). To be sure, we recognize that the Examiner does not appear to have specifically considered, nor did Patent Owner otherwise highlight during prosecution, Popplewell's or Popplewell '212's teachings regarding the viability of PMO-A. We address this failure under the second part of the *Advanced Bionics* framework.

We also determine that the teachings of the Sazani article relied upon in the Petition are substantially the same as the Sazani '591 reference considered during prosecution. Petitioner relies upon Sazani for its teachings regarding the conjugation of a triethylglycol moiety to the 5' end of a PMO. Pet. 43, 47–48. During prosecution, the Examiner relied upon Sazani '591 as teaching the modification of AOs used for inducing exon 53 skipping. Ex. 2007, 8. Sazani '591 specifically discloses that “the moiety that enhances solubility of the oligomer in aqueous medium is triethylene glycol [which] may be conjugated to the oligomer at the 5' end of the oligomer.” Ex. 1024 ¶ 46. Although Sazani differs from Sazani '591 insofar as it discloses the complete structure of AVI-4658, and provides additional safety/genotoxicity information, Petitioner has not relied upon those additional teachings in Sazani to support its unpatentability arguments in this proceeding.

b) Material Error by the Office

Petitioner argues that “the Office erred in allowing the claims of the '741 patent in view of Popplewell, which teaches a method of administering to a DMD patient PMO-A (+35+59), a PMO the *same length* as and targeting a sequence within exon 53 shifted *just one nucleotide* from the PMOs recited in the claims of the '741 patent.” *Id.* at 62. Petitioner further argues that “[t]he Examiner's Notice of Allowance for the grandparent '361

patent, issued in reliance on NS's unexpected results argument, reveals that the Examiner overlooked that an AO targeting +36+60 displayed similar (and perhaps less) skipping efficacy than an AO targeting the same sequence as the closest prior art, PMO-A (+35+59)." *Id.* at 63.

Patent Owner argues that "Petitioner cannot establish that the Examiner relied—let alone based his allowance of the claims—on Patent Owner's evidence of unexpected results," and that "assuming that the Examiner had relied on Patent Owner's evidence, Petitioner cannot establish that his reliance constitutes material error." Prelim. Resp. 38. First, Patent Owner argues that there is no material error in accepting evidence of unexpected results if the Examiner did not allow the claims solely based on unexpected results. *Id.* (citing *GlaxoSmithKline Consumer Healthcare Holdings (US) LLC v. Cipla Ltd.*, IPR2020-00369, Paper 7, 14 (July 31, 2020)). Patent Owner argues that the prosecution history demonstrates that amending the claims contributed to allowance, independent of the argued unexpected results. *See id.* at 40–42 (citing Ex. 2010, 2; Ex. 2055, 3–7).

Second, Patent Owner further contends that accepting Patent Owner's evidence of unexpected results would not have constituted a material error because an indirect comparison is not *per se* improper, and that it was reasonable for the examiner to consider a comparison of the claimed AO to PMO-G. *Id.* at 35–37

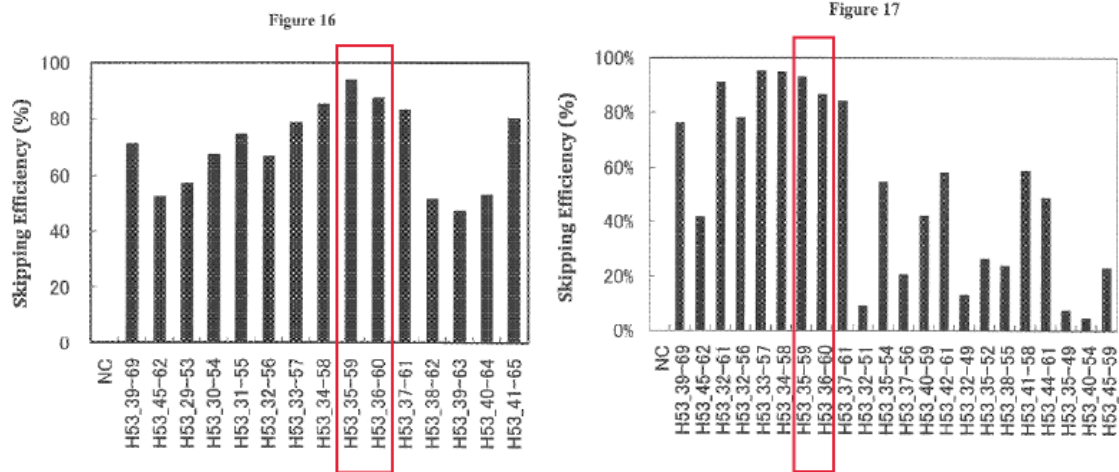
We agree with Petitioner that the Office appears to have materially erred during prosecution insofar as there is no indication that the Examiner fully considered Popplewell's teachings regarding PMO-A. As discussed above, Petitioner has demonstrated a reasonable likelihood of success in proving that the challenged claims of the '741 patent would have been obvious based on a motivation to modify PMO-A with a reasonable

expectation of success. In allowing the claims during prosecution, the Examiner appears to have focused only on Popplewell 212's disclosures regarding PMO-G, and did not cite to any specific passages related to the viability of PMO-A. Ex. 1011, 31–36, 53–59. The Examiner did not otherwise explain why PMO-A would not have been considered in the obviousness analysis given that it has a sequence that is shifted by only one nucleotide base as compared to SEQ ID NO: 57.

Likewise, to the extent that the Examiner relied upon and was persuaded by Patent Owner's unexpected results arguments as the basis for allowance, we find that to also be a material error. As noted by Petitioner, Patent Owner during prosecution argued unexpected results based on an indirect comparison of the efficacy of PMO-G as disclosed in Popplewell '212 with the AOs of SEQ ID NO: 57. Pet. 54–55; *see also id.* at 63–64 (citing Ex. 1099 ¶ 153). Specifically, Petitioner contends that during prosecution, the applicant argued “that a 2'-OMePS of SEQ ID NO: 57 had unexpected superiority over the “top performer” disclosed in [Popplewell '212] (PMO-G, (+30+59)).” Pet. 53 (citing Ex. 1011, 70). However, Petitioner contends that the evidence of unexpected results was an indirect comparison, which did not directly compare the two oligomers. *See id.* at 53–55 (citing Ex. 1011, 70; Ex. 1099 ¶¶ 150–154). Petitioner argues that the indirect comparison is unreliable as the experiment differed in significant aspects, the applicant failed to evaluate multiple concentrations, and the studies lacked error bars. *Id.* at 53 (citing Ex. 1099 ¶ 153).

Petitioner argues that the Examiner overlooked a direct comparison between an oligomer having the same sequence as Popplewell's PMO-A (+35+39) and the oligomer of SEQ ID NO: 57 (+36+60). *Id.* at 55–56 (citing Ex. 1001, Figs. 16 and 17; Ex. 1099 ¶ 155–156). Petitioner argues that the

direct comparison is illustrated in Figures 16 and 17 of the '741 patent, reproduced with annotations below.



Figures 16 and 17 include bar graphs illustrating skipping efficiency percentage with Petitioner's annotations highlighting two results, those of H53_35-59 and H53_36-60. *See id.* at 55-56. Both H53_35-59 and H53_36-60 displayed greater than 80% skipping efficiency, with H53_35-59 showing greater skipping efficiency than H53_36-60, although the bar graphs do not include error bars. *See id.* Petitioner argues that the data "reveals that AOs having the same target sequence as the challenged claims perform no better than, and perhaps less well than, an AO with the same target sequence as the closest prior art." *Id.* at 56 (citing Ex. 1099 ¶¶ 157-159). Petitioner further argues that "some degree of increased efficacy for an AO targeting +36+60 as compared to the PMOs disclosed in Popplewell" would not have been unexpected and would not undercut a reasonable expectation of success. *Id.* at 57.

Considering the unrebutted testimony of record, we agree with Petitioner that the above evidence does not support a finding of unexpected results for SEQ ID NO: 57. To the contrary, the direct comparison in Figures 16 and 17, above, suggests that SEQ ID NO: 57 has equivalent, if

not worse efficacy, than a comparable AO with the nucleotide sequence of Popplewell's PMO-A. We agree that this was error insofar as the Examiner overlooked this evidence. Moreover, in this proceeding, Petitioner presents additional expert testimony by its declarant Dr. Corey that was not considered during prosecution showing that a conclusion of unexpected results is not warranted based on the proper, direct comparison to PMO-A. Ex. 1099 ¶¶ 150–159; *see also id.* ¶¶ 160–164 (discussing evidence of unexpected results submitted in European counterpart of the '741 patent); Pet. 57, fn.5 (same).

We accordingly decline to exercise our discretion under 35 U.S.C. § 325(d) to deny institution.

G. Discretion Under 35 U.S.C. § 314(a).

Patent Owner contends that we should exercise our discretion to deny institution under § 314(a) because of a Mutual Confidentiality Agreement between the parties. Prelim. Resp. 71. Patent Owner argues that filing a petition for *inter partes* review violates the Agreement's forum selection clause, which requires all potential actions to be filed in the United States District Court for the District of Delaware. *Id.* at 66–67 (citing Ex. 2026 § 1). Patent Owner acknowledges that the District of Delaware has already denied Patent Owner's Motion for Preliminary Injunction seeking withdrawal of this and related Petitions due to the Agreement. *See id.* at 68. Nevertheless, Patent Owner argues that the Board should deny this Petition so that the Federal Circuit can address the issue on appeal. *Id.* at 73. Finally, Patent Owner argues that considerations of efficiency, fairness, and the merits favor discretionary denial. *Id.* at 70–72.

Petitioner responds that “[t]he Board has consistently refused to interpret and enforce contractual forum-selection clauses in deciding whether to institute post-grant proceedings.” Reply 6–7 (citing *Samsung Elecs. Co. v. NuCurrent, Inc.*, IPR2019-00861, Paper 15, 20 (PTAB Feb. 7, 2020); *Bally Gaming, Inc. v. New Vision Gaming & Dev., Inc.*, CBM2018-00006, Paper 47, 7–8 (PTAB June 19, 2019); *Dot Hill Sys. Corp. v. Crossroads Sys., Inc.*, IPR2015-00822, Paper 18, 6–10 (PTAB Sept. 17, 2015)). Petitioner further contends that the District of Delaware has already denied Patent Owner’s request for preliminary injunction on this issue, finding that the Agreement indicates that the parties intended to allow IPRs to proceed. *Id.* at 7 (citing Ex. 1103, 5).

We have considered Patent Owner’s arguments related to the forum selection clause in the parties’ Agreement. We determine, however, that the particular facts of this case, including the District of Delaware’s denial of a preliminary injunction, do not warrant exercise our discretion to deny institution on this basis.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that the challenged claims of the ’741 patent are unpatentable. We therefore institute trial on all challenged claims under the ground raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (Indicating that a decision whether to institute an *inter partes* review “require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition.”); 37 C.F.R. § 42.108(a). At this stage of the proceeding, we have

not made a final determination with respect to the patentability of any of the challenged claims.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response). In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board’s Rules

IV. ORDER

ORDERED, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–12 of the ’741 patent is instituted with respect to the grounds set forth in the Petition;

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), that the *inter partes* review of the ’741 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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Patent 10,647,741 B2

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