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571-272-7822

Paper 19
Date: January 13, 2022

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.

IPR2021-01136
Patent 10,407,461 B2

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

JENKS, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. *Background*

Sarepta Therapeutics, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1 and 2 ("the challenged claims) of U.S. Patent No. 10,407,461 B2 (Ex. 1001, "the '461 patent"). Paper 1 ("Pet."). Nippon Shinyaku Co., Ltd. ("Patent Owner") filed a Patent Owner Preliminary Response to the Petition. Paper 11 ("Prelim. Resp."). Petitioner filed an authorized Reply to the Preliminary Response (Paper 15, "Reply"), and Patent Owner filed a corresponding Sur-reply (Paper 17, "Sur-reply).

B. *Summary of the Institution Decision*

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has demonstrated a reasonable likelihood that at least one claim of the '461 Patent is unpatentable, we institute an *inter partes* review of all challenged claims based on the Ground raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *see also* Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial) ("Guidance").

Our findings of fact, conclusions of law, and reasoning discussed below are based on the evidentiary record developed thus far, and made for the sole purpose of determining whether the Petition meets the threshold for instituting review. This decision to institute trial is not a final decision as to the patentability of any challenged claim or the construction of any claim limitation. Any final decision will be based on the full record developed during trial.

C. *Real Parties in Interest*

Petitioner identifies itself, Sarepta Therapeutics, Inc., as the real party-in-interest. Pet. 57. Patent Owner, identifies itself, Nippon Shinyaku Co. Ltd. and National Center of Neurology and Psychiatry as real parties-in-interest. Paper 3, 1.

D. *Related Matters and Chain of Priority*

The '461 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 7, 1.

In addition to the '461 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. 10,487,106 B2 ("the '106 patent") in IPR2021-01137; U.S. Patent No. 10,647,741 B2 ("the '741 patent") in IPR2021-01138; 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 7, 1; Paper 8, 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 8, 1.

E. *Asserted Ground of Unpatentability*

Petitioner challenges the patentability of claims 1 and 2 of the '461 patent on the following ground:

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1, 2	103	Popplewell,[2] Sazani[3]

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of David R. Corey, Ph.D. Ex. 1097. Based on the preliminary record before us, we determine that Dr. Corey is qualified to offer testimony on the knowledge of one of ordinary skill in the art as of any of the asserted priority dates of the '461 patent. *See, e.g., id.* ¶¶ 3–9, 21–65 (Dr. Corey's statements as to his background and qualifications, and background on the relevant technology); ¶¶ 91–93 (Dr. Corey's opinion regarding the definition of one of ordinary skill in the art); Appendix A (Dr. Corey's curriculum vitae).

F. *The '461 Patent (Ex. 1001)*

The '461 patent is titled "Antisense Nucleic Acids." *Id.* at (54). The '461 patent describes antisense oligomers ("AO") that induce skipping of

[1] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. § 103 that became effective on March 16, 2013. Because the '461 patent issued from an application that is a continuation of an application filed before March 16, 2013, we apply the pre-AIA versions of the statutory bases for unpatentability.

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

[3] Sazani et al., *Safety Pharmacology and Genotoxicity Evaluation of AVI-4658*, 29 Intl. J. Toxicology 2:143–156 (2010) (Ex. 1022).

exon 53 in the human dystrophin gene during translation. Ex. 1001, 3:10–13. The '461 patent issued on Sept. 10, 2019 from U.S. Application No. 16/364,451, filed March 26, 2019, which is a continuation of U.S. Application No. 15/619,996, filed June 12, 2017, now U.S. Patent No. 10,329,319, which is a continuation of U.S. Application No. 14/615,504, filed Feb. 6, 2015, now U.S. Patent No. 9,708,361, which is a continuation of U.S. Application No. 13/819,520, filed Apr. 10, 2013, now U.S. Pat. No. 9,079,934, which is a PCT National Stage of PCT/JP2011/070318[4] filed Aug. 31, 2011, which claims priority from JP Application No. 2010-196032 filed Sep. 1, 2010. Ex. 1001, (21), (22), (30), (45), (63).

"Duchenne muscular dystrophy (DMD) is caused by the lack of functional dystrophin protein, most commonly as a result of a range of out-of-frame mutations in the *DMD* gene." Ex. 1021, Abstract; *see* Ex. 1001, 1:37–38, 64–67. According to the Specification, inducing exon skipping is expected to treat Duchenne muscular dystrophy ("DMD"). Ex. 1001, 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 H53_36–60

[4] Petitioner contends that a 25-mer antisense-oligonucleotide that is 100% complementary to positions +36+60 of exon 53 was first disclosed as H53_36–60 in Table 7 of PCT/JP2011/070318, and, as such, the claims are not entitled to an earliest priority date of September 1, 2010 but are only entitled to the priority of August 31, 2011. Pet. 8–9. Patent Owner does not argue otherwise. *See generally* Prelim. Resp.

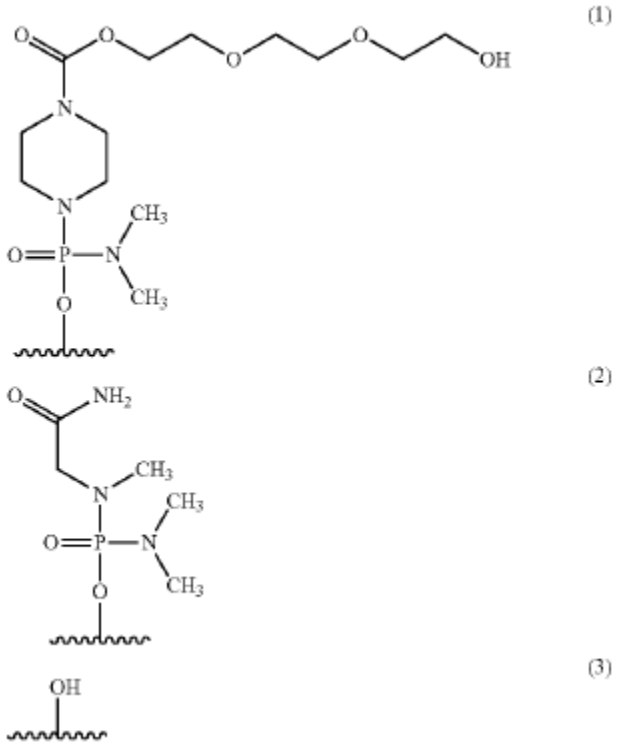
> approximately 8% of all DMD patients may be treated by skipping the 53rd exon (hereinafter referred to as "exon 53"). In recent years, a plurality of research organizations reported on the studies where exon 53 in the dystrophin gene was targeted for exon skipping. . . . However, a [high efficiency]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

Id. at 2:49–56.

According to the '461 patent, the disclosed antisense oligomers skip exon 53 with high efficiency by targeting specific nucleotide sequences in the mRNA precursor ("pre-mRNA"). *See 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 11:18–25.

The '461 patent discloses that the antisense oligomers may include oligonucleotides, morpholino oligomers, or peptide nucleic acids. *Id.* at 11:35–39. 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 11:46–49. 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 13:64–14:45; *see also* Ex. 1097 ¶ 46 ("PMOs, a type of 'morpholino,'" have a six-membered morpholinyl moiety instead of a ribose. PMO subunits are linked through uncharged

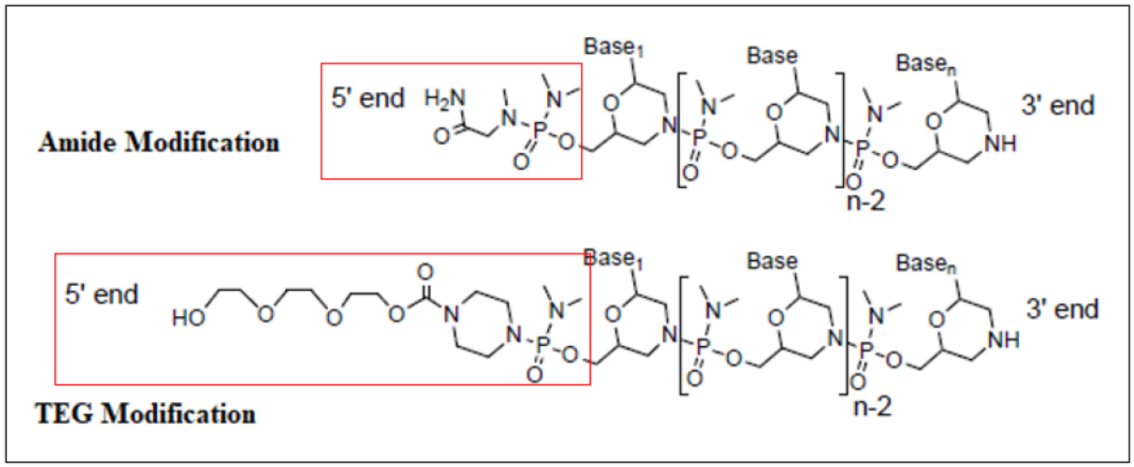
phosphorodiamidate linkages."). The 5′ end of the oligomer may include the structures reproduced below:



Structures 1–3 illustrate triethylene glycol (1), amide (2), and (3)-hydroxyl substitutions. *Id.* at 24:34–67. 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 39:19–25, 44.

An excerpt from Figure 1 of Ex. 1053,[5] as annotated by Dr. Corey, is reproduced below.

[5] Moulton and Jiang, "*Gene Knockdowns in Adult Animals: PPMOs and Vivo-Morpholinos*," 14 Molecules 1304–1323 (2009) ("Moulton").



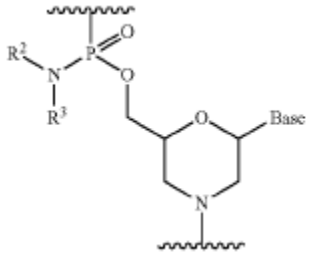
See Ex. 1097 ¶ 49. The above figure shows exemplary morpholino oligos with amide or triethylene glycol (TEG) moieties (indicated by red annotation) added to their 5' ends. *Id.*

According to Dr. Corey, PMOs and 2'-OMePSs were "[t]wo of the most common classes of AOs used as of August 31, 2011." Ex. 1097 ¶ 42. Dr. Corey explains that "2'-OMePSs have a structure similar to RNA but the 2'-OH position of the ribose ring has been methylated, and instead of using a phosphodiester link between nucleotides, one of the non-bridging oxygen atoms of the phosphate group is substituted with a sulfur atom to create a phosphorothioate linkage." *Id.* ¶ 44; *see id* at ¶ 42 (comparing structure of 2'-OMePSs and PMOs). The Specification describes *in vitro* assays performed using antisense oligomers of 2'-O-methoxy-phosphorothioates (2'-OMe-S-RNA) "purchased from Japan Bio Services." Ex. 1001, 40:20–42:43 (Example 6). As set forth in Table 7, these include antisense oligomer H53_36–60 (SEQ. ID NO: 57), having the nucleotide sequence 5'-GUUGCCUCCGGUUCUGAAGGUGUUC-3'. *Id.* at 40:47.

1. Illustrative Claims

Claims 1 and 2 of the ’461 patent are reproduced below:

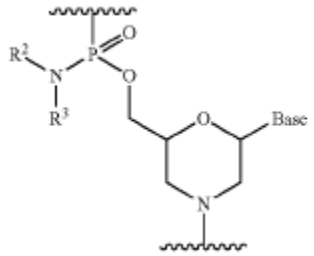
> 1. A phosphorodiamidate morpholino oligomer (PMO) antisense oligomer that causes skipping of the 53rd exon in a human dystrophin pre-mRNA, consisting of a 25-mer oligomer that is 100% complementary to the target sequence 5'-GAACACCUUCAGAACCGGAGGCAAC-3' (SEQ ID NO: 124) of said human dystrophin pre-mRNA, wherein said PMO antisense oligomer hybridizes to said target sequence with Watson-Crick base pairing under physiological conditions, wherein each phosphorodiamidate morpholino monomer of said PMO antisense oligomer has the formula:



> wherein each of R^2 and R^3 represents a methyl; and
>
> wherein Base is a nucleobase selected from the group consisting of uracil, cytosine, thymine, adenine, and guanine.

Id. at 83:44–84:45.

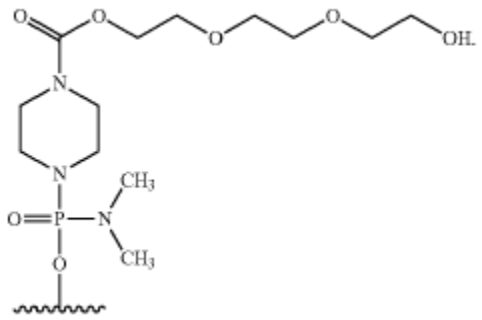
> 2. A phosphorodiamidate morpholino oligomer (PMO) antisense oligomer that causes skipping of the 53rd exon in a human dystrophin pre-mRNA, consisting of a 25-mer oligomer that is 100% complementary to the target sequence 5'-GAACACCUUCAGAACCGGAGGCAAC-3' (SEQ ID NO: 124) of said human dystrophin pre-mRNA, wherein said PMO antisense oligomer hybridizes to said target sequence with Watson-Crick base pairing under physiological conditions, wherein each phosphorodiamidate morpholino monomer of said PMO antisense oligomer has the formula:



wherein each of R^2 and R^3 represents a methyl; and

wherein Base is a nucleobase selected from the group consisting of uracil, cytosine, thymine, adenine, and guanine; and

wherein the 5' end of said PMO antisense oligomer has the formula:



Id. at 84:46–85:19.

2. Relevant Prosecution History

The ’461 patent was filed with two preliminary amendments dated March 26, 2019 and April 4, 2019. *See* Ex. 1013, 12–23. The second Preliminary Amendment added new claims 16 and 17, which issued as claims 1 and 2 of the ’461 patent. *See id.* at 20–21. 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 22. The Applicant conducted an interview with the Examiner during which the Examiner agreed “that the specification as filed provides inherent/implicit support for the amendments filed 4/4/2019.”

Id. at 25 (Interview Summary). The application was allowed after the Applicant filed terminal disclaimers obviating provisional double patenting rejections over the claims of Application Nos. 16/359,213 and 16/369,427. *See id.* 27–35. The Applicant amended the claims after allowance, cancelling claim 15 and correcting a typographical error in claim 16 (now claim 1). *Id.* at 36–39.

During the prosecution of the '461 patent's grandparent application (Application No. 14/615,504, now the '361 patent), the Examiner rejected the claims as obvious over Popplewell '212[6] and Sazani '591[7]. *See* Ex. 1011, 31–36 (Non-Final Act. dated March 25, 2016); 53–61 (Final Act. dated October 27, 2016); Ex. 2007; Ex. 2009.[8] 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 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

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[6] US 2010/0168212 A1, published July 1, 2010 to Popplewell et al. (Ex. 1023).
[7] US 2010/0130591 A1, published May 27, 2010 to Sazani et al. (Ex. 1024).
[8] The prosecution history of the '361 patent is included in the record as Exhibits 1011 and 2005–2012. We cite Exhibit 1011, unless otherwise specified.

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." Ex. 1011, 70 (citing Ex. 1023 ¶ 74, Fig. 8). The Applicant further argued that claimed 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.

II. ANALYSIS

A. *Principles of Law*

"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).

To prevail in its challenge to Patent Owner's claims, Petitioner must demonstrate by a preponderance of the evidence[9] that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *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 "the scope and content of the prior art"; "differences between the prior art and the claims at issue"; and "the level of ordinary skill in the art." *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

[9] The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

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. *Level of Ordinary Skill in the Art*

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

> Petitioner asserts that a person of ordinary skill in the art would have 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. A POSA would

> also 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. Further, a POSA 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.

Pet. 28–29 (citing Ex. 1097 ¶¶ 91, 92). Patent Owner does not dispute Petitioner's definition of the person of ordinary skill. Prelim. Resp. 14. Because Petitioner's proposed definition is unopposed and appears consistent with the Specification and art of record, we apply it here.

C. *Overview of Asserted References*

1. Popplewell (Ex. 1021)

Popplewell discloses antisense oligonucleotide sequences targeting exon 53 of the human DMD gene. Ex. 1021, 102. Specifically, Popplewell tests 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 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% (±4.10%), 68% (±4.77%) and 68% (±4.14 %) exon skipping respectively (classified as Type 1)[10] (Fig. 1)." *Id.* at 104. Figure 1 is reproduced below.

[10] Popplewell classified antisense oligonucleotides according to skipping efficacy: "PMOs that produced over 50 % exon skipping were designated as

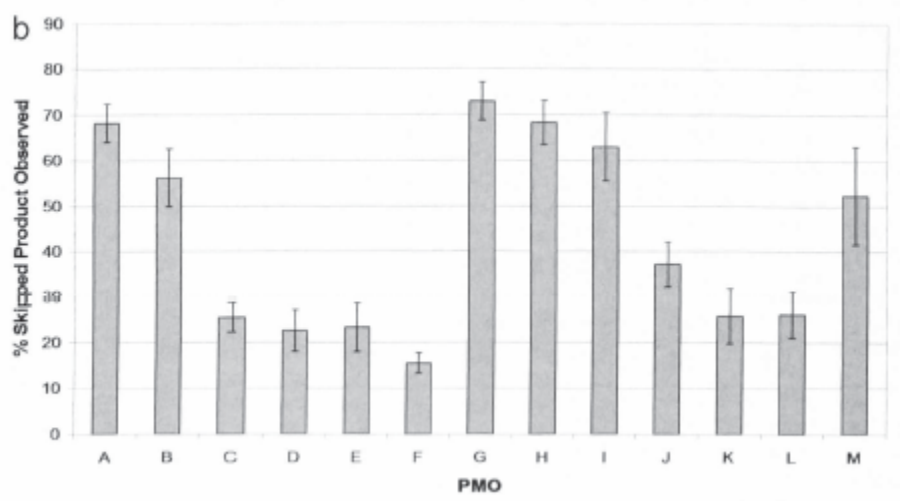

Figure 1 is a bar graph showing the percentage of exon skipping achieved for each PMO A–M. *Id.* at 106. Popplewell selected the six most effective PMOs (i.e. Type 1) (-A, -B, -G, -H, -I and -M)[11] for dose-response and time-course experiments because the "more efficacious PMOs should produce sustained and pronounced exon skipping when applied at lower concentrations." *Id.* at 104.

In the dose-dependent experiments, Popplewell discloses that PMOs -G and -H induced exon skipping levels of 30% at low concentrations, but higher concentrations were needed for 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 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

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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.*

[11] 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. 1097 ¶ 106.

> 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 discloses 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. 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.

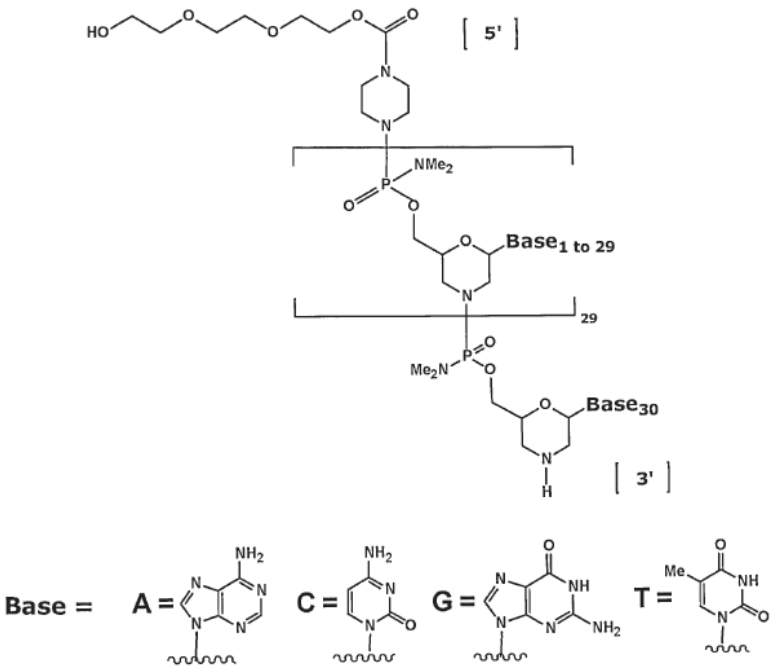


Figure 1 illustrates a PMO subunit, substituted with bases including adenine, cytosine, guanine, and thymine.

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.*

D. *Discretionary Denial*

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. 15–41; Sur-Reply 1–8. Patent Owner also argues that we should exercise our discretion under 35 U.S.C. § 314(a) because of the Parties' Mutual Confidentiality Agreement which is the subject of concurrent litigation. *See id.* at 65–73; Sur-Reply 8. Petitioner addresses Patent Owner's arguments on §§ 325(d) and 314(a). *See* Reply 1–8.

1. 35 U.S.C. § 325(d)

a) Legal Framework

Pursuant to 35 U.S.C. § 325(d), in determining whether to institute an *inter partes* review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art. or arguments previously were presented to the Office." The Board evaluates two issues in addressing 35 U.S.C. § 325(d):

> (1) 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, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*"). With respect to the first issue, previously "presented" art includes, among other things, "art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent." *Id.* at 7–8. With respect to the second issue, institution generally will be denied if a "petitioner fails to make a showing of material error," and "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.* at 8–9. "[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

We consider several non-exclusive factors as set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec.

15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*"), which "provide useful insight into how to apply the framework" under § 325(d). *Advanced Bionics*, 9. These non-exclusive factors include:

> (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, 17–18 (formatting added). "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.

b) Was the Same or Substantially the Same Art or Arguments Presented to the Office?

Patent Owner argues that Popplewell was submitted in an information disclosure statement ("IDS") during prosecution of the grandparent '361 patent and is listed on the face of the '461 patent. Prelim. Resp. 16–19 (citing Ex. 2007, 15; Ex. 1001, (56)). Patent Owner further argues that the

Examiner allowed the claims over a similar disclosure in Popplewell '212. *Id.* at 19–24. Accordingly, Patent Owner argues that Popplewell is cumulative of Popplewell '212, with a detailed comparison of the references. *Id.* at 24–26.

Petitioner contends that there are material differences between Popplewell and Popplewell '212. Pet. 53–55. In particular, 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 54. 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. 27–30. 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 28–30. 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.* at 30. 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 30–31 (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. 55–56; 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.*

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, 16; Ex. 2012, 2; Ex. 2007, 15. Moreover, Popplewell is discussed in the Specification of the '461 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, 45. 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.

c) Did the Office Err in a Manner Material to the Patentability of Challenged Claims?

Having determined that the same or substantially the same prior art was previously presented to the Office, we turn to the second part of the *Advanced Bionics* framework, which requires an assessment of whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Here, Petitioner argues that "the Office erred in allowing the claims of the '461 patent in view of Popplewell, which teaches 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 '461 patent." Pet. 54. 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

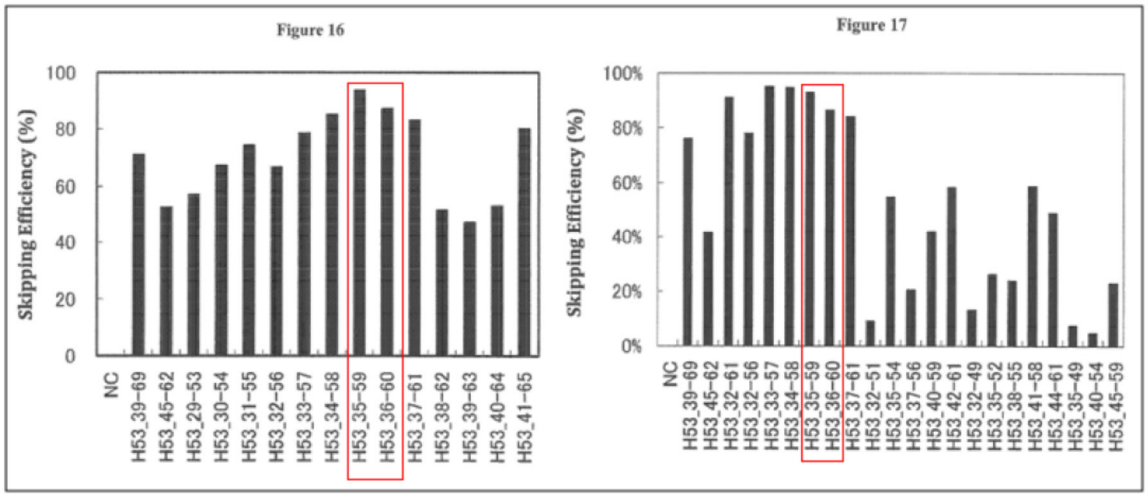
targeting the same sequence as the closest prior art, PMO-A (+35+59)." *Id.* at 56.

Patent Owner contends that Petitioner points to nothing in the Notice of Allowance indicating that the Examiner relied "solely" on Patent Owner's evidence of unexpected results in allowing the claims. Prelim. Resp. 34. To the contrary, Patent Owner reads the prosecution history as demonstrating that the Examiner allowed the claims based on, at least in part, Patent Owner's amendment removing SEQ ID NO: 11 from the claims and limiting them to a sequence consisting of SEQ ID NO: 57. *Id.* at 54–55. 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 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 below, Petitioner has demonstrated a reasonable likelihood of success in proving that the challenged claims of the '461 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 the claimed oligomer that is 100% complementary to the target sequence of SEQ ID NO: 124.

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 claimed AOs that is 100% complementary to the target sequence of SEQ ID NO: 124. Pet. 45–51. Specifically, Petitioner contends that during prosecution, the applicant argued "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 the '212 Publication (PMO-G, (+30+59))." Pet. 45–46 (citing Ex. 1011, 69–71). However, Petitioner contends that the evidence of unexpected results was an indirect comparison, which did not directly compare the two oligomers. *See id.* at 46–47 (citing Ex. 1011, 69–71; Ex. 1097 ¶¶ 136–140). 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 47 (citing Ex. 1097 ¶ 139).

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 AOs targeting the +36+60 sequence of exon 53 recited in the claims. Pet. 48–49 (citing Ex. 1001, Figs. 16 and 17; Ex. 1097 ¶ 141–142). Petitioner argues that the direct comparison is illustrated in Figures 16 and 17 of the '461 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. Pet. 48–49. 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 49 (citing Ex. 1097 ¶¶ 141–142). Petitioner further argues that "some degree of increased efficacy for an AO targeting +36+60 as compared to the PMOs disclosed in Popplewell (which it has not), such a difference in degree would not have been unexpected and would not undercut a reasonable expectation of success for an AO targeting +36+60." *Id.* at 50.

Considering the unrebutted testimony of record, we agree with Petitioner that the above evidence does not support a finding of unexpected results for the claimed oligomer that is 100% complementary to the target sequence of SEQ ID NO: 124. To the contrary, the direct comparison in

Figures 16 and 17, above, suggests that the oligomer that is 100% complementary to the target sequence of SEQ ID NO: 124 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 declarant testimony by 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. 1097 ¶¶ 136–150; *see also id.* ¶¶ 146–148 (discussing evidence of unexpected results submitted in European counterpart of the '361 patent); Pet. 50, fn.5 (same).

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

2. 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. 65–73. 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 66–68 (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 67–68. Nevertheless, Patent Owner argues that the Board should deny this Petition so that the Federal Circuit can address the issue on appeal. *Id.* at 74. Finally, Patent Owner argues that considerations of efficiency, fairness, and the merits favor discretionary denial. *Id.* at 71–73.

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.

E. *Obviousness in view of Popplewell and Sazani*

1. Analysis of Claim 1

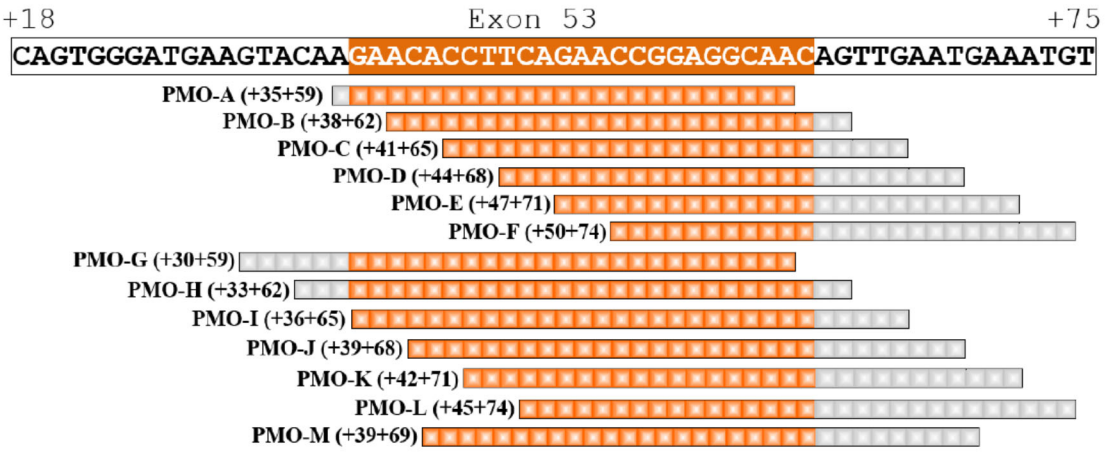
Petitioner contends that claim 1 is invalid for obviousness over Popplewell and Sazani. Pet. 29–57. Patent Owner opposes. Prelim. Resp. 42–65.

Popplewell discloses a phosphorodiamidate morpholino oligomer (PMO) consisting of a 25-mer antisense oligomer that is 100% complementary, according to Watson-Crick base pairing, to the 35th to the 59th nucleotides from the 5′ end of the 53rd exon in the human dystrophin pre-mRNA. *See* Ex. 1021, 102, 105 (Table 1, PMO-A). 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, i.e., the target sequence 5'-GAACACCUUCAGAACCGGAGGCAAC-3' (SEQ ID NO: 124). *See id.* at 105. Sazani discloses PMO monomer subunits having the formula of claim 1 wherein each of R^2 and R^3 represents a methyl, wherein the Base is cytosine, thymine, adenine, and guanine, and further including a triethylene glycol moiety at the 5′ end of the PMO. *See* Ex. 1022, 145, Fig. 1b. Accordingly, the issue before us is whether the prior art would have suggested to 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.

a) Rationale for Focusing on PMO-A

Petitioner points to Popplewell's testing of 13 PMOs, PMOs A through M, "whose 'target sites are within the sequence +29 to +74 of exon 53, the region previously shown to be in open conformation, binding to which interferes with spliceosome-mediated pre-mRNA splicing, such that exon 53 is skipped.'" Pet. 26 (quoting Ex. 1021, 104; Ex. 1097 ¶ 67). The following figure, generated by Dr. Corey, illustrates the relative alignment of these 13 PMOs relative to the target region of the AOs claimed by the '461 patent (shown in orange). Ex. 1097 ¶ 67; *see* Ex. 1021, 104, Table 1 (showing nucleotide start and stop information).



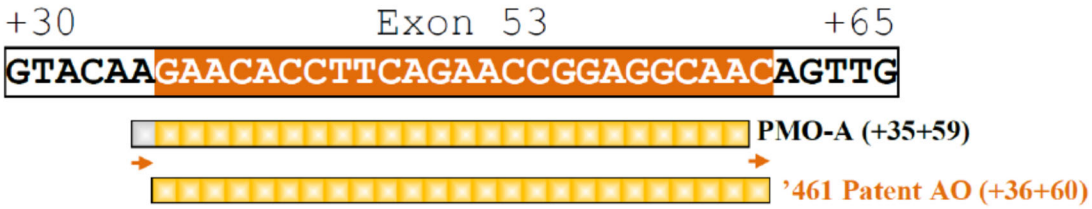
The above figure illustrates the relative alignment of PMOs A through M tested in Popplewell, within the region spanning nucleotides +18 through +75 of Exon 53. Pet. 26–27; Ex. 1097 ¶¶ 67–68.

Petitioner argues that Popplewell recommends PMOs targeting a narrower region spanning nucleotides +30+65 of exon 53 of the DMD gene for clinical trials. *See* Pet. 32–34 (citing Ex. 1021, 109); *see* Ex. 1097 ¶¶ 16, 104–105 (Dr. Corey's testimony that, "results, by different laboratories, with different oligomer chemistries, provide remarkably robust support for a POSA to focus on the (+30+65) hotspot target region for testing additional AOs").

Petitioner further argues that Popplewell teaches two 25-mers, PMO-A and PMO-B, that target the +30+65 sequence of exon 53, of which PMO-A (+35+59) was the most effective. *Id.* at 34–35 (citing Ex. 1021, 109; Ex. 1097 ¶ 107). Quoting Popplewell's suggestion to conduct a "stepped base-by-base screening of AOs across the entirety of exon 53," Petitioner asserts that one of ordinary skill in the art "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 35 (citing Ex. 1021, 108; Ex. 1097 ¶ 111).

Petitioner contends that using a stepwise array AO screening approach such as suggested by Popplewell, one 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 sequence of exon 53 (i.e., complementary to SEQ ID NO: 124) as claimed." Pet. 35–36 (citing, e.g., Ex. 1097 ¶ 111). In support, Petitioner compares the sequences as illustrated below.



The top line of above illustration shows Exon 53 nucleic acids +30+65 with nucleic acids +36+60 highlighted in orange. *Id.* at 36 (citing Ex. 1097 ¶ 111). Aligned with Exon 53 are the sequences of PMO-A (+35+59), followed below by SEQ ID NO: 124 (+36+60). *Id.* Arrows indicate 5' to 3' directionality. *Id.* Petitioner notes that SEQ ID NO: 124 is the same length as PMO-A (25 nucleotides), and "is shifted just *one nucleotide* towards the 3' end of exon 53 as compared to PMO-A." *Id.* (citing Ex. 1044, Fig. 2; Ex. 1040, Fig. 1; Ex. 1097 ¶¶ 115–116).

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 38 (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.* (citing Ex. 1021, 109; Ex. 1097 ¶ 118). 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 39 (citing Ex. 1097 ¶¶ 40–41, 119; Ex. 1043, 874, Table 1).

In response, Patent Owner argues that, absent hindsight, Petitioner fails to establish that one of ordinary skill in the art would have selected PMO-A as a starting point under the lead compound test. Prelim. Resp. 42–43. The lead compound test typically follows a two-prong inquiry considering first, whether one of ordinary skill would have selected one or more lead compounds as a starting point for further development and, second, whether the prior art would have supplied sufficient motivation to modify a lead compound to arrive at the compound claimed with a reasonable expectation of success. *See Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012).

As Patent Owner admits, Petitioner does not 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. 42–48. 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.

34. 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, Patent Owner argues 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. 42–43. Patent Owner's arguments, however, rest 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.C.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. 43–44. 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. 16–17, 39–40 (citing Ex. 1043, 874, Table1; Ex. 1097 ¶¶ 40–41, 44, 119). 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. 45 (quoting *Otsuka*, 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. 1097 ¶ 61. 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. 45.[12] 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. 1021, 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 48–51 (citing Ex. 2017, 23; Ex. 2019, 24; Ex. 2049, 13). While 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

[12] We note that 5 of the 6 AOs specifically identified by Patent Owner in this section appear to be 18-mers. *See id.* at 45 (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.

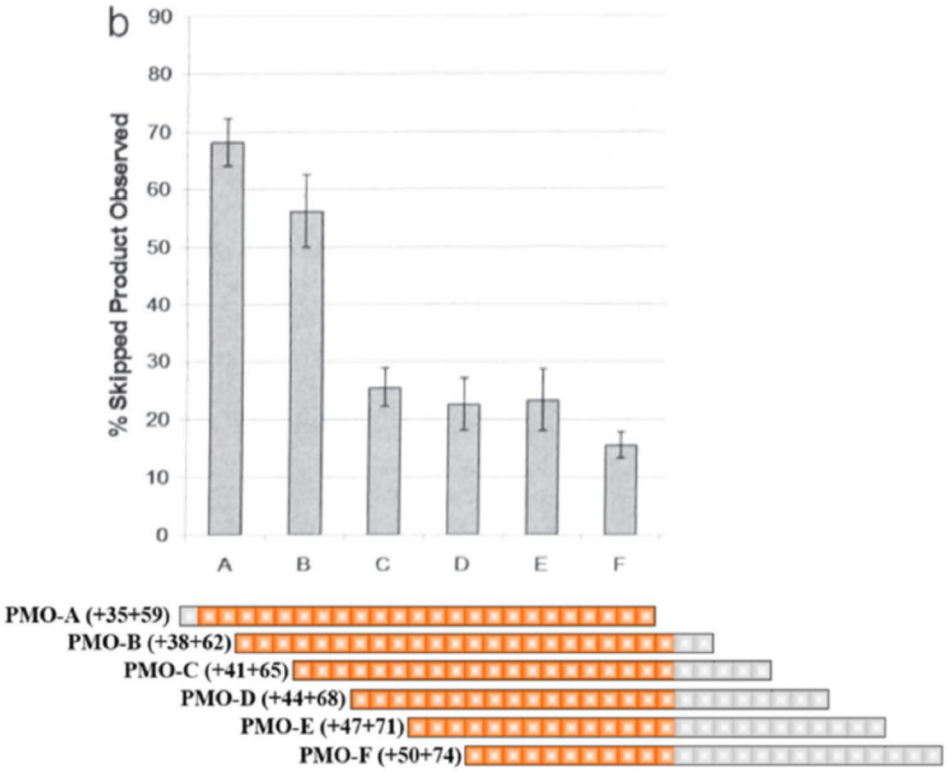
application. It also appears that Petitioner's prior arguments did not persuade the Examiner and it eventually abandoned the application. Pet. 39 (citing Ex. 1063, 1–2).[13]

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

b) Motivation to Modify PMO-A

Patent Owner argues that Petitioner has failed to show a motivation to modify PMO-A in a manner that would result in an oligomer that is 100% complimentary to SEQ ID NO: 124. Prelim. Resp. 52–55. To the contrary, Patent Owner argues, "Popplewell leads a POSA in a direction divergent from that proposed by Petitioner" because "PMO-A had a poor efficiency of only 12.7%," which decreased when shifting the sequences in the 3′ direction. *See id.*, 53–54 (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 54. Patent Owner illustrates its argument with the following figure:

[13] 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 December 14, 2018 Responses." *See* Prelim. Resp. 51 (citing Ex. 2019, Ex. 2017) (emphasis removed).



The above figure, reproduced from page 54 of the Preliminary Response, includes a portion of Popplewell's Figure 1b, and correlates the skipping efficacy of 25-mers, PMO-A through F with their position along exon 53. Orange shading appears to represent overlap complementary sequence to SEQ ID NO: 124.

As an initial matter, Patent Owner's statement that "PMO-A had a poor efficiency of only 12.7%," does not reflect the experimental data conducted in Popplewell. *See* Prelim. Resp. 53 (citing Ex. 1021, Table 1). To the contrary, Popplewell presents in Table 1, data from "[t]wenty-four AOs designed to target exon 53 of the DMD gene . . . previously tested in normal human skeletal muscle cells (hSkMCs)." Ex. 1021, 104. Popplewell implicitly disparages this earlier data, explaining that it conducted additional research because "studies in normal hSkMCs are limited as they do not

allow assessment of the therapeutic effect at the protein level (i.e., dystrophin restoration)." *Id.* As discussed in section II.C.1, above, based on this additional research, Popplewell characterized PMO-A as among the most effective (Type 1) PMO's tested and a viable candidate for clinical trials. Indeed, rather than having "poor efficiency of only 12.7%" Patent Owner's figure illustrates that PMO-A was 68% in the represented in vitro assay. *See id.* at 104 ("PMOs -G, -H and -A were the most efficient, producing a mean of 73 % (±4.10%), 68 % (±4.77%) and 68 % (±4.14 %) exon skipping respectively (classified as Type I) (Fig. 1)."); *see also id.* at 106 Fig. 1c (no statistical difference between PMOs -G, -H and –A); Ex. 1097 ¶¶ 101–102.

Patent Owner's argument that a 3′ shift in the position of PMOs A through F correlates with reduced efficacy in this in vitro assay, however, does appear to weigh against shifting the target site in that direction. We, nevertheless, note that in Popplewell's in vivo assay PMO-A had the greatest skipping efficacy. Ex. 1021, 107. Because PMO-A was the only 25-mer in that cohort, it is not clear that the correlation Patent Owner relies on applies to the in vivo environment.

We also note Petitioner's argument that "the near-simultaneous development by others of an AO targeting the +36+60 sequence of exon 53 is objective evidence of obviousness." Pet. 51. Specifically, Petitioner argues that other researchers (Prosensa) filed an application five months after the PCT application describing an AO targeting the (+36+60) sequence of exon 53 which is 100% complementary to SEQ ID NO: 124. *See id.* at 51–52 (citing Ex. 1066, 1, 9–11, 58; Ex. 1097 ¶¶ 152–153, 155, 157–158). 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).

Finally, we note Dr. Corey's testimony that "[t]he (+30+65) hotspot region in exon 53 identified in Popplewell was consistent with earlier reports in the prior art of effective AOs targeting exon 53," and would have motivated one of ordinary skill in the art to explore related AOs in that region. Ex. 1097 ¶¶ 103–105. Considering the record before us, we provisionally credit Dr. Corey's testimony that one of ordinary skill in the art "would have designed a one-nucleotide stepped array using PMO-A (+35+59) as the starting point[,] would have tested the AOs for their ability to cause exon 53 skipping" and, thereby, "AOs 100% Complementary to the (+36+60) Sequence of Exon 53." Ex. 1097 ¶¶ 106–107.

On the present record, Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to undertake a one-nucleotide stepped array in the (+30+65) region of exon 53, and focusing on PMO-A, would have arrived at a sequence 100% complimentary to SEQ ID NO:124 as recited in claim 1. Our final determination, however, is expected to address a fuller record. [14]

[14] 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. 34. 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

c) Reasonable Expectation of Success

Petitioner argues that a person of ordinary skill in the art would have had a reasonable expectation of success in making a 25-mer PMO that is 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding human dystrophin pre-mRNA sequence (i.e., SEQ ID NO: 124) with Watson-Crick base pairing under physiological conditions) and that induces exon 53 skipping. Pet. 40 (citing Ex. 1097 ¶¶ 120–129). Specifically, Petitioner argues that Popplewell discloses multiple PMOs complementary to the hotspot +30+65 of exon 53, as well as methods for evaluating whether the PMOs induce exons skipping. *See id.* at 40–41 (citing Ex. 1021, 103, 106; Ex. 1097 ¶¶ 120, 122, 124–127). 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. 1097 ¶ 16.

Patent Owner argues that Petitioner failed to establish a reasonable expectation of success in a highly unpredictable art. Prelim. Resp. 55–58. 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 55–56 (citing Ex. 1097 ¶¶ 42, 110).

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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).

On the present record, Petitioner has the better argument. As noted by Petitioner, the '461 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 a sequence 100% complimentary to SEQ ID NO:124 as recited in claim 1.

2. Analysis of Claim 2

Claim 2 is identical to claim 1, except that it also recites "wherein the 5′ end of said PMO antisense oligomer" has a triethylene glycol modification. Ex. 1001, 85:4–19. Focusing on the 5′ triethylene glycol moiety, Petitioner relies on Sanzani for this element. *See* Pet. 44–45 (citing e.g., Ex. 1047 ¶¶ 49, 156; Ex. 1075 ¶ 44; Ex. 1076 ¶ 338; Ex. 1077, 12:9–11; Ex. 1097 ¶¶ 50, 132); section II.C.2, above (disclosing safety and efficacy data of a PMO AVI-4658 having a 5' TEG modification). According to Petitioner, one of ordinary skill in the art

> would have had motivation and a reasonable expectation of success in making and using an effective PMO that is 100% complementary to the +36+60 sequence of exon 53 (which

> would thus hybridize to the corresponding human dystrophin pre-mRNA sequence (i.e., SEQ ID NO: 124) with Watson-Crick base pairing under physiological conditions), that contains the recited PMO monomeric subunit, wherein each nucleobase is selected from uracil, cytosine, thymine, adenine, and guanine, and is attached to a triethylene glycol moiety at the 5' end. (EX1097, ¶¶130–135.)

Pet. 45.

Patent Owner argues that Petitioner has not established a motivation to modify the claimed AO sequence to include a 5′ TEG moiety. Prelim. Resp. 60–63. Patent Owner notes that Summerton,[15] 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 61 (citing Ex. 1077, 12:7–11). Patent Owner points out that although Sanzani added a 5' TEG moiety to a 30 nucleotide oligonucleotide, claimed oligomer is only a 25-mer. *Id*. 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

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

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 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 an oligomer that is 100% complimentary to SEQ ID NO: 124 to include a 5′ TEG moiety as required by claim 2.

3. Objective Evidence of Nonobviousness

Patent Owner is relying on unexpected results based arguments made by Petitioner during the prosecution of Petitioner's own unrelated, now abandoned, patent application claiming AOs targeting exon 53 of the DMD

gene. *See* Prelim. Resp. 63–65. Arguments made on a different record in an unrelated application are not persuasive. We note that Petitioner's prior arguments did not persuade the Examiner and it eventually abandoned the application. Ex. 1063, 1–2.

We are also not persuaded by unexpected results as discussed in the context of its §325(d) arguments above. *See id.* at 34 ("[T]he fact that an Examiner may have erred in accepting evidence of unexpected results does not constitute material error if the record shows that '[t]he Examiner did not allow the claims ***solely*** based on the applicant's showing of unexpected results.'" *Glaxosmithkline Consumer Healthcare Holdings (US) LLC v. Cipla Ltd.*, IPR2020-00369, Paper 7 at 14 (July 31, 2020).). Patent Owner is, nevertheless, welcome to timely introduce evidence of secondary considerations at trial.

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 '461 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

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1 and 2 of the '461 patent is instituted with respect to the grounds set forth in the Petition; and

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 '461 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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