No. _____

In the

Supreme Court of the United States

DUKE UNIVERSITY,

Petitioner,

v.

BIOMARIN PHARMACEUTICAL INC.,

Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

In enacting the Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 6(a), 125 Stat. 284, 299 (2011) ("AIA"), Congress created a powerful new mechanism for challenging patents called "inter partes review." *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2136 (2016). Relying on this new procedure, a panel of the Patent Trial and Appeal Board, consisting of three administrative patent judges, revoked Duke's patent claims despite unrebutted evidence of a long-felt but unsolved need, failure of others, industry praise, and commercial success.

While Duke's case was pending on appeal, the Federal Circuit decided in another case, *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), reh'g denied, 953 F.3d 760 (2020) (en banc), that the administrative patent judges who conduct inter partes reviews hold office in violation of the Appointments Clause. The Federal Circuit has repeatedly refused to apply that ruling to cases like this one where the appellant did not challenge the appointments in its opening brief on appeal.

The questions presented are:

1. Whether a court of appeals can invoke forfeiture to refuse to address an Appointments Clause violation in a pending appeal despite an intervening change in law.

2. Whether the U.S. Patent and Trademark Office Director's delegation of authority to institute inter partes reviews to administrative patent judges acting

as principal officers outside the Director's review violates 35 U.S.C. § 314, which vests institution authority solely in the Director.

3. Whether establishing a nexus between a patentee's invention and objective evidence of nonobviousness under *Graham v. John Deere Co.*, 383 U.S. 1 (1966), requires the patentee to negate every other conceivable reason for a product's commercial success and industry praise.

PARTIES TO THE PROCEEDING

Petitioner Duke University was the patent owner in the proceedings before the Patent Trial and Appeal Board and the appellant in the court of appeals. Synpac Venture Capital, L.P. (indirectly owned by China Synthetic Rubber Corporation) was a real party in interest.

Respondent BioMarin Pharmaceutical Inc. was petitioner in proceedings before the Patent Trial and Appeal Board and appellees in the court of appeals.

CORPORATE DISCLOSURE STATEMENT

Pursuant to this Court's Rule 29.6, petitioner Duke University states that it has no parent corporation and that no publicly held company owns 10% or more of its stock.

STATEMENT OF RELATED PROCEEDINGS

The proceedings in the United States Court of Appeals for the Federal Circuit identified below are directly related to the above captioned case in this Court.

Duke Univ. v. Biomarin Pharm. Inc., Federal Circuit Case No. 2018-1696. The Federal Circuit entered its Judgment, reported at 2019 WL 5092904, on October 11, 2019.

Duke Univ. v. BioMarin Pharm. Inc., Federal Circuit Case No. 2016-1106. The Federal Circuit entered its Opinion, reported at 2017 WL 1458866, on April 25, 2017.

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PETITION FOR WRIT OF CERTIORARI

The Appointments Clause, U.S. Const. art. II, § 2, cl. 2, stands as "a bulwark against one branch aggrandizing its power at the expense of another branch." *Ryder v. United States*, 515 U.S. 177, 182 (1995). "By requiring the joint participation of the President and the Senate, the Appointments Clause was designed to ensure public accountability for both the making of a bad appointment and the rejection of a good one." *Edmond v. United States*, 520 U.S. 651, 660 (1997).

The administrative patent judges ("APJs") who adjudicate inter partes reviews and revoke patent rights as part of the Patent Trial and Appeal Board ("Board") operate in violation of this core constitutional protection. In fact, less than three weeks after summarily affirming the Board's decision here, the Federal Circuit held in *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), *reh'g denied*, 953 F.3d 760 (2020) (en banc), that "APJs are principal officers under Title 35 as currently constituted," and "[a]s such, they must be appointed by the President and confirmed by the Senate." *Id.* at 1335. They are not.

Just like the patent owner in *Arthrex*, Duke's patent rights were abrogated by an unconstitutionally appointed panel of APJs. And even though Duke timely raised this intervening change of law in a petition for rehearing, the Federal Circuit declined to apply that change here. Indeed, wielding forfeiture as a blunt instrument, the court has tried to confine the Appointments Clause infection to a limited number of

Board proceedings—only those with clairvoyant patent owners or fortuitous post-*Arthrex* timing. *See Arthrex, Inc. v. Smith & Nephew, Inc.*, 953 F.3d 760, 764 n.4 (Fed. Cir. 2020) (en banc) (Moore, J., concurring in denial of reh'g en banc) (purporting to limit "the universe of cases which could be vacated and remanded" to "81").

Forfeiture, however, does not apply where there is an intervening change of law. *Curtis Publ'g Co. v. Butts*, 388 U.S. 130, 142-43 (1967) ("[T]he mere failure to interpose [a constitutional] defense prior to the announcement of a decision which might support it cannot prevent a litigant from later invoking such a ground."); *see also James B. Beam Distilling Co. v. Georgia*, 501 U.S. 529, 537 (1991) ("[T]he principle that litigants in similar situations should be treated the same [is] a fundamental component of *stare decisis* and the rule of law . . . ."). Even more, the Appointments Clause has never been about convenience—the accountability and separation-of-powers issues here are no less "exceptionally important" than they were in *Arthrex*. The Federal Circuit's misuse of forfeiture to sidestep an intervening change in law is an important and recurring issue warranting this Court's review.

The problems with APJs do not end there. Disregarding the AIA's bifurcated decision-making structure and the Patent Act's other limits on the statutory power to delegate his functions, the Director has promulgated a regulation diverting all institution decisions from the Director to the Board. 37 C.F.R. § 42.4(a). Under that regulation, gatekeeping institution decisions and merits adjudication are now

combined in the Board, and more specifically, APJs. The Director's delegation of institution authority to APJs—operating as principal officers whom the Director cannot "review, vacate, or correct," *Arthrex*, 941 F.3d at 1335—is irreconcilable with the statute, which vests institution authority solely with the Director. *See* 35 U.S.C. § 314.

The Federal Circuit's summary affirmance of the Board's obviousness decision here only underscores the importance of the Appointments Clause as a check against unaccountable executive power. Duke presented unrebutted evidence that use of the only drugs approved by the U.S. Food and Drug Administration ("FDA") for treating patients suffering from Pompe disease—Myozyme® and Lumizyme®—practices method claim 9 of its U.S. Patent No. 7,056,712 ("the '712 patent"). For decades, scientists had tried—but failed—to treat this fatal disease. The "[m]edical [b]reakthrough[]" in claim 9, embodied by Myozyme and Lumizyme, has been hailed as a "[w]onder drug." CA-Appx2222-2225; CA-Appx2212-2213.[1] But skirting Duke's unrebutted evidence of a nexus between its claimed invention and accolades, the Board required Duke to additionally prove that its objective evidence of nonobviousness was *not* due to some other patent or factor. In other words, the Board imposed a rigid requirement on Duke to prove a negative. The Board's rule—tacitly endorsed by the Federal Circuit's summary affirmance—cannot be squared with this Court's "expansive and flexible approach" to the obviousness question. *KSR Int'l Co.*

[1] "CA-Appx" refers to the Joint Appendix filed in the court of appeals, Fed. Cir. No. 18-1696 (filed May 3, 2019), Dkt. 30.

v. Teleflex Inc., 550 U.S. 398, 415 (2007). If, as the Board held here, a patentee must first prove the negative that commercial success or industry praise is *not* due to all other imaginable contributing factors, then the fourth *Graham* factor is a dead letter.

OPINIONS BELOW

The Federal Circuit's second decision in this case—a summary affirmance without opinion—is unreported but is available at *Duke University v. BioMarin Pharmaceutical Inc.*, 779 F. App'x 750 (Fed. Cir. 2019), and reproduced at App. A. The court's order denying rehearing en banc is unreported but is reproduced at App. G. The Patent Trial and Appeal Board's supplemental final written decision is not reported but is reproduced at App. B.

The Federal Circuit's first decision in this case is unreported but is available at *Duke University v. BioMarin Pharmaceutical Inc.*, 685 F. App'x 967 (Fed. Cir. 2017), and reproduced at App. C. The Patent Trial and Appeal Board's original final written decision is not reported but is reproduced at App. E.

JURISDICTION

The court of appeals entered its summary affirmance on October 11, 2019. Petitioner filed a petition for rehearing en banc, which the court denied on February 3, 2020. This Court has extended the deadline to file a petition for a writ of certiorari due on or after March 19, 2020, to 150 days. This Court has jurisdiction under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

The Appointments Clause, U.S. Const. art. II, § 2, cl. 2, provides as follows:

> [The President] shall have power, by and with the advice and consent of the Senate, to make treaties, provided two thirds of the Senators present concur; and he shall nominate, and by and with the advice and consent of the Senate, shall appoint ambassadors, other public ministers and consuls, judges of the Supreme Court, and all other officers of the United States, whose appointments are not herein otherwise provided for, and which shall be established by law: but the Congress may by law vest the appointment of such inferior officers, as they think proper, in the President alone, in the courts of law, or in the heads of departments.

35 U.S.C. § 103 (2006)[2] is titled "Conditions for patentability; non-obvious subject matter," and provides in relevant part that:

> (a) A patent may not be obtained though the invention is not identically disclosed or

[2] Congress amended 35 U.S.C. § 103 when it enacted the AIA. *See* AIA, § 3(c), 125 Stat. at 287. Nevertheless, the pre-AIA patent statute discussed in this petition still applies to patents and applications with an effective filing date before March 16, 2013, including Duke's patent at issue here. *See* AIA, § 3(n)(1), 125 Stat. at 293.

> described as set forth in section 102 of this title, 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 said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 314 (2012) is titled "Institution of inter partes review," and provides in relevant part that:

> (a) Threshold.—The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.
>
> (b) Timing.—The Director shall determine whether to institute an inter partes review under this chapter pursuant to a petition filed under section 311 within 3 months after—
>
> (1) receiving a preliminary response to the petition under section 313; or

> (2) if no such preliminary response is filed, the last date on which such response may be filed.

STATEMENT OF THE CASE

A. Duke's Invention

Pompe disease—also known as glycogen storage disease type II ("GSD-II")—is a devastating condition caused by a deficiency of acid α-glucosidase ("GAA"), a critical protein that breaks down glycogen to glucose in the body. Without functional GAA, glycogen accumulates in body tissues, especially in skeletal muscles and heart cells. CA-Appx153(1:20-22). This accumulation causes cellular deterioration, leading to muscle failure and, almost always, death. CA-Appx153(1:31-44).

Scientists had recognized a deficiency of the GAA enzyme as the cause of Pompe disease as far back as the early 1960s. And for decades after, researchers tried treating patients by administering exogenous human acid α-glucosidase ("hGAA") produced from various sources, including human placenta, the liver, and fungus. But before the '712 patent, "previous attempts at enzyme replacement therapy in Pompe disease had failed." CA-Appx631-632(8:26-9:30). As BioMarin's expert, Dr. Gregory Pastores, conceded, there was "basically 30-plus years of failures by other researchers to . . . treat Pompe's disease in human patients." CA-Appx1258(271:5-11).

The inventor of the '712 patent, Dr. Yuan-Tsong Chen, succeeded where others had failed by

administering recombinant hGAA ("rhGAA") produced in Chinese hamster ovary ("CHO") cell cultures. The '712 patent teaches that, "[i]n a particularly preferred embodiment, the GAA is the precursor form of recombinant human GAA." CA-Appx154(3:66-67).

Claim 1 of the '712 patent is directed to a method of treating Pompe disease using a therapeutically effective amount of hGAA produced in CHO cells. CA-Appx158(12:45-51). And claim 9, which depends on claim 1, covers the "particularly preferred embodiment" in which the hGAA from CHO cells is administered in "precursor form." CA-Appx154(3:66-67); CA-Appx159(13:9-12).

The FDA has approved only two drugs for treating Pompe disease: Myozyme and Lumizyme. The use of both drugs practices the method in claim 9. CA-Appx2009; CA-Appx1888. The FDA-approved prescribing information states that the hGAA in those products is "produced by recombinant DNA technology in a [CHO] cell line," CA-Appx3815, CA-Appx3830, and has a total mass of approximately 110 kDa and 109 kDa respectively, thus reflecting that the hGAA in both drugs is exclusively in precursor form. CA-Appx3816; CA-Appx3831; *see also* CA-Appx4.

For many patients, Myozyme and Lumizyme have made the difference between life and death. Appx1868. Even today, these drugs remain the only commercially available treatment for Pompe disease. Appx1914. Because they save lives where others failed, Myozyme and Lumizyme have been a commercial success and have won acclaim. While

Pompe disease is very rare, Myozyme and Lumizyme sales from 2006 through 2013 totaled approximately $3 billion. CA-Appx2099-2102; *see also* CA-Appx1256(269:10-12) (BioMarin's expert conceding that Myozyme "has been a commercial success [in] the marketplace").

Myozyme has been described in published articles as a "[m]edical [b]reakthrough[]" and a "[w]onder drug." CA-Appx2222-2225; CA-Appx2212-2213. Genzyme received the prestigious James Watson Helix Award for its development of Myozyme as a "life-saving therapy," CA-Appx2217-2218, and the Galien Award, which recognizes the most important new drugs introduced to the market. CA-Appx2219.

Genzyme, the sole supplier of Myozyme, has taken a license to make and sell products practicing the '712 patent since 2000. The royalties paid for the technology claimed in the '712 patent underscore the invention's value and commercial advantage over other technologies. CA-Appx2110-2113.

B. Procedural History

BioMarin filed a petition for inter partes review, and the Patent Trial and Appeal Board ("Board") made up of a panel of three administrative patent judges ("APJs") acting on authority delegated by the Director of the U.S. Patent and Trademark Office, instituted review on various grounds. In a final written decision, CA-Appx46-88, those same three APJs—neither appointed by the President nor confirmed by the Senate—found claims 1-9, 12, 15, 20, and 21 of the '712 patent invalid as anticipated, and

claims 1-9, 11, 12, 20, and 21 invalid as obvious. CA-Appx63-64; CA-Appx74. Addressing claim 9, the Board read the term "precursor" as "encompass[ing] administering both precursor and non-precursor forms [of hGAA] at the same time," and "not limited to administering exclusively a precursor form and no other form." CA-Appx53.

In Duke's first appeal, the Federal Circuit disagreed with the Board's construction of "precursor" and held that the correct construction is "*exclusively* a precursor of recombinant hGAA that has been produced in CHO cell cultures." *Duke Univ.*, 685 F. App'x at 975 (emphasis added). Applying the correct construction, the Court found that the allegedly anticipating prior art did not disclose "administering *exclusively* a precursor of rhGAA produced in CHO cell cultures." *Id.* at 976 (emphasis added). The Court then vacated the Board's obviousness finding for claim 9 and remanded for a determination of whether that claim would have been obvious under the correct construction of "precursor." *Id.* at 977.

In addition to correcting the Board's claim construction, the court of appeals directed the Board to consider Duke's "proffered objective indicia" of nonobviousness. *Id.*; *see also Graham*, 383 U.S. at 36 (objective evidence "may also serve to 'guard against slipping into use of hindsight,' and to resist the temptation to read into the prior art the teachings of the invention in issue" (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (6th Cir. 1964))). In fact, the Court expressly noted its misgivings about the Board's treatment of the objective evidence, including its failure to apply a

presumption of nexus between the objective evidence and Duke's invention:

> Notably, Duke's objections to the Board's treatment of its evidence of objective indicia of non-obviousness—*including its failure to apply a presumption of nexus*—appear well taken.

Duke Univ., 685 F. App'x at 977 n.2 (emphasis added).

Rather than confront the court's stated concerns on remand, the Board—consisting of the same three APJs as before—dismissed Duke's objective evidence of nonobviousness and reached the same result. Even though unrebutted evidence showed that the use of Myozyme and Lumizyme practices the method of claim 9, the Board again failed to apply a presumption of nexus between the claimed invention and the objective evidence of nonobviousness. CA-Appx18-19. According to the Board, a presumption of nexus did not apply because the record "does not elucidate adequately the impact of the '712 patent, as compared to other relevant patents." CA-Appx18. And without a presumption of nexus, the Board effectively sidestepped Duke's objective evidence of nonobviousness. *See* CA-Appx18-19.

Duke appealed to the Federal Circuit again. But this time, the court did not issue a written opinion. Instead, it issued a "Notice of Entry of Judgment Without Opinion" pursuant to Federal Circuit Rule 36, summarily affirming the Board's decision without explanation. App. A.

C. The *Arthrex* Decision

Less than three weeks after summarily affirming the Board's decision here, the Federal Circuit decided *Arthrex*, holding that the APJs who oversee inter partes reviews hold office in violation of the Appointments Clause. 941 F.3d at 1335. APJs are appointed by the Secretary of Commerce, an arrangement appropriate only for inferior officers. *Id.* at 1327. The court held that APJs are principal rather than inferior officers due to "[t]he lack of any presidentially-appointed officer who can review, vacate, or correct [their] decisions" and the Secretary's "limited removal power." *Id.* at 1335. Attempting to cleanse the constitutional violation, the court severed the APJs removal protections under Title 5 and remanded the case for a new hearing before a different panel of APJs. *Id.* at 1335-40 (citing *Lucia v. SEC*, 138 S. Ct. 2044 (2018)).

Duke timely filed a petition for rehearing, urging that *Arthrex* was an intervening change of law and that Duke's patent rights were abrogated by an unconstitutionally appointed panel of APJs. And because APJs operate as "principal officers" rather than the Director's subordinates, Duke further explained that the Director's delegation of his authority to institute inter partes review to APJs violates 35 U.S.C. § 314. The court of appeals denied rehearing. App. G.

REASONS FOR GRANTING THE PETITION

This case presents three important issues where the Federal Circuit has repeatedly departed from this

Court's precedents and the statutory mandate. This Court has held that under the Appointments Clause, "[o]nly the President, with the advice and consent of the Senate, can appoint a principal officer." *Lucia*, 138 S. Ct. at 2051 n.3. And the Federal Circuit has recently recognized that APJs operate as principal officers who were neither appointed by the President nor confirmed by the Senate. *Arthrex*, 941 F.3d at 1335. Nevertheless, refusing to apply a change in law to pending appeals, the Federal Circuit has looked the other way and allowed unconstitutionally appointed APJs to abrogate patent rights. If an inter partes review is to determine the validity of Duke's patent—or any duly issued patent—it must be conducted and decided by a panel of APJs appointed under a constitutionally valid statutory scheme. What's more, the Federal Circuit continues to bless the Director's delegation of his institution authority to APJs acting as principal officers whom he has no authority to "review, vacate, or correct." *Arthrex*, 941 F.3d at 1335. Congress, however, vested institution authority solely with Director, and he cannot replace Congress' choice with his own.

The aggrandizement of unreviewable adjudicatory power in unaccountable APJs—both at institution and at the final written decision stage—has troubling consequences. Here, APJs defied this Court's decades-old precedent directing courts to consider objective "indicia" as part of the obviousness inquiry. *Graham*, 383 U.S. at 17-18. And the Federal Circuit approved with a one-line order. This Court should grant review.

I. The Court Should Grant Review to Address All Cases Pending on Appeal Where Unconstitutionally Appointed Administrative Patent Judges Have Revoked Patent Rights

Within the window for Duke to seek rehearing, the Federal Circuit decided that the statutory method for appointing APJs violates the Appointments Clause. *See Arthrex*, 941 F.3d. at 1335. That decision's reasoning applies equally here, and Duke promptly brought the decision to the Federal Circuit's attention in a timely petition for rehearing. C.A. Dkt. 54. The court, however, refused to apply *Arthrex* to this case. But *Arthrex* was a significant change in law, and the court's misapplication of forfeiture to a fundamental constitutional violation warrants review.

A. Administrative Patent Judges Operate in Violation of the Appointments Clause

Under the Appointments Clause, principal officers must be nominated by the President and confirmed by the Senate, while inferior officers may be appointed by a department head. U.S. Const. art. II, § 2. The secretary of Commerce appoints APJs—an approach permissible only if they are inferior officers. 35 U.S.C. § 6(a).

Arthrex correctly held that they are not. "'[I]nferior officers' are officers whose work is directed and supervised at some level" by a principal officer. *Edmond*, 520 U.S. at 662-63. But there is no such direction or supervision here—the Director has no authority "to single-handedly review, nullify or reverse a final written decision issued by a panel of

APJs." *Arthrex*, 941 F.3d at 1329. APJ decisions are appealable only to Article III courts. In fact, the statute provides that after a patent holder has exhausted appeal rights from a final written decision of the Board, "the Director *shall* issue and publish a certificate canceling any claim of the patent finally determined to be unpatentable." 35 U.S.C. § 318(b) (emphasis added); *see also SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354 (2018) (holding that the word "shall" in § 318(a) "imposes a nondiscretionary duty" that "is both mandatory and comprehensive"). The APJs of the Board thus have the "power to render a final decision on behalf of the United States." *Edmond*, 520 U.S. at 665.

That the Director maintains the ability to designate certain Board decisions as "precedential" within the PTO[3] does not alter the fact that, with respect to invalidation of patents in an inter partes review, the Director has no power to alter a decision of the Board. "It is not enough that other officers may be identified who formally maintain a higher rank, or possess responsibilities of a greater magnitude. If that were the intention, the Constitution might have used the phrase 'lesser officer.'" *Edmond*, 520 U.S. at 662-63.

Nor does the Director's ability to "stack" panels with additional APJs constitute the type of "direction" and "supervision" required under *Edmond*. Even

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[3] *See* Patent Trial and Appeal Board, Standard Operating Procedure 2 (Revision 10), § III.C, *available at* https://www.uspto.gov/patents-application-process/appealing-patent-decisions/procedures/standard-operating-procedures-0.

ignoring the serious due process questions this practice raises, the authority to designate the members of particular panels is not a substitute for the direct-review authority that the Court found "significant" in *Edmond*. *Id.* at 665 ("*What is significant* is that the judges of the Court of Criminal Appeals have no power to render a final decision on behalf of the United States unless permitted to do so by other Executive officers." (emphasis added)); *see also* Gary Lawson, *Appointments and Illegal Adjudication: The America Invents Act Through A Constitutional Lens*, 26 Geo. Mason L. Rev. 26, 59 (2018) ("The power to pick the panels is not the power to decide.").

At bottom, "[t]he lack of control over APJ decisions does not allow the President to ensure the laws are faithfully executed because 'he cannot oversee the faithfulness of the officers who execute them.'" *Arthrex*, 941 F.3d at 1335 (quoting *Free Enter. Fund v. Pub. Co. Accounting Oversight Bd.*, 561 U.S. 477, 484 (2010)). APJs are principal officers who were neither appointed by the President nor confirmed by the Senate in violation of the Appointments Clause. *Id.*

B. The Applicability of *Arthrex*'s Change in Law to Pending Cases Is a Recurring and Important Issue

All of the Board proceedings in this case suffered from the same defect as in *Arthrex*—the APJs who abrogated Duke's patent rights held office in violation of the Constitution. The Federal Circuit, however, refused to grant Duke any relief. App. G. Indeed, that

court has repeatedly refused to apply *Arthrex* to cases like this where the appellant did not raise the Appointments Clause issue in its opening appeal brief. Whether a court may refuse to consider a constitutional claim in pending cases on forfeiture grounds—despite an intervening change in law—is a recurring issue that warrants this Court's review.

The day after *Arthrex*, a different Federal Circuit panel refused to apply the decision where the appellant had not raised an Appointments Clause challenge in its opening brief, denying a motion to vacate and remand. *See Customedia Techs., LLC v. Dish Network Corp.*, 941 F.3d 1173, 1174 (Fed. Cir. 2019). According to the panel, it was "well established that arguments not raised in the opening brief are waived." *Id.* (quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006)). But the panel did not confront that *Arthrex* was a change in law. Nor did it grapple with the fact that its holding contradicted the court's application of forfeiture after *SAS*. *See Polaris Indus., Inc. v. Arctic Cat, Inc.*, 724 F. App'x 948, 949-50 (Fed. Cir. 2018) ("[A] party does not waive an argument that arises from a significant change in law during the pendency of an appeal."). The court ultimately denied reconsideration en banc over Judge Newman's dissent, No. 19-1001, Dkt. 63 (Dec. 23, 2019), and later denied rehearing en banc of the decision on the merits, *id.*, Dkt. 73 (Mar. 5, 2020).

That was just the beginning. Another Federal Circuit panel confronted the same issue in *Sanofi-Aventis Deutschland GmbH v. Mylan Pharmaceuticals Inc.*, 791 F. App'x 916 (Fed. Cir.

2019). Relying on *Customedia*, the majority refused to consider the constitutional claim. *Id.* at 928 n.4. Judge Newman dissented, reasoning that, "at the time these appeals were filed, there was no holding of illegality of appointments of the PTAB's Administrative Patent Judges," and "[i]t is well established that when the law changes while a case is on appeal, the changed law applies." *Id.* at 931-32 (Newman J., dissenting) (citing *Thorpe v. Hous. Auth. of Durham*, 393 U.S. 268, 282 (1969)). Despite the intra-circuit split, the court denied rehearing en banc. No. 19-1368, Dkt. 69 (Fed. Cir. Jan. 28, 2020). Sanofi sought a stay from this Court, which the Chief Justice initially granted but which the Court later denied after the respondent argued, among other things, that there was no threat of irreparable harm. No. 19A886.

Other patent owners with pending appeals and violated constitutional rights have similarly been told "too bad." *See, e.g.*, *Bos. Sci. Neuro-modulation Corp. v. Nevro Corp.*, No. 19-1582, Dkt. 56 (Fed. Cir. Nov. 22, 2019) (denying leave to file supplemental brief addressing change in law regarding Appointments Clause); *id.*, Dkt. 73 (Fed. Cir. Jan. 23, 2020) (denying reconsideration en banc over Judge Newman's dissent); *Arthrex, Inc. v. Smith & Nephew, Inc.*, No. 18-1584, Dkt. 72 (Fed. Cir. Nov. 1, 2019) (raising change in law regarding Appointments Clause); *id.*, Dkt. 75 (Fed. Cir. Nov. 8, 2019) (denying reconsideration en banc); *Customedia Techs., LLC v. Dish Network Corp.*, No. 19-1001, Dkt. 64 (Fed. Cir. Jan. 7, 2020) (raising change in law regarding Appointments Clause); *id.*, Dkt. 73 (Fed. Cir. Mar. 5, 2020) (denying reconsideration en banc). The recurring nature of the question is no surprise—the

Appointments Clause flaw affects every appeal from an inter partes review that was still pending when the court decided *Arthrex*.

And the question is an important one—the Court has recognized "the danger of one branch's aggrandizing its power at the expense of another branch." *Freytag v. Comm'r*, 501 U.S. 868, 878-79 (1991). "The Appointments Clause not only guards against this encroachment but also preserves another aspect of the Constitution's structural integrity by preventing the diffusion of the appointment power." *Id.* It ensures too "that those who exercise the power of the United States are accountable to the President, who himself is accountable to the people." *Dep't of Transp. v. Ass'n of Am. R.R.*, 575 U.S. 43, 63 (2015) (Alito, J., concurring).

That accountability is especially urgent for the Board's APJs, who wield the power to revoke an inventor's property right in an issued patent. Since the effective date of the AIA, the Board has invalidated at least one patent claim in 81% of the AIA proceedings that have reached a final written decision, and 78% of those decisions have invalidated *all* claims of an issued patent. *See* PTO, *Trial Statistics IPR, PGR, CMB* at 11 (Jan. 2020), *available at* https://www.uspto.gov/sites/default/files/documents/trial_statistics_20200131.pdf.

The need for political accountability in adjudicating patent rights is only underscored by the Court's recent decision in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, 138 S. Ct. 1365

(2018). The Court there held that patents involve public rights susceptible to the determination of the political branches. *See id.* at 1374. "When the PTO 'adjudicate[s] the patentability of inventions,' it is 'exercising the executive power.'" *Id.* (alteration in original) (quoting *Freytag*, 501 U.S. at 910). And the exercise of that power must be made by officials sufficiently accountable to the President, within whom the power is vested. *See* U.S. Const. art. II, § 1, cl. 1; *see also Free Enter. Fund*, 561 U.S. at 496-97; *Freytag*, 501 U.S. at 884 ("The Framers understood . . . that by limiting the appointment power, they could ensure that those who wielded it were accountable to political force and the will of the people.").

C. The Federal Circuit's Approach to Forfeiture Is Wrong

The Federal Circuit's knee-jerk application of forfeiture defies this Court's settled precedent. While parties are typically required to raise all arguments in an opening brief, that rule simply does not apply where there is an intervening change of law—especially on a constitutional question—while the appeal is pending.

This Court has steadfastly refused to find forfeiture where there has been an intervening change in law. "[T]he mere failure to interpose [a constitutional] defense prior to the announcement of a decision which might support it cannot prevent a litigant from later invoking such a ground." *Curtis Publ'g*, 388 U.S. at 142-43; *see also Hormel v. Helvering*, 312 U.S. 552, 558-59 (1941) (holding that an exception to the waiver rule exists where "there

have been judicial interpretations of existing law after decision below and pending appeal—interpretations which if applied might have materially altered the result"). Where the law has changed, the "failure to raise the claim in an opening brief reflects not a lack of diligence, but merely a want of clairvoyance." *Joseph v. United States*, 574 U.S. 1038, 1039 (2014) (Kagan, J., respecting denial of certiorari).

The Court's rule against applying forfeiture where there is an intervening change of law exists for precisely this scenario—a constitutional decision that upends the legal landscape. Indeed, the Federal Circuit had twice rejected the same Appointments Clause challenge that ultimately was successful in *Arthrex*. *See Trading Techs. Int'l, Inc. v. IBG LLC*, 771 F. App'x 493 (Fed. Cir. 2019); *Bedgear, LLC v. Fredman Bros. Furniture Co.*, 779 F. App'x 748 (Fed. Cir. 2019), *reh'g granted, judgment vacated*, No. 18-2170, 2020 WL 2050663 (Fed. Cir. Apr. 29, 2020). And this Court denied certiorari in a case presenting the same Appointments Clause question. *Smartflash LLC v. Samsung Elecs. Am., Inc.*, 139 S. Ct. 276 (2018); Petition for Writ of Certiorari at 18, *Smartflash LLC*, No. 18-189, 2018 WL 3913634 (U.S. Aug. 9, 2018).

Outside observers have similarly viewed *Arthrex* as dramatically changing the law. For example, the Chairman of the House Committee on the Judiciary described it as "remarkable" that *Arthrex* questioned "the constitutionality of the PTAB's structure" after "the many cases that have gone before the PTAB and then to federal court, and an earlier constitutional challenge to the PTAB that the Supreme Court rejected." *The PTAB & the Appointments Clause:*

Implications of Recent Court Decisions Before the Subcomm. on Courts, IP, and the Internet of the H. Comm. of the Judiciary, 116th Cong. (Nov. 19, 2019) (statement of Rep. J. Nadler).

Even where petitioners have failed to raise them before the court of appeals, this Court has reviewed structural constitutional challenges to an adjudicator's authority. *See, e.g.*, *Nguyen v. United States*, 539 U.S. 69, 73, 80-81 (2003) (addressing challenge to territorial judge's participation on appellate panel raised for the first time in petition for certiorari); *Freytag*, 501 U.S. at 879 (reviewing Appointments Clause challenge despite waiver due to "the strong interest of the federal judiciary in maintaining the constitutional plan of separation of powers" (citation omitted)). And those principles are even more important here where the only reason for the alleged forfeiture was that the law changed while Duke's appeal was pending. *See Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993) ("When this Court applies a rule of federal law to the parties before it, that rule is the controlling interpretation of federal law and must be given full retroactive effect in all cases still open on direct review . . . ."); *Thorpe*, 393 U.S. at 281 ("[A]n appellate court must apply the law in effect at the time it renders its decision.").

D. The Court Should Either Grant the Petition or Hold the Case Pending *Arthrex*

The Court should grant review in this case to decide how the intervening change of law in *Arthrex* applies to all cases pending on appeal. Alternatively, the Court should hold this case while it considers the petition

recently filed in *Arthrex* itself. See *Arthrex, Inc. v. Smith & Nephew, Inc.*, No. __ (U.S. Jun. 30, 2020).

Because the Federal Circuit held a provision of law unconstitutional, there is a high likelihood that the Court will grant review in *Arthrex*. *See Maricopa Cty. v. Lopez-Valenzuela*, 574 U.S. 1006, 1007 (2014) (Thomas, J., respecting denial of stay) (noting the "strong presumption" of review for decisions holding a federal statute unconstitutional). And while the Federal Circuit correctly determined that APJs operate in violation of the Appointments Clause, its remedy—severing Title 5 removal protections for APJs, *Arthrex*, 941 F.3d at 1335-40—does not cure the problem. In fact, it creates new ones requiring this Court's intervention.

For one thing, APJs retain their power to issue final written decisions that are unreviewable by any other executive officer, whether or not they have tenure protections. This Court has held that the power to issue a final decision without meaningful review is "significant" to a decision maker's principal officer status. *Edmond*, 520 U.S. at 665; *Dep't of Transp.*, 575 U.S. at 64 (Alito, J., concurring) ("As to that 'binding' decision, who is the supervisor? Inferior officers can do many things, but nothing final should appear in the Federal Register unless a Presidential appointee has at least signed off on it."). Even after *Arthrex*, APJs continue to adjudicate patent rights in violation of the Appointments Clause.

Worse, there is no evidence that "Congress would have divested APJs of their Title 5 removal protections to cure any alleged constitutional defect in

their appointment." *Arthrex*, 953 F.3d at 781 (Hughes, J., dissenting from denial of reh'g en banc); *see also Bowsher v. Synar*, 478 U.S. 714, 735 (1986) (courts may not sever removal restrictions to remedy a constitutional violation if "striking the removal provisions would lead to a statute that Congress would probably have refused to adopt"). And most remarkably, the Federal Circuit's severance of Title 5 removal protections contravenes the independence and impartial decision-making envisioned by Congress and secured by due process and the Administrative Procedure Act. *Schweiker v. McClure*, 456 U.S. 188, 195 (1982) ("As this Court repeatedly has recognized, due process demands impartiality on the part of those who function in judicial or quasi-judicial capacities."); *see also Thryv, Inc. v. Click-To-Call Techs., LP*,, 590 U.S. ____, No. 18-916, 2020 WL 1906544, at *17 (U.S. Apr. 20, 2020) (Gorsuch, J., dissenting) ("[T]he Constitution promises an independent judge in any case involving the deprivation of life, liberty, or property[.]"); *Utica Packing Co. v. Block*, 781 F.2d 71, 78 (6th Cir. 1986) ("There is no guarantee of fairness when the one who appoints a judge has the power to remove the judge before the end of proceedings for rendering a decision which displeases the appointer.").

The Court should grant review to give Congress "the opportunity to craft the appropriate fix." *Arthrex*, 953 F.3d at 781 (Hughes, J., dissenting from denial of reh'g en banc). Alternatively, this Court should hold the petition not only for *Arthrex*, but potentially for *Sanofi* and *Customedia* too.

II. The Court Should Grant Review to Determine Whether the Director's Delegation of Institution Authority to Administrative Patent Judges Acting as Principal Officers Violates 35 U.S.C. § 314 and Due Process of Law

In enacting the AIA, Congress created two distinct phases for inter partes reviews—institution first, and then a review proceeding culminating in a final written decision. *See* 35 U.S.C. §§ 314, 316, 318. And while APJs are tasked with adjudicating patent validity by "conduct[ing] each inter partes review," 35 U.S.C. 316(c), Congress unequivocally vested authority to *institute* inter partes reviews solely with the Director. 35 U.S.C. § 314(a), (b) ("The Director shall determine whether to institute an inter partes review . . . ."). The Director, however, has delegated his institution authority to the Board and its APJs. 37 C.F.R. § 42.4(a) ("The Board institutes the trial on behalf of the Director.").

Years before deciding *Arthrex*, a fractured[4] Federal Circuit panel had held that the Director was permitted to delegate institution authority to "subordinate officers"—in this case, APJs of the Board. *See Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1031-33 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 625 (2017). But now the court has

[4] As Judge Newman noted in her *Ethicon* dissent, "[t]he statute requires that these proceedings be separated, the first decision required to be made by the Director, and the second decision made by the Board." 812 F.3d at 1035 (Newman, J., dissenting). In fact, bifurcation between the Director and the Board was critical to protecting due process guarantees of "a fair trial in a fair tribunal." *Id.* at 1038 (citation omitted).

recognized that APJs were not subordinate after all—rather, they are "principal officers." *Arthrex*, 941 F.3d at 1325-35. That is, the Director has been delegating his institution authority to a body of APJs that he could not properly "review, vacate, or correct." *Id.* at 1335. Indeed, the Director's "control and supervision of the APJs is not sufficient to render them inferior officers."[5] *Id.*

The inter partes review of Duke's '712 patent violated the statute from the very beginning.[6] The same APJs who would ultimately revoke Duke's patent rights first instituted inter partes review here not as the Director's subordinates, but as independent principal officers whom the Director did not supervise. *Id.* It is no answer to say that delegating institution authority to APJs is more convenient or efficient for the Director. "'[J]ust as Congress' choice of words is presumed to be deliberate' and deserving of judicial respect, 'so too are its structural choices.'" *SAS*, 138 S. Ct. at 1355 (quoting *Univ. of Tex. Sw. Med. Ctr. v. Nassar*, 570 U.S. 338, 353 (2013)). In fact, this Court has expressly rejected elevating administrative

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[5] The court in *Arthrex* saw no "infirmity in the institution decision as the statute clearly bestows such authority on the Director pursuant to 35 U.S.C. § 314." 941 F.3d at 1340. But the court did not analyze the implications of its holding that APJs were "principal officers" on the Director's delegation of his institution authority to the Board under 37 C.F.R. § 42.4(a).

[6] Forfeiture is inapposite here too. *Arthrex* is a fundamental change in the law that is fatal to the Director's delegation of institution authority to the Board. *See Hormel*, 312 U.S. at 558-59.

convenience and speed above the text of the inter partes review statute:

> Each side offers plausible reasons why its approach might make for the more efficient policy. But who should win that debate isn't our call to make. Policy arguments are properly addressed to Congress, not this Court. It is Congress's job to enact policy and it is this Court's job to follow the policy Congress has prescribed.

Id. at 1357-58.

This is not to say that the Director must personally handle each institution decision. Congress provided that he may delegate his duties to officers and employees whom he appoints or hires. *See* 35 U.S.C. § 3(b)(3) (providing that "[t]he Director shall . . . appoint such officers, employees . . . , and agents of the Office as the Director considers necessary" and "delegate to them such of the powers vested in the Office as the Director may determine").

But delegating his institution duty to APJs—hired by the Secretary of Commerce and acting as unreviewable principal officers—is another matter. Congress's provision of limited express delegation authority in § 3(b)(3) can only mean that it did not intend to permit other delegations by implication. To hold otherwise would furnish the Director with an unbounded delegation authority that renders § 314(b) entirely superfluous. *See Corley v. United States*, 556 U.S. 303, 314 (2009) (rejecting interpretation "at odds with one of the most basic interpretive canons" of

avoiding surplusage). "Here again we know that if Congress wanted to adopt the Director's approach it knew exactly how to do so." *SAS*, 138 S. Ct. at 1356. Congress could have simply assigned institution authority to the Board. It did not.

III. The Court Should Grant Review to Reestablish the Role of Objective Evidence of Nonobviousness

The structural separation of power and accountability ensured by the Appointments Clause matter. Look no further than the Board's decision here.

For over 50 years, this Court has emphasized a flexible obviousness analysis, including consideration of objective evidence—also known as secondary considerations—to "'guard against slipping into use of hindsight,' and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 U.S. at 36 (quoting *Monroe Auto Equip.*, 332 F.2d at 412). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy." *Id.* at 17-18.

Under settled precedent, a nexus is presumed between a patented invention and objective evidence "when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056,

1071 (Fed. Cir. 2018) (quoting *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016)); *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) ("A prima facie case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent.").

Objective evidence plays a critical role because it is "not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Like the rest of the obviousness analysis, consideration of objective evidence requires "an expansive and flexible approach." *KSR*, 550 U.S. at 415. And where the Federal Circuit has imposed its own rigid rules in the name of uniformity and consistency, this Court has intervened. *Id.* at 399.

Notwithstanding this Court's rejection of inflexible obviousness rules, the Board here attached additional burdens that relegate objective evidence to an afterthought. Take the Board's statement requiring Duke to separate "the impact of the '712 patent, as compared to other relevant patents," on licensing, commercial success, and industry praise. CA-Appx18. But a patentee is not required "to prove as part of its prima facie case that the commercial success of the patented invention is *not* due to factors other than the patented invention." *Demaco*, 851 F.2d at 1394. Rather, "[i]t is sufficient to show that the commercial success was of the patented invention itself." *Id.* And

that rule is sound—"[a] requirement for proof of the negative of all imaginable contributing factors would be unfairly burdensome, and contrary to the ordinary rules of evidence." *Id.*; *see also Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 571 U.S. 191, 200-01 (2014) (rejecting shifting the burden to declaratory judgment patent licensee "to negate every conceivable infringement theory").

For decades, scientists had tried—and failed—to treat Pompe disease. The "[m]edical [b]reakthrough[]" embodied by Myozyme and Lumizyme has been hailed as a "[w]onder drug." CA-Appx2222-2225; CA-Appx2212-2213. Duke established a nexus by putting forward unrebutted evidence that Myozyme and Lumizyme are the invention "disclosed and claimed" in claim 9. *WBIP*, 829 F.3d at 1329; *see also* CA-Appx2009; CA-Appx1888. In fact, the FDA-approved prescribing information explains that the hGAA in Myozyme and Lumizyme for treating Pompe disease is "produced by recombinant DNA technology in a [CHO] cell line." CA-Appx3815; CA-Appx3830. What's more, the hGAA in Myozyme and Lumizyme has a total mass of approximately 110 kDa and 109 kDa respectively—that is, the hGAA in both drugs is *exclusively* in precursor form as required in claim 9. CA-Appx3816; CA-Appx3831; *see also* CA-Appx4. That should have been enough.

Once a patentee shows a prima facie nexus, "the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). "The presumed nexus cannot be rebutted with mere

argument; evidence must be put forth." *Id.* BioMarin, however, provided no evidence rebutting the fact that administering Myozyme and Lumizyme to treat Pompe disease practices claim 9 of the '712 patent. *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 734, 747 (Fed. Cir. 2016) ("When the patentee has presented undisputed evidence that its product is the invention disclosed in the challenged claims, it is error for the Board to find to the contrary without further explanation."). By refusing to credit Duke's unrebutted evidence unless Duke proved a negative, the Board's APJs reduced objective indicia of nonobviousness to a nullity. And the Federal Circuit's summary affirmance invites more of the same.

It makes no difference that other patents may also be relevant to Myozyme and Lumizyme. Other Federal Circuit panels have recognized that objective evidence can be simultaneously linked to commercial products with multiple patents. *See, e.g., Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730-31 (Fed. Cir. 2017) ("[M]ultiple patents do not necessarily detract from evidence of commercial success of a product or process, which speaks to the *merits of the invention*, not to how many patents are owned by a patentee."); *PPC Broadband*, 815 F.3d at 737 n.1, 746-47 (presumption of nexus applied to three patents covering patentee's commercial product); *Gator Tail, LLC v. Mud Buddy LLC*, 618 F. App'x 992, 995, 999-1000 (Fed. Cir. 2015) (presumption of nexus applied to two patents covering the same commercial product). The Federal Circuit's failure to follow its own precedent is yet another reason for this Court to intervene.

Time and again, this Court has admonished the Federal Circuit to avoid rigid rules, not just when deciding obviousness, but in all patent contexts. *KSR*, 550 U.S. at 418-19 (rejecting "rigid" application of "teaching, suggestion, or motivation" test under 35 U.S.C. § 103); *see also Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1934 (2016) (rejecting the Federal Circuit's rigid test for enhanced damages under 35 U.S.C. § 284); *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 554-55 (2014) (rejecting the Federal Circuit's "exceptional" case rule under 35 U.S.C. § 285 as "overly rigid"); *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014) (rejecting strict "insolubly ambiguous" test under 35 U.S.C. § 112(b)); *Bilski v. Kappos*, 561 U.S. 593, 603-04 (2010) (rejecting strict application of "machine-or-transformation test" under 35 U.S.C. § 101); *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 390 (2006) (rejecting rigid, patent-specific rule for injunctive relief).

Objective evidence of nonobviousness is no different, and the rigid application of negative burdens is a recurring problem that defies this Court's precedent. *See Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1375-76 (Fed. Cir. 2019) (requiring patent owner to prove that unclaimed features are *not* responsible for objective evidence of nonobviousness); *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010) (requiring patentee to prove that product's success was *not* due to a different patented invention), *vacated on other grounds*, 374 F. App'x 35 (2010). With APJs operating as unaccountable principal officers and the Federal Circuit summarily affirming the cancelation of patent

rights with one-line orders,[7] this Court should grant review to reestablish the flexible role of objective evidence in the obviousness inquiry.

CONCLUSION

For these reasons, this Court should grant the petition for certiorari.

Respectfully submitted,

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[7] "It has been calculated that for the first two quarters of 2018, over 50% of PTAB appeals were decided by Rule 36 affirmances (196 out of 389)." Rebecca A. Lindhorst, *Because I Said So: The Federal Circuit, the PTAB, and the Problem With Rule 36 Affirmances*, 69 Case W. Res. L. Rev. 247, 252 (2018).

APPENDIX

APPENDIX A — JUDGMENT OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED OCTOBER 11, 2019

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1696

DUKE UNIVERSITY,

Appellant,

v.

BIOMARIN PHARMACEUTICAL INC.,

Appellee.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00535.

JUDGMENT

THIS CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

PER CURIAM (NEWMAN, LOURIE, and TARANTO, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

Appendix A

ENTERED BY ORDER OF THE COURT

October 11, 2019	/s/ Peter R. Marksteiner
Date	Peter R. Marksteiner
	Clerk of Court

APPENDIX B — SUPPLEMENTAL FINAL WRITTEN DECISION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, DATED JANUARY 17, 2018

UNITED STATES PATENT
AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL
AND APPEAL BOARD

Case IPR2013-00535
Patent 7,056,712 B2

BIOMARIN PHARMACEUTICAL INC.,

Petitioner,

v.

DUKE UNIVERSITY,

Patent Owner.

Before JACQUELINE WRIGHT BONILLA, *Vice Chief Administrative Patent Judge,* LORA M. GREEN and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

Appendix B

SUPPLEMENTAL FINAL WRITTEN DECISION
Proceedings on Remand
35 U.S.C. §§ 144 and 318(a)

I. BACKGROUND

The Board previously addressed the merits of the parties' arguments in a Final Written Decision issued February 23, 2015. Paper 86, "Decision" or "Dec."[1] Relevant to this remand, we determined in our Decision that claims 1 and 9 of U.S. Patent No. 7,056,712 (Exhibit 1001, "the '712 patent") were unpatentable as anticipated by van Bree[2] and/or as obvious over the combination of Reuser '771[3] and Van Hove 1997.[4] Dec. 18–19, 24. Following entry of that Decision, Patent Owner Duke University ("Patent Owner") filed a Notice of Appeal (Paper 91), and the Federal Circuit issued a decision remanding the case to the Board with regard to claim 9 of the '712 patent. *Duke Univ. v. BioMarin Pharm. Inc.*, 685 F. App'x 967 (Fed. Cir. 2017) ("*Duke*"). In its decision, the Federal Circuit modified the construction of the term "precursor"

1. The procedural history of the case prior to the Final Written Decision is summarized in that Decision (Paper 86, 1–4).

2. van Bree et al., U.S. Patent No. 7,351,410 B2, issued Apr. 1, 2008 (Ex. 1005).

3. Reuser et al., WO 97/05771, published Feb. 20, 1997 (Ex. 1004).

4. Van Hove et al., *Purification of recombinant human precursor acid α-glucosidase*, 43(3) Biochemistry & Molecular Biology Int'l 613–623 (1997) (Ex. 1007).

recited in claim 9, reversed our finding that claim 9 was anticipated by van Bree, vacated our obviousness conclusion with respect to claim 9, and remanded for us to apply its claim construction of the term "precursor" in our analysis. *Id.*

We have considered anew the record developed during trial and reviewed the parties' positions in light of the Federal Circuit's decision. For the reasons set forth below, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claim 9 of the '712 patent is unpatentable as obvious over the combination of Reuser '771 and Van Hove 1997.

II. DISCUSSION

A. The Issue on Remand

In our prior Decision, we construed the term "precursor" in claim 9 to mean "any precursor of recombinant hGAA (e.g. a 110-kD form)" that is "exclusively . . . produced in CHO cell cultures." Dec. 8; *see also* Paper 59 ("PO Resp.") 22. We further added the following guidance:

> We clarify . . . that claim 1, upon which claim 9 depends, recites a method *comprising* administering hGAA. Neither claim 1 nor claim 9 precludes administering a non-precursor form of hGAA or rhGAA, even if claim 9 requires administering a precursor of recombinant hGAA that has been produced in CHO cell cultures.

> Claims 1 and 9 encompass administering both precursor and non-precursor forms at the same time, and are not limited to administering exclusively a precursor form and no other form.

Id.

The Federal Circuit disagreed with our construction and held that the proper construction of "precursor" in claim 9 is "exclusively a precursor of recombinant hGAA that has been produced in CHO cell cultures." *Duke*, 685 F. App'x at 975 (Fed. Cir. 2017). The Federal Circuit provided the following explanation:

> Claim 9 requires that "*the* [hGAA] *is* a precursor" and refers to claim 1 for the antecedent basis of "the [hGAA]." '712 patent col. 13 ll. 9–12 (emphases added). That sentence structure makes clear that the "is a precursor" phrase limits the form of hGAA to a precursor form. The claim language and structure thus support the conclusion that "the [hGAA]" in claim 9 is exclusively a precursor of hGAA.

Duke, 685 F. App'x at 975. The court further noted that, "[b]ecause we have modified the construction of 'precursor,' we do not have the benefit of the Board's considered analysis whether claim 9 would have been obvious under the correct construction." *Id.*

On remand, the court presented a specific question to be answered by the Board. That question is whether the

combination of Reuser and Van Hove "teach or suggest administering exclusively a precursor of rhGAA produced in CHO cell cultures" as recited in claim 9. To fully address this questions, we include in our discussion an analysis of independent claim 1, from which claim 9 depends.[5]

B. The '712 Patent

The '712 patent relates to methods of treating glycogen storage disease type II ("GSD-II"). Ex. 1001, Abstract. Glycogen storage disease type II, also known as Pompe disease or acid maltase deficiency, is a genetic muscle disorder caused by a deficiency of acid α-glucosidase ("GAA"), a glycogen degrading lysosomal enzyme. *Id*. at 1:12–15. The disclosed methods involve enzyme replacement therapy ("ERT"), including administering to an individual a therapeutically effective amount of GAA. *Id*. at 1:62–66; 2:20–27. In a preferred embodiment, the method uses recombinant human acid α-glucosidase ("rhGAA"), such as recombinant human GAA in its precursor form (110 kD), produced in Chinese hamster ovary ("CHO") cell cultures. *Id*. at 3:57–4:4, 8:53–55, 12:16–26. In certain embodiments, the method involves administering GAA in conjunction with other agents, such as immunosuppressants. *Id*. at 5:29–33. The '712 patent

5. The Federal Circuit affirmed our finding that claim 1 is anticipated by van Bree, and as such, determined that addressing our obviousness finding with regard to claims 1 was unnecessary. *Duke*, 685 F. App'x at 973, 976. Accordingly, we reiterate our obviousness finding with regard to claim 1 and reconsider our obviousness determination with regard to claim 9 as mandated by the court. *Id.* at 977.

discloses that the precursor form of human GAA "contains motifs which allow efficient receptor-mediated uptake of GAA." *Id.* at 3:62-63.

C. The Challenged Claims on Remand

Claims 1 and 9 provide as follows:

> 1. A method of treating glycogen storage disease type II in a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures.
>
> 9. The method of claim 1, wherein the human acid α-glucosidase is a precursor of recombinant human acid α-glucosidase that has been produced in chinese hamster ovary cell cultures.

D. Obviousness Over Reuser '771 and Van Hove 1997

Petitioner contends that claims 1 and 9 of the '712 patent would have been obvious over Reuser '771 in view of Van Hove 1997. Pet. 26–33. Petitioner provides a claim chart to explain how the references allegedly disclose or suggest claimed subject matter, and relies upon the Pastores Declaration (Ex. 1020) and Croughan Declaration (Ex. 1021), to support its positions. Pet. 26–33,

Appendix 2 (citing Ex. 1004, 9:24–25). Patent Owner responds that Petitioner fails to establish that claims 1 and 9 would have been obvious over the cited prior art (Paper 59, "PO Resp."), relying upon Declarations by Dr. Melissa Wasserstein (Ex. 2019), Dr. Richard Cummings (Ex. 2020), and Mr. Phillip Green (Ex. 2021).

1. Reuser '771 (Ex. 1004)

Reuser '771 relates generally to the production of lysosomal proteins, such as GAA, in the milk of transgenic animals. Ex. 1004, 1:11–2:15. Reuser '771 describes "[g]lycogen storage disease type II (GSD II; Pompe disease; acid maltase deficiency) . . ." as having three clinical forms; infantile, juvenile and adult. *Id.* at 2:13–22. Reuser '771 states that "attempts have been made to treat patients having lysosomal storage diseases by (intravenous) administration of the missing enzyme, i.e., enzyme therapy," and describes prior animal testing involving "intravenously administering purified acid α-glucosidase in phosphorylated and unphosphorylated forms to mice." *Id.* at 2:32–3:4.

In this context, Reuser '771 describes isolating lysosomal enzymes from human and animal sources, and states that an "alternative way to produce human acid α-glucosidase is to transfect the acid α-glucosidase gene into a stable eukaryotic cell line (e.g., CHO) as a cDNA or genomic construct operably linked to a suitable promoter." *Id.* at 3:15–18. Because such production methods can be expensive, however, Reuser '771 describes another approach of using recombinant proteins produced in the milk of a transgenic animal. *Id.* at 3:19–27.

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Reuser '771 teaches that "[t]he proteolytic processing of acid α-glucosidase is complex," and the "main species recognized are a 110/100 kDa precursor, a 95 kDa intermediate and 76 kDa and 70 kDa mature forms." *Id.* at 9:19–26. Reuser '771 teaches further that "post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." *Id.* at 9:29–34.

Examples in Reuser '771 describe constructing transgenic mice that express human GAA, as well as analyzing the activity of hGAA produced in the milk of transgenic mouse lines. *Id.* at 21:14–28:24. In Example 3, recombinant "[a]cid α-glucosidase purified from the milk was [] tested for phosphorylation by administrating the enzyme to cultured fibroblasts from patients with GSD II (deficient in endogenous acid α-glucosidase)." *Id.* at 27:29–32. As also described in this example, "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α-glucosidase purified from bovine testis, human urine and medium of transfected CHO cells." *Id.* at 28:10–14. In addition, "the N-terminal amino acid sequence of the recombinant α-glucosidase produced in the milk of mice *was shown to be the same as that of α-glucosidase precursor from human urine*." *Id.* at 28:20–23 (emphasis added).

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2. Van Hove 1997 (Ex. 1007)

Van Hove 1997 describes a method for purifying recombinant human precursor acid α-glucosidase. Ex. 1007, 613–614. Van Hove 1997 states that "[a]cid α-glucosidase (GAA) (E.C. 3.2.1.20) is synthesized as a 110 kDa precursor enzyme which matures through a 95 kDa endosomal intermediate into 76 and 67 kDA mature lysosomal enzymes." *Id.* at 613. "The precursor 110 kDa acid α-glucosidase isolated from tissue culture medium is endocytosed efficiently via the mannose-6-phosphate receptor, and corrects patient cells in vitro." *Id.* at 613–614.

The reference states that "[l]arge quantities of recombinant acid α-glucosidase are needed for in vivo experimentation of enzyme replacement therapy in Pompe disease," and "eventually for use in medicine." *Id.* It further states that "commonly used purification method of acid α-glucosidase is based on the affinity of the enzyme for the dextran α-1,6 glycosidic bonds, retarding its elution on Sephadex gel," but that, "[i]n contrast to the mature enzyme, the large 110 kDa precursor enzyme separates poorly on [certain Sephadex gels]." *Id.* at 617. It describes a "revised" purification method producing "large quantities" of recombinant hGAA in CHO cells, including recombinant precursor GAA. *Id.* at 613–614, 617. It also states that the disclosed method "is amenable to scale up, and has increased speed, and improved reproducibility with similar high yield and purification efficiency when compared to previous methods." *Id.* at 613. Recombinant human GAA was produced using CHO cells. *Id.* at 614; *see also*, *id.* at 613 ("Recently production in transfected

Chinese hamster ovary cells of large quantities, up to 90 mg/l, of recombinant human acid α-glucosidase has become available.").

When discussing Pompe disease, Van Hove 1997 further states that "[p]atients with the most common infantile form present with a progressive myopathy and hypertropic cardiomyopathy leading to death before age two years." *Id.* at 613.

3. Analysis—claim 1

Petitioner contends that Reuser '771, either alone or in view of Van Hove 1997, discloses or suggests every element of claim 1, citing a claim chart and supporting evidence. Pet. 26–33; Appendix 2. For example, regarding "administering to the individual a therapeutically effective amount of human acid α-glucosidase" recited in claim 1, Petitioner points to teachings in Reuser '771 that disclose administering to a GSD-II patient "from about 0.1 to 10 mg of purified enzyme per kilogram of body weight." Pet. 29–30 (emphasis omitted); Appendix 2; Ex. 1004, 20:9–28. We note that the '712 patent itself similarly describes a "preferred" therapeutically effective amount "in the range of about 1–10 mg enzyme/kg body weight." Ex. 1001, 6:11–17.

Petitioner contends that the only element in challenged claim 1 that is not mentioned expressly in Reuser '771 is administering hGAA "periodically at an administration interval." Pet. 28. Petitioner also contends, however, relying on testimony by Dr. Pastores, that a person of

ordinary skill would have understood "that ERT [enzyme replacement therapy] for GSD-II is not a one shot cure but would require repeated and spaced administrations for the rest of the patient's life." *Id.* (citing Ex. 1020 ¶¶ 60, 61, 84–87, 90, 98).

Patent Owner contends that an ordinary artisan would not have "combined Reuser and Van Hove, *i.e.*, replaced the hGAA produced in transgenic animals described in Reuser with the hGAA produced in CHO cells described in Van Hove," relying on Declarations by Dr. Cummings (Ex. 2020) and Dr. Wasserstein (Ex. 2019). PO Resp. 30–31. We conclude that a preponderance of the evidence establishes otherwise.

We find that Reuser '771 suggests using, in its methods, rhGAA from sources other than milk of transgenic mice, including as produced in CHO cell culture. For example, Reuser '771 teaches that "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α-glucosidase purified from bovine testis, human urine and medium of transfected CHO cells." Ex 1004, 28:10–18. In addition, Van Hove 1997 describes methods for making large quantities of rhGAA in CHO cells, and at least suggests using such rhGAA for the treatment of Pompe disease. Ex. 1007, 613–614. In light of disclosures in the two references, both discussing rhGAA produced in CHO cells and methods of treating Pompe disease, we find that one would have had reason to combine the teachings of those references.

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Patent Owner acknowledges that the above-mentioned statement in Reuser '771 (PO Resp. 31; Ex 1004, 28:10–18), but contends that an ordinary artisan reading the reference would not have thought that hGAA from transgenic mice and CHO cells shared similarities because Reuser '771 "cites only previous *in vitro* studies," and no in vivo data, in support. PO Resp. 31–32. That contention assumes, however, that one would have understood that statements in Reuser '771, indicating that hGAA from both sources (transgenic mice and CHO cells) would work to restore endogenous GAA activity, were affirmatively incorrect in the absence of *in vivo* data. A showing of obviousness here does not require *in vivo* data as "proof" that an otherwise clear statement in Reuser '771 is correct, when it is reasonably based on *in vitro* studies and other information discussed in the reference.

As the Supreme Court has explained:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 402–403 (2007). Here, Reuser '771 identified rhGAA produced in CHO cells, in particular, and, especially in view of Van Hove 1997, provided "good reason to pursue the known

options within his or her technical grasp" using such rhGAA for the treatment of Pompe disease, as taught by Reuser '771, including at the administration doses and intervals disclosed in Reuser '771.

In its Response, Patent Owner also acknowledges that Reuser '771 teaches that "[p]ost translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." PO Resp. 32; Ex 1004, 9:29–34. Patent Owner contends that this statement in Reuser '771 relates to processing of the amino acid sequence of hGAA, but not glycosylation or phosphorylation of hGAA. PO Resp. 32 (citing Ex. 2020 ¶ 136).

Patent Owner's contention in this regard is not persuasive. Reuser '771 includes a section titled "Conformation of Lysosomal Proteins" discussing post translational processing of GAA, which includes glycosylation, phosphorylation, and proteolysis. Ex. 1004, 8:25–10:3. It is in relation to "post translational processing," not just proteolytic processing, that Reuser '771 states that the processing is similar for natural GAA and rhGAA expressed in cultured mammalian cells, such as CHO cells. *Id.* at 8:26–9:34.

Patent Owner also contends that an ordinary artisan reading Van Hove 1997, as well as Van Hove 1996 (Ex. 1016) and Canfield (Ex. 2016), would have understood "the relative inferiority of CHO cells as a source for GAA." PO Resp. 33–35. For example, Patent Owner contends

that Reuser '771 describes that transgenic animals were capable of secreting lysosomal proteins "at high levels of at least 10, 50, 100, 500, 1000, 2000, 5000 or 10,000 μg/ml," while "Van Hove 1997 described the production of GAA using CHO cells in concentrations of up to only 90 μg/ml." *Id*. at 33 (citing Ex. 2020 ¶ 130 (citing Ex. 1004, 17:16–17; Ex. 1007, 613)).

We disagree that Van Hove 1997 describes production in concentrations of up to only 90 μg/ml. Rather, Patent Owner points to where Van Hove 1997 refers to earlier work by others, including Van Hove 1996, producing GAA in such quantities. PO Resp. 33; Ex. 1007, 613. In any event, Van Hove 1997 expressly teaches how to produce rhGAA in CHO cells, and Van Hove 1997 and Reuser '771 both provided the motivation to use such rhGAA in the methods described Reuser '771.

Relying on Van Hove 1996 (Ex. 1016) and Canfield (Ex. 2016), Patent Owner also contends that an ordinary artisan would have had no reason to use hGAA produced in CHO cell cultures in the methods of Reuser '771, and no reasonable expectation of success that rhGAA produced in CHO cells, as taught by Van Hove 1997, would have worked in the methods disclosed in Reuser '771. PO Resp. 34–38. Patent Owner again relies on the alleged teaching in Van Hove 1996 that rhGAA produced in CHO cells were "undesirably taken up by the liver," as well as Canfield's alleged teaching that rhGAA in Van Hove 1996 were not sufficiently phosphorylated. *Id.* at 34–35, 37. As stated in our Decision to Institute, we do not agree with Patent Owner's characterization of those references. Paper 16,

13–15, 28–29. For example, Van Hove 1996 teaches that its rhGAA produced in CHO cells exhibited "strikingly increased enzyme levels in the heart following intravenous injection" in animal *in vivo* studies. Ex. 1016, 69, 2nd col.; Petitioner's Reply to PO Resp. (Paper 67, "Reply") 9. Canfield describes methods for producing "[h]igh mannose lysosomal hydrolases," and methods for treating "lysosomal storage diseases by administering a disease treating amount of the highly phosphorylated lysosomal hydrolases of the present invention to a patient." Ex. 2016, 21:38–22:62. In that context, Canfield describes that "[i]n a preferred embodiment, recombinant human acid alpha glucosidase ('rh-GAA') is prepared by culturing CHO cells secreting rh-GAA in Iscove's Media modified by the addition of an alpha 1,2-mannosidase inhibitor." *Id.* at 22:23–27. In relation to its own hGAA produced in CHO cell cultures, Canfield describes that "74% of the rh-GAA oligosaccharides were phosphorylated," and "[s]ince each molecule of rh-GAA contains 7 N-linked oligosaccharides, 100% of the rh-GAA molecules are likely to contain the mannose-phosphate modification." *Id.* at 22:40–48.

In view of the above, we determine that Petitioner has established by a preponderance of the evidence that an ordinary artisan reading Reuser '771, in view of Van Hove 1997, would have had reason to use rhGAA produced in CHO cells in the methods disclosed in Reuser '771, and would have had a reasonable expectation of success in doing so in view Van Hove 1997.

4. Analysis—claim 9

Petitioner contends that Reuser '771, either alone or in view of Van Hove 1997, discloses or suggests administering a precursor of recombinant human acid α-glucosidase that has been produced in chinese hamster ovary cell cultures. Pet. 30–33, 48–51; Appendix 2. To support its position, Petitioner directs our attention to where Reuser '771 describes recombinant hGAA, including the 110 kDa precursor form of the enzyme. Pet. 30–31 (citing Ex. 1004, 9:30–34; 8:53–54; 9:24–25; 28:19–24; Ex. 1020 ¶ 57; Ex. 1021 ¶¶ 90–94). Petitioner further identifies where Reuser '771 teaches post translational processing of lysosomal precursor proteins and that the post translational processing of natural hGAA is similar to that of recombinant hGAA expressed in CHO cells. *Id.* (citing Ex. 1001, 8:53–54; Ex. 1004, 9:19–34); *see also* Ex. 1004, 1:18–36; Ex. 1020 ¶¶ 49, 56–57, 68–69; Ex. 1021 ¶¶ 79, 90–94. Reuser '771 further teaches that "enzyme therapy is most effective when the enzyme being administered is phosphorylated at the 6' position of a mannose side chain group," and that "[t]he greater accumulation of the phosphorylated form of the enzyme can be explained by uptake being mediated by a mannose-6-phosphate receptor present on the surface of muscle and other cells." Ex. 1004, 2–3 (citing Ex. 1064).

Patent Owner argues that "[n]either Reuser nor Van Hove suggest administering exclusively a precursor of hGAA from CHO cells to treat GSD-II." PO Resp. 36. With regard to Reuser '771, Patent Owner further contends that this reference at most discusses "some similarities between precursors of hGAA from different sources." *Id.*

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Having considered the arguments and evidence of record, we conclude that the preponderance of evidence establishes that a person of ordinary skill in the art would have had reason to administer exclusively a precursor of recombinant hGAA from CHO cells to treat GSD-II. Reuser '771 does more than merely discuss similarities between precursors of hGAA from different sources. Reuser '771 also teaches that recombinant lysosomal proteins, such as hGAA, are preferably processed similarly as naturally occurring lysosomal proteins. Ex. 1004, 8:26–8. Reuser '771 teaches that naturally occurring lysosomal proteins are produced as precursor proteins, containing an N-terminal signal peptide, and undergo a series of post-translational modifications that function to target lysosomal proteins to the lysosomes. *Id.* at 8:26–10:3; Ex. 1020 ¶ 47 ("[I]t was known that α-glucosidase (GAA) occurred in a precursor form and a cleaved mature form; while the mature form was active in the lysosomes, the precursor form was the best form for efficient uptake into cells."). The post-translational modifications include glycosylation and phosphorylation of mannose residues and cleavage of the N-terminal signal peptide. Ex. 1004, 8:26–10:3.

A person of ordinary skill in the art would have understood that these posttranslational modifications are important for the efficient uptake of hGAA into the cells and for proper targeting of the enzyme to the lysosome. Here, we credit the unrebutted testimony of Dr. Pastores "that when GAA is produced for a therapeutic use, either in CHO cells or in the milk of a recombinant mammal, the enzyme should be produced in the precursor form

with the proper glycosylation/ phosporylation of mannose residues." Ex. 1020 ¶ 57; *see also* Ex. 1021 ¶¶ 91–92 ("the rhGAA described by Reuser '771 for therapeutic use would be the 110kd precursor form"); Pet. 31. We further credit the following testimony of Dr. Croughan:

> [0078] By 1995, human α-glucosidase, also called GAA, had been successfully made by recombinant CHO cells, isolated and characterized (Fuller et al, 1995, Ex 1015). In addition, the uptake pathway into the relevant target cells through the mannose-6-phosphate receptor was known for a number of years (Di Marco et al, 1985, Ex 1053; Reuser et al, 1995, p S62-S63, Ex 1039).
>
> . . .
>
> [0079] The best form of recombinant human α-glucosidase for clinical trials would be the 110 kD precursor form, which is properly glycosylated with mannose-6-phosphate groups. Recombinant human α-glucosidase is sometimes called recombinant human GAA (rhGAA).
>
> [0081] As of July 17, 1999, it was known that GAA occurred in a precursor form and cleaved mature form and that while the mature form was active in the lysosomes, the precursor form was the best form for efficient for uptake into cells. It was further known that mannose-

> 6-phosphate moieties were needed for uptake. (Fuller et al, 1995, Ex 1015; Van Hove et al, 1996, Ex 1016). Thus, if I was considering the appropriate form of human α-glucosidase to use in an ERT for Pompe Disease during the time frame in question (i.e., as of July 17, 1999), it was clear based on what was known about human α-glucosidase, that the 110kD precursor form (glycosylated with mannose-6-phosphate residues) was highly preferred and further that forms lacking mannose-6-phosphate residues would be ineffective.
>
> [0082] It was known at the time that the precursor form of the enzyme has the proper mannose-6-phosphorylation for uptake into the lysosomes. Indeed all of the in vitro and preclinical in vivo studies consistently pointed to using the precursor form of the GAA enzyme having mannose-6-phosphate glycosylation (Fuller et al, 1995, Ex 1015; Van Hove et al, 1996, Ex 1016; Bivjoet et al, 1996, 20 Ex 1036; Van Hove et al, 1997, Ex 1007, etc.). For example, the precursor form was used in the preclinical quail studies (Kikuchi et al, Feb. 1998, Ex 1006).

Ex. 1021 ¶¶ 78–82 (emphasis omitted); *see also* Ex. 1020 ¶ 48 ("It was known at the time that the precursor form of the enzyme has the proper mannose-6-phosphorylation for uptake into the lysosomes. Indeed all of the *in vitro* and preclinical *in vivo* studies consistently pointed to using the

precursor form of the GAA enzyme having mannose-6-phosphate glycosylation."); Ex. 2019 ¶ 29 ("Research in the late 1980s and early 1990s focused on identifying the route for intracellular delivery (ultimately determined to be through the mannose- 6-phosphate receptors)."). Teaching in Van Hove 1997 is consistent with this testimony where it states that "precursor 110 kDa acid α-glucosidase isolated from tissue culture medium is endocytosed efficiently via the mannose-6-phosphate receptor, and corrects patient cells in vitro." Ex. 1007, 613–614.

Accordingly, we conclude the preponderance of evidence establishes that a person of ordinary skill in the art would have administered exclusively a precursor of recombinant hGAA as required by claim 9 in order to ensure that the recombinant enzyme was efficiently taken up by cells and mimicked the targeting and activity of the naturally occurring enzyme.

E. Secondary Considerations

We recognize that factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468,

1471–1472 (Fed. Cir. 1984). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17; *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

To be relevant, evidence of non-obviousness must be commensurate in scope with the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971)); *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998). In that regard, in order to be accorded substantial weight, there must be a nexus between the merits of the claimed invention and the evidence of secondary considerations. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). "Nexus" is a legally and factually sufficient connection between the objective evidence and the claimed invention, such that the objective evidence should be considered in determining non-obviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). "The burden of proof as to . . . nexus resides with the patent[owner]." *Id.*; *see Paulsen*, 30 F.3d at 1482. "In meeting its burden of proof, the patent[owner] in the first instance bears the burden of coming forward with evidence sufficient to constitute a prima facie case of the requisite nexus." *Demaco*, 851 F.2d at 1392; *see Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310–11 (Fed. Cir. 2010). "When the patent[owner] has presented a prima facie case of nexus, the burden of coming forward with evidence in rebuttal shifts to the [patent] challenger," i.e., the petitioner. *Demaco*, 851 F.2d at 1393; *Crocs*, 598 F.3d at 1311.

In this case, Patent Owner contends that several lines of objective evidence (or "secondary considerations") demonstrate the non-obviousness of the challenged claims. PO Resp. 55–58. In particular, Patent Owner argues long-felt need and failure by others (*id.* at 56), unexpected results (*id.* at 56–57), licensing (*id.* at 57), commercial success (*id.* at 57–58), and praise and industry acceptance (*id.* at 58).

All of the challenged claims recite a method of treating GSD-II disease by administering hGAA produced in a CHO cell culture. Patent Owner's arguments with regard to each of the secondary considerations, however, fail to establish a nexus between those recited methods and the asserted objective evidence of non-obviousness. Accordingly, the objective evidence does not persuade us that the challenged claims would have been non-obvious. When we balance Petitioner's evidence of obviousness against Patent Owner's asserted objective evidence of non-obviousness, we determine that a preponderance of the evidence supports Petitioner's position that challenged claims would have been obvious over the cited references. Our detailed discussion follows.

1. Licensing, Commercial Success, and Praise and Industry Acceptance

We first note that Patent Owner and its expert, Mr. Green, do not explain adequately how the subject matter of claim 9 of the '712 patent relates to sales of commercially sold products, such as Myozyme and Lumizyme, or any other secondary considerations cited by Patent Owner.

See PO Resp. 56–58; Ex. 2021 ¶¶ 26–59. Patent Owner does not show adequately that Myozyme and Lumizyme are "the invention disclosed and claimed" in claim 9. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (2016). In particular, the record before us also does not elucidate adequately the impact of the '712 patent, as compared to other relevant patents, such as van Bree '410 (Ex. 1005) and '226 patents and the Reuser '045 patent (Ex. 1032), on licensing revenues. *See* Reply 13–14 (citing Ex 2021; Ex 2083, 47–50; Ex. 1144, 14-15; Ex. 1032, 1160); *see also* Ex. 2074, 15 (stating that Myozyme/Lumizyme is "protected by U.S. Patent Numbers 6,118,045, . . . 7,351,410 [(Ex. 1005)], . . . and 7,655,226.").

Thus, Patent Owner's commercial success analysis is insufficient to overcome Petitioner's showing of obviousness here, in part, because Patent Owner does not sufficiently establish a nexus between the sales of Myozyme and Lumizyme and the claims of the '712 patent, as compared to the features of those products covered by other patents. *See* Ex. 1032, 1160. We cannot conclude from the evidence before us what portion of the sales, if any, are due to the merits of the invention of the '712 patent and not, for example, the van Bree patent (Ex. 1005). *J.T. Eaton*, 106 F.3d at 1571 (Fed. Cir. 1997) ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art."). Accordingly, we are not persuaded that Patent Owner's evidence of commercial success supports the non-obviousness of the challenged claims.

Moreover, in relation to licensing, as noted by Petitioner, Patent Owner does not discuss or address whether other patents or intellectual property might have been involved in the "two significant rights transfers" mentioned by Patent Owner. PO Resp. 57; Reply 13. Likewise, the record before us does not show adequately a nexus between what is recited in the challenged claims of the '712 patent in particular and the commercial success of Myozyme/Lumizyme or the asserted praise and industry acceptance. PO Resp. 57–58 (citing Ex. 2021 ¶ 57, 36). For instance, although Patent Owner points us to a Declaration by Mr. Green discussing Myozyme/Lumizyme sales and royalty rates, Patent Owner does not explain adequately, or point us to where the Declaration addresses the required nexus. *Id*. Consequently, we cannot conclude from the evidence before us what portion of the licensing sales or praise is due to the merits of the invention of the '712 patent and not, for example, the van Bree patent (Ex. 1005).

In view of the above, we determine that Petitioner has presented sufficient evidence to rebut any presumption of nexus between the commercial success, licensing, and praise of Myozyme and Lumizyme and the claimed invention. Reply 14, citing Exs. 1005, 1032, 1144, 1160.

2. Long-Felt Need and Failure By Others

With regard to long-felt need and failure by others, Patent Owner contends as follows:

> It is a point of agreement among the experts that, for decades prior to 2000, researchers had attempted without success to devise therapeutic treatment for Pompe disease based on enzyme replacement therapy. (*See, e.g.*, Ex. 1020, Pastores Decl. ¶¶22-25; Ex. 2019, Wasserstein ¶¶117-118.) As noted by Dr. Wasserstein, "there had been a lengthy history of failed attempts by others to devise such a treatment," and "[m]any patients died, over the years, because there was no effective therapeutic treatment available." (Ex. 2019, Wasserstein ¶117.) In this long wake of failures by others, the '712 Patent provides the first disclosure of successful therapeutic treatment for Pompe disease with hGAA produced in CHO cell cultures.

PO Resp. 56.

The record shows that, for decades prior to 1995, the year Reuser '771 was filed, researchers attempted to develop therapeutic treatment for Pompe disease based on enzyme replacement therapy. Ex. 1020 ¶¶ 13–30; Ex. 1021 ¶¶ 77–100; Ex 2019 ¶ 29. The record also shows that a major technical hurdle in the early years of that research was identifying a route for intracellular delivery. *Id.* A major breakthrough in the development of a therapeutic treatment for Pompe disease was thus the identification of the uptake pathway into the relevant target cells through the mannose-6-phosphate receptor. *Id.*; Ex. 1004, 2 ("For lysosomal diseases other than Gaucher disease the evidence suggests that enzyme therapy is most effective

when the enzyme being administered is phosphorylated at the 6' position of a mannose side chain group."); Ex. 1007, 613–4 ("The precursor 110 kDa acid α-glucosidase isolated from tissue culture medium is endocytosed efficiently via the mannose-6-phosphate receptor, and corrects patient cells in vitro."). The record before us sufficiently establishes that by 1997, the remaining obstacle for successful treatment of human patients, identified and addressed by van Hove 1997, was the production of sufficient quantities of enzyme. Ex. 1007, Summary; *see also* Ex. 1030 ¶ 30; Ex. 1021, ¶ 110; Ex 1039, 7.

In view of the above, we find that Patent Owner does not provide evidence sufficient to permit a determination as to what long-felt need was met by any alleged novel feature of the claims of the '712 patent. As such, the record before us does not sufficiently indicate that the claimed subject matter itself satisfied a long-felt need. *See Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem."); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness."); *accord In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977); *see also In re Piasecki*, 745 F.2d 1468, 1475 (Fed. Cir. 1984) (finding patent owner must present affidavits or other factual evidence of "a failure of others to provide a feasible solution to [a] longstanding problem" and evidence "that experts did not foresee" the solution claimed). As such,

we are not persuaded that Patent Owner's evidence of long-felt need sufficiently supports the non-obviousness of the challenged claims.

3. Unexpected Results

With regard to unexpected results, Patent Owner contends as follows:

> Dr. Wasserstein has opined that the invention claimed by the '712 Patent has "proved more successful than anyone could reasonably have expected." (Exhibit 2019, Wasserstein ¶¶118–119.) The methods taught by the '712 Patent "not only provided therapeutic relief (and made the difference between life and death for patients) but enabled many patients to lead reasonably normal and productive lives. These results far surpassed what a POSA would have anticipated and were truly unexpected." (Id.) These unexpected results are additional objective indicia of non-obviousness for the claims of the '712 Patent.

PO Resp. 56–7.

Patent Owner's arguments do not persuade us that a person of ordinary skill in the art would not have determined the results of the methods of claims 1 and 9 to be unexpected in view of state of the art at the time of the invention. For example, Patent Owner does not explain adequately why the "successful therapeutic treatment for

Pompe disease with hGAA produced in CHO cell cultures" as disclosed in the '712 patent would have been unexpected upon reading Reuser '771, in view of Van Hove 1997 and other references, or how the subject matter of '712 patent overcame a "failure of others." *Id.* at 56–57. For instance, the record before us indicates no evidence that the method taught in Reuser '771 (Ex. 1004, 18:11–20:28), using rhGAA produced in CHO cells as suggested in Reuser '771 and Van Hove 1997, would not have been expected to work in human patients in view of positive in vitro and in vivo data demonstrating the effectiveness of the methodology. Ex. 1020 ¶¶ 39, 45–51, 69, 73, 79, 99; Ex. 1021 ¶ 82.

III. CONCLUSION

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude Petitioner has established by a preponderance of the evidence that an ordinary artisan reading Reuser '771, in view of Van Hove 1997, with knowledge of Van Hove 1996, Canfield and other references discussed herein, would have had reason to use rhGAA produced in CHO cells, as taught by Van Hove 1997, in the methods disclosed in Reuser '771, and would have had a reasonable expectation of success in doing so, in view of those references. Accordingly, Petitioner has established by a preponderance of the evidence that claims 1 and 9 of the

'712 patent would have been obvious over Reuser '771, in view of Van Hove 1997.

IV. ORDER

Accordingly, the Order of the Board's February 23, 2015 Final Written Decision is hereby amended as follows:

ORDERED that claim 9 of U.S. Patent No. 7,056,712 has been shown to be unpatentable; and

FURTHER ORDERED that, because this is a final decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

APPENDIX C — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED APRIL 25, 2017

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

DUKE UNIVERSITY,

Appellant

v

BIOMARIN PHARMACEUTICAL INC.,

Appellee

2016-1106

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00535.

April 25, 2017, Decided

Before LOURIE, O'MALLEY, and TARANTO,
Circuit Judges.

OPINION

LOURIE, *Circuit Judge.*

Duke University ("Duke") appeals from the decision of the U.S. Patent and Trademark Office ("PTO") Patent

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Trial and Appeal Board ("Board") in an *inter partes* review ("IPR") holding claims 1-9, 11, 12, 15, and 18-21 of U.S. Patent 7,056,712 (the "'712 patent") unpatentable. *See BioMarin Pharm. Inc. v. Duke Univ.*, No. IPR2013-00535, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196 (P.T.A.B. Feb. 23, 2015) ("*Board Decision*"), *aff'd on reh'g*, 2015 WL 4467381 (P.T.A.B. July 14, 2015) ("*Rehearing Decision*"). Because the Board erred in holding claims 9 and 19 unpatentable, but did not otherwise err, we *affirm in part, reverse in part, vacate in part*, and *remand*.

Background

I. The '712 Patent

Duke owns the '712 Patent, directed to methods for treating glycogen storage disease type II ("GSD-II" or "Pompe disease") using enzyme replacement therapy. '712 Patent col. 2 ll. 45-50. Pompe disease is a genetic disorder affecting muscles caused by a deficiency of acid α-glucosidase ("GAA"), a lysosomal enzyme that breaks down glycogen. *Id.* col. 1 ll. 12-15. The deficiency results in the accumulation of lysosomal glycogen in most of the body's tissues and most seriously affects the cardiac and skeletal muscles. *Id.* col. 1 ll. 20-22.

Pompe disease has multiple forms. *Id.* col. 1 ll. 28-44. The most severe form is infantile, which is characterized by less than 1% of normal GAA activity. *Id.* Affected individuals with the infantile form usually die of cardiac failure by one year of age. *Id.*

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The '712 Patent describes the successful treatment of three infants suffering from infantile Pompe disease by administering recombinant human GAA ("rhGAA") twice weekly to the infants. *Id.* col. 2 ll. 50-55, col. 6 l. 59-col. 12 l. 26. The patent discloses that the "rhGAA was purified primarily as the 110-kD precursor protein" and was produced in Chinese hamster ovary ("CHO") cell cultures. *Id.* col. 8 ll. 48-55. The patent explains that administration in "precursor form" is a "preferred embodiment" because "the precursor contains motifs which allow efficient receptor-mediated update of GAA." *Id.* col. 3 ll. 60-63; *see also id.* col. 2 ll. 4-9. Additionally, rhGAA produced in CHO cells is "a particularly preferred embodiment." *Id.* col. 4 ll. 1-4.

The treated "infants demonstrated improvement of cardiac status, pulmonary function, and neurodevelopment, as well as reduction of glycogen levels in tissue." *Id.* col. 2 ll. 53-55; *see also id.* col. 9 l. 64-col. 12 l. 14. Two of the three infants developed anti-rhGAA antibodies after the initiation of enzyme replacement therapy. *Id.* col. 9 ll. 54-59, Figs. 1A-1C. As the amount of anti-rhGAA antibodies increased in the two infants, the "clinical improvements (noted early during therapy . . .) were no longer advancing." *Id.* col. 9 ll. 59-61.

The '712 Patent teaches that GAA can be administered in conjunction with other agents, e.g., "immunosuppressants or other immunotherapeutic agents which counteract anti-GAA antibodies." *Id.* col. 5 ll. 29-33. It states that "[i]n a particularly preferred embodiment, the immunosuppressive or immunotherapeutic regime is

begun prior to the first administration of GAA, in order to minimize the possibility of production of anti-GAA anti-bodies." *Id.* col. 5 ll. 55-59.

Claims 1 and 20 are the only independent claims, are illustrative of what is claimed, and read as follows:

> 1. A method of treating glycogen storage disease type II in a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese [sic] hamster ovary cell cultures.

Id. col. 12 ll. 45-51.

> 20. A method of treating cardiomyopathy associated with glycogen storage disease type II in an human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese [sic] hamster ovary cell culture.

Id. col. 14 ll. 13-19.

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Claims 9 and 18 depend from claim 1. Claim 9 contains the additional limitation "wherein the human acid α-glucosidase is a *precursor* of recombinant human acid α-glucosidase that has been produced in chinese [sic] hamster ovary cell cultures." *Id.* col. 13 ll. 9-12 (emphasis added). Claim 18 adds "wherein the human acid α-glucosidase is administered in conjunction with an immunosuppressant." *Id.* col. 14 ll. 7-9. Claim 19 depends from claim 18 and further adds "wherein the immunosuppressant is *administered prior to any administration* of human acid α-glucosidase to the individual." *Id.* col. 14 ll. 10-12 (emphasis added).

II. The Board's Final Written Decision

BioMarin Pharmaceutical Inc. ("BioMarin") filed a petition for IPR of claims 1-9, 11, 12, 15, and 18-21 of the '712 Patent. The Board instituted review and ultimately held that all of the challenged claims are unpatentable as anticipated by U.S. Patent 7,351,410 ("van Bree") and/or as obvious over PCT Publication WO 97/05771 ("Reuser") in view of Johan L.K. Van Hove et al., *Purification of Recombinant Human Precursor Acid* α*-Glucosidase*, 43(3) BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL 613-23 (1997) ("Van Hove") either alone or in combination with other references, including Roscoe O. Brady et al., *Management of Neutralizing Antibody to Ceredase in a Patient with Type 3 Gaucher Disease*, 100(6) PEDIATRICS e11 (1997) ("Brady").

The Board construed certain claim limitations, including "precursor" in claim 9 and "administered prior

to any administration" in claim 19. The Board noted that Duke "proposes that the term 'precursor' in claim 9 means 'any precursor of recombinant hGAA (e.g. a 110-kD form)' that is 'exclusively . . . produced in CHO cell cultures.'" *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *4 (alteration in original). The Board "agree[d]" with this construction, but clarified that "[n]either claim 1 nor claim 9 precludes administering a non-precursor form of hGAA or rhGAA . . . ." *Id.* The Board construed "administered prior to any administration" in claim 19 "to refer to administering an immunosuppressant prior to the first administration of hGAA to the individual." *Id.*

A. The Prior Art

van Bree and Reuser disclose methods of producing rhGAA in transgenic mammals and its use in enzyme replacement therapy to treat Pompe disease. van Bree col. 2 ll. 33-36, col. 4 ll. 54-55; Reuser p. 4 ll. 14-37, p. 18 ll. 12-14. They both disclose that the main species of hGAA are a 110/100 kD precursor, a 95kD intermediate, and 76 kD and 70 kD mature forms. van Bree col. 6 ll. 6-8; Reuser p. 9 ll. 24-26. van Bree states that administration of GAA "is preferably predominantly (i.e., >50%) in the precursor form of about 100-110 kD." van Bree col. 13 ll. 48-50. van Bree and Reuser state that CHO cells are an alternative way to produce hGAA, but note disadvantages—labor and expense, respectively—with this approach. van Bree col. 13 ll. 58-64; Reuser p. 3 ll. 15-22.

Both references describe the post-translational processing of GAA, including glycosylation and

phosphorylation. They recognize the function of GAA mannose 6 phosphate in mediating transport of lysosomal proteins. van Bree col. 5 ll. 54-57, col. 6 ll. 17-24; Reuser p. 9 ll. 6-9, p. 9 l. 35-p. 10 l. 3. Both explain that "post translational processing of natural [hGAA] and of recombinant forms of [hGAA] as expressed in cultured mammalian cells like . . . CHO cells is similar." van Bree col. 6 ll. 11-15; Reuser p. 9 ll. 30-33. Both state that "restoration of the endogenous [GAA] activity by [GAA] isolated from mouse milk was as efficient as restoration by [GAA] purified from bovine testis, human urine and medium of transfected CHO cells." van Bree col. 20 ll. 32-36; Reuser p. 28 ll. 11-14.

Van Hove teaches a method for purifying large quantities of rhGAA expressed in CHO cells for use in Pompe disease enzyme replacement therapy. J.A. 491. Van Hove states that "precursor 110 kD [GAA] isolated from tissue culture medium is endocytosed efficiently via the mannose-6-phosphate receptor, and corrects patient cells in vitro." J.A. 491-92.

Brady discloses administering an immunosuppressant to treat an immune response to enzyme replacement therapy in the treatment of Gaucher disease with Ceredase. J.A. 526. Gaucher disease is a genetic disorder caused by a deficiency of the lysosomal enzyme glucocerebrosidase. *Id.*; Reuser p. 1 l. 37-p. 2 l. 9.

B. The Rejections

The Board found that van Bree anticipates claims 1-9, 12, 15, 20, and 21. It rejected Duke's argument that

an ordinary artisan would have understood that the administration amounts and intervals disclosed in van Bree for transgenic mice would not have been applicable to hGAA produced in CHO cell cultures because of the difference in properties, e.g., glycosylation and phosphorylation patterns, of hGAA produced in transgenic animals and CHO cells. *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *10. The Board explained that "van Bree '410 itself indicates hGAA produced in CHO cells would have similar characteristics as hGAA produced in transgenic mice, including glycosylation and phosphorylation patterns." *Id.* It ultimately found that van Bree "describes administering hGAA produced in CHO cell cultures to patients in the same manner, i.e., using the same amounts and dosage intervals, as described for hGAA produced in transgenic animals." 2015 Pat. App. LEXIS 2305, [WL] at *11.

Regarding claim 9, the Board reiterated that its construction of "precursor" "encompass[es] administering both precursor and non-precursor forms of rhGAA at the same time, and [is] not limited to administering exclusively a precursor form and no other form." 2015 Pat. App. LEXIS 2305, [WL] at *12. The Board found that "van Bree '410 describes administering a precursor of recombinant hGAA produced in CHO cell cultures, even assuming that the reference [only] teaches administering a mixture which is preferably predominantly (i.e., >50%) in the precursor form of about 100-110 kD." *Id.* (internal quotations omitted).

The Board also concluded that claims 1-9, 11, 12, 15, and 18-21 were unpatentable as obvious over Reuser in

view of Van Hove, either alone or in combination with other references, including Brady. The Board found that a skilled artisan would have had reason to combine the teachings of Reuser and Van Hove because "both discuss[] rhGAA produced in CHO cells and methods of treating Pompe disease." 2015 Pat. App. LEXIS 2305, [WL] at *18. The Board explained that "Reuser '771 identified rhGAA produced in CHO cells, in particular, and, especially in view of Van Hove 1997, provided 'good reason to pursue the known options within his or her technical grasp' using such rhGAA for the treatment of Pompe disease, as taught by Reuser '771, including at the administration doses and intervals disclosed in Reuser '771." *Id.* (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 402-03, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007)).

The Board rejected Duke's contention that a skilled artisan would have understood CHO cells to be a relatively inferior source of GAA based on the amounts of GAA disclosed as being produced in Van Hove (90 μg/ml) and Reuser ("at least . . . 10,000 μg/ml"). 2015 Pat. App. LEXIS 2305, [WL] at *19 (quoting Patent Owner Response at 33). The Board found that Van Hove did not "describe[] production in concentrations of up to only 90 μg/ml." *Id.* The Board again rejected Duke's arguments premised on the alleged differences between hGAA produced in transgenic mammals and hGAA produced in CHO cell cultures and found that a skilled artisan would have had a reasonable expectation of success in combining Reuser and Van Hove. 2015 Pat. App. LEXIS 2305, [WL] at *20.

Regarding claim 9, the Board found that Reuser recites a precursor form of rhGAA and teaches that the

main species of GAA include a 110/100 kDa precursor. 2015 Pat. App. LEXIS 2305, [WL] at *16. The Board did not discuss whether Reuser discloses administering exclusively a precursor of rhGAA.

As for claim 19, the Board found that "Brady teaches administering both enzyme and immunosuppressant on 'Day 1,' i.e., the first day of treatment in the individual" and "again prior to subsequent administrations of the enzyme." 2015 Pat. App. LEXIS 2305, [WL] at *26. The Board explained that "Brady teaches administering the immunosuppressant in this fashion in an 'effort to immunosuppress the patient' and reduce neutralizing antibodies in the individual." *Id.* (quoting Brady 3). Thus, the Board concluded that claims 18 and 19 would have been obvious over Reuser in view of Van Hove and Brady.

The Board also considered Duke's evidence relating to objective indicia of nonobviousness, but found that none of it was persuasive. 2015 Pat. App. LEXIS 2305, [WL] at *27. Duke alleged that long-felt need, failure of others, unexpected results, licensing, commercial success, praise, and industry acceptance evidenced the nonobviousness of the claims, but the Board found that Duke failed to establish a nexus between the claims and the proffered objective indicia. *Id.*

III. The Board's Rehearing Decision

The Board granted Duke's request for rehearing to reconsider the teachings of Brady in relation to the subject matter of claim 19, and modified its analysis. On

rehearing, all three administrative patent judges ("APJs") agreed that "Brady does not disclose administering immunosuppressant prior to any and all administration of hGAA, as required by claim 19." *Rehearing Decision*, 2015 WL 4467381, at *4 (majority opinion), *9 (APJ Bonilla, dissenting). Despite this modification to its previous factual findings, a split panel still held that claim 19 would have been obvious over Reuser in view of Van Hove and Brady.

The majority explained that "[t]he choice of administering immunosuppressant before an adverse immune response develops in a patient, or after a patient has experienced an adverse immune response, are predictable variations producing the same result—prevention of an adverse immune response to foreign protein." *Id.* at *8. The majority relied on the testimony of Dr. Pastores, one of BioMarin's experts, in reaching its obviousness conclusion.

The dissenting APJ would have held that BioMarin failed to meet its burden with respect to claim 19. The APJ concluded that "[n]either [BioMarin] in its Petition or Reply, nor Dr. Pastores in his cited testimony adequately explains, however, how Brady (or Grabowski) teaches or suggests administering an immunosuppressant to a patient before the patient has exhibited any sign of an adverse reaction to the enzyme therapy." *Id.* at *11 (APJ Bonilla, dissenting). The APJ explained that "[w]hile Dr. Pastores' conclusory statements may indicate what 'could be' done if 'there is a high incidence' of antibody response, he does not explain, nor provide evidence showing, what

an ordinary artisan *would have done* in this regard prior to the filing date of the '712 Patent, or what one *would have understood* in relation to incidents of 'high antibody titers' in response to exogenous enzyme therapy." *Id.* (APJ Bonilla, dissenting) (emphases in original).

Duke timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).

Discussion

We review the Board's legal determinations de novo, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), but we review the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding. *Consol. Edison Co. of New York v. NLRB*, 305 U.S. 197, 229, 59 S. Ct. 206, 83 L. Ed. 126 (1938).

I. Anticipation

We first address Duke's argument that the Board erred in finding that van Bree anticipated claims 1-9, 12, 15, 20, and 21 of the '712 Patent. Anticipation is a question of fact that we review for substantial evidence. *In re Rambus, Inc.*, 753 F.3d 1253, 1256 (Fed. Cir. 2014). A prior art document may anticipate a claim if it describes every element of the claimed invention, either expressly or inherently. *Husky Injection Molding Sys. Ltd. v. Athena Automation Ltd.*, 838 F.3d 1236, 1248 (Fed. Cir.

2016). An anticipatory reference must be enabled, but "no 'actual creation or reduction to practice' is required." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380-81 (Fed. Cir. 2003)).

Because Duke does not argue dependent claims 2-8, 12, 15, and 21 "separately or attempt to distinguish them from the prior art," these "dependent claims stand or fall with their attendant independent claim." *In re Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1330 n.3 (Fed. Cir. 2016); *see also In re Margolis*, 785 F.2d 1029, 1030 (Fed. Cir. 1986) (stating that where dependent claims "were not argued separately, [they] need not be separately considered").

A. Independent Claims 1 and 20

Duke argues that the Board's anticipation findings were not supported by substantial evidence. Duke contends that van Bree does not disclose administering hGAA derived from CHO cells to human patients with Pompe disease in a therapeutically effective amount, periodically at administration intervals, as required by the independent claims. Duke challenges the applicability of teachings "focus[ed]" on hGAA produced in "the milk of transgenic nonhuman animals" to hGAA produced in CHO cell cultures. Appellant's Br. 41. Duke asserts that no expert opined that van Bree disclosed all the limitations of any claim.

BioMarin responds that substantial evidence does support the Board's findings. BioMarin contends that van

Bree discloses all of the limitations in the independent claims and that actual reduction to practice of the claimed methods is not required for there to be an anticipation. BioMarin asserts that the Board was free to independently assess the teachings of van Bree and was not required to rely on expert testimony.

We agree with BioMarin that the Board's anticipation findings with respect to claims 1 and 20 were supported by substantial evidence. van Bree states that "the invention provides methods of treating a patient with Pompe's disease" that "entail administering to the patient a therapeutically effective amount of [hGAA]." van Bree col. 2 ll. 33-36. van Bree provides dosage amounts and periodic administration intervals for administering hGAA. *See, e.g., id.* col. 2 ll. 36-42, col. 14 ll. 1-29. van Bree states that the "[hGAA] is preferably obtained in the milk of a nonhuman transgenic mammal," *id.* col. 2 ll. 43-45, and provides examples of producing and testing hGAA from transgenic mice and rabbits, *id.* col. 16 l. 20-col. 24 l. 7. van Bree also contains examples discussing human clinical trials in which hGAA was or would be administered that do not specify the source of the hGAA. *Id.* col. 24 l. 10-col. 26 l. 67. The question thus is whether the Board correctly found that van Bree's teachings, which focus on hGAA produced by transgenic mammals, are applicable to hGAA produced in CHO cells, as required by the independent claims.[1]

1. We note that Duke has not raised an enablement challenge to van Bree and that, in any event, proof of efficacy or an actual reduction to practice using CHO cell cultures is not required for a reference to be an anticipation of the challenged method of treatment claims. *In re Gleave*,

We conclude that the disclosure in van Bree supports the Board's finding that its teachings applied to GAA produced in CHO cell cultures. van Bree links its teachings to CHO cell cultures with respect to structure and post translational processing, including glycosylation and phosphorylation. *See id.* col. 5 l. 35-col. 6 l. 24. It explains that "post translational processing of natural [hGAA] and of recombinant forms of [hGAA] as expressed in . . . CHO cells is similar." *Id.* col. 6 ll. 11-15. In the "Therapeutic Methods" section, van Bree teaches that a CHO cell line is "an alternative way to produce [hGAA]." *Id.* col. 13 ll. 58-60. In an example, van Bree reports that "restoration of the endogenous [GAA] activity by [GAA] isolated from mouse milk was as efficient as restoration by [GAA] purified from . . . CHO cells." *Id.* col. 20 ll. 32-36. Those statements constitute substantial evidence supporting the Board's finding that van Bree "describes administering hGAA produced in CHO cell cultures to patients in the same manner, i.e., using the same amounts and dosage intervals, as described for hGAA produced in transgenic animals." *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *11.

Expert testimony was not necessary to support the Board's anticipation determination. Here, the disclosures of van Bree alone were sufficiently clear and on point to constitute substantial evidence to support the Board's anticipation findings. Thus, the Board "could permissibly 'rely on its own reading of [van Bree]—supported by

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560 F.3d at 1334; *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (explaining "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation").

the Petition's observations about it'—to find that the [limitations] were disclosed." *In re NuVasive, Inc.*, 841 F.3d 966, 973 (Fed. Cir. 2016) (quoting *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1074 (Fed. Cir. 2015)).

Duke also argues that the Board "acted outside its statutory authority in instituting an IPR and in its Final Decision by adopting anticipation theories that BioMarin never raised." Appellant's Br. 46. We reject this argument on its merits insofar as it challenges the Board's final decision.

BioMarin argued in the petition that van Bree anticipates the relevant claims and did not limit its arguments to the claim construction position rejected by the Board. *See* J.A. 146-50 (BioMarin's Petition). Duke had an opportunity to, and did in fact, respond to those arguments. *See* J.A. 263-75 (Duke's Patent Owner Response). Thus, the Board properly "base[d] its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). That conclusion leaves no live issue as to Duke's challenge to the institution decision on the very same ground: that challenge is either unreviewable or, if reviewed, incorrect (for the reason just stated), and so could not benefit Duke.

B. Dependent Claim 9

Duke argues that under a correct construction of "precursor" van Bree does not anticipate claim 9 and

that the correct construction is "exclusively a precursor of recombinant hGAA that has been produced in CHO cell cultures." Appellant's Br. 46. Duke asserts that this construction is supported by the written description and the closed transitional term "is" preceding "precursor" in claim 9. Duke contends that the Board properly adopted this construction, but then improperly applied it. Specifically, Duke asserts that the Board erred by applying "a scope for claim 9 that 'encompass[es] administering both precursor and non-precursor forms of rhGAA at the same time, and [is] not limited to administering exclusively a precursor form and no other form.'" *Id.* at 47 (quoting *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *12). Duke also argues that BioMarin waived any challenge to Duke's construction by not proposing an alternative during the IPR.

Applying its proposed construction of "precursor," Duke argues that van Bree does not anticipate claim 9 because van Bree does not disclose administering rhGAA produced from CHO cells exclusively in precursor form. Duke contends that van Bree describes a mixture of precursor and non-precursor forms.

BioMarin responds that the Board properly construed "precursor" as "any precursor of recombinant hGAA (e.g., a 110-kD form) that is exclusively produced in CHO cell cultures," and that under that construction van Bree anticipates claim 9. Appellee's Br. 56. BioMarin contends that the Board cited "*part* of" Duke's proposed construction, but "did not adopt the entirety" of it as "made clear by the use of ellipses and reinforced" by the

Board's statements about the scope of the language. *Id.* (emphasis in original). BioMarin asserts that the record does not support limiting claim 9 to the administration of exclusively precursor and no other form of GAA.

We begin with Duke's argument relating to the proper construction of the term "precursor" in claim 9. In an IPR, a patent claim is given "its broadest reasonable construction in light of the specification of the patent in which it appears." *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142, 195 L. Ed. 2d 423 (2016) (quoting 37 C.F.R. § 42.100(b)). "[W]e review the Board's ultimate claim constructions de novo and its underlying factual determinations involving extrinsic evidence for substantial evidence." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1297 (Fed. Cir. 2015) (citing *Teva Pharms. USA Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841-42, 190 L. Ed. 2d 719 (2015)). Here, because the intrinsic record alone determines the proper construction of "precursor," we review the Board's construction de novo. *See Shire Dev., LLC v. Watson Pharms., Inc.*, 787 F.3d 1359, 1364, 1368 (Fed. Cir. 2015) (citing *Teva*, 135 S. Ct. at 840-42).

As an initial matter, we agree with BioMarin that the Board construed "precursor" to mean any precursor of recombinant hGAA (e.g., a 110-kD form) that is exclusively produced in CHO cell cultures. The Board made clear that its construction was not limited to administration of exclusively precursor rhGAA, *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *4 ("Neither claim 1 nor claim 9 precludes administering a non-precursor form of hGAA or rhGAA . . . ."), *12 ("[W]e construe

'precursor' in claim 9 . . . as encompassing administering both precursor and non-precursor forms of rhGAA at the same time, and not limited to administering exclusively a precursor form and no other form.").

However, our agreement with BioMarin as to what the Board held is not the same as agreeing with the Board's holding. On this point, we disagree with the Board's construction and agree with Duke that the proper construction of "precursor" in claim 9 is "exclusively a precursor of recombinant hGAA that has been produced in CHO cell cultures." Claim 9 requires that "*the* [hGAA] *is* a precursor" and refers to claim 1 for the antecedent basis of "the [hGAA]." '712 Patent col. 13 ll. 9-12 (emphases added). That sentence structure makes clear that the "is a precursor" phrase limits the form of hGAA to a precursor form. The claim language and structure thus support the conclusion that "the [hGAA]" in claim 9 is exclusively a precursor of hGAA.

The written description also supports Duke's proposed construction. The patent repeatedly refers to "precursor" as a "form" of GAA. *See id.* col. 2 ll. 4-9, col. 3 ll. 58-67, col. 12 ll. 20-22. The patent teaches administering a particular form of hGAA, e.g., precursor form, with certain characteristics, i.e., "a form that . . . targets tissues . . . affected by the disease." *Id.* col. 3 ll. 57-67. When referring to particular forms of GAA, it does not describe administering a mixture of those forms. Specifically, it states:

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> In the methods of the invention, human acid α-glucosidase (GAA) is administered to the individual. The GAA is in *a form* that, when administered, targets tissues such as the tissues affected by the disease (e.g., heart, muscle). In one preferred embodiment, the human GAA is administered in its *precursor form*, as the precursor contains motifs which allow efficient receptor-mediated uptake of GAA. Alternatively, a *mature form* of human GAA that has been modified to contain motifs to allow efficient uptake of GAA, can be administered. In a particularly preferred embodiment, the GAA is the *precursor form* of recombinant human GAA.

Id. (emphases added). Thus, the written description also supports a conclusion that "precursor" in claim 9 refers to exclusively a precursor form of hGAA. The Board erred in concluding otherwise.

Applying the correct construction, we agree with Duke that van Bree does not disclose a "precursor." The Board did not find that van Bree discloses administering exclusively a precursor of rhGAA produced in CHO cell cultures. *See Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *12. And BioMarin does not argue on appeal that van Bree's disclosure teaches the "precursor" limitation of claim 9 under the correct construction. Thus, we reverse the Board's finding that claim 9 was anticipated.

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II. Obviousness

We now turn to Duke's arguments that the Board erred in concluding that claims 1-9, 11, 12, 15, and 18-21 were unpatentable as obvious over Reuser in view of Van Hove, either alone or in combination with other references, including Brady. Because addressing Duke's arguments relating to whether van Bree anticipates claims 1 and 20 resolves this appeal, except with respect to claims 9 and 19, we need not address Duke's arguments relating to the Board's conclusion that claims 1 and 20 were unpatentable as obvious. Duke does not argue dependent claims 2-8, 11, 12, 15, 18, and 21 "separately or attempt to distinguish them from the prior art," so these "dependent claims stand or fall with their attendant independent claim." *In re Warsaw Orthopedic*, 832 F.3d at 1330 n.3; *see also In re Margolis*, 785 F.2d at 1030.

However, we need to address the obviousness question with respect to claims 9 and 19. Obviousness is a question of law, based on underlying factual findings, including what a reference teaches, whether a person of ordinary skill in the art would have been motivated to combine references, and any relevant objective indicia of nonobviousness. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1047-48, 1051 (Fed. Cir. 2016) (en banc).

A. Dependent Claim 9

Duke argues that under the correct construction of "precursor," Reuser in view of Van Hove does not render claim 9 unpatentable as obvious. Duke contends that

neither reference teaches or suggests administering rhGAA produced from CHO cells exclusively in precursor form.

BioMarin responds that, even under Duke's construction of "precursor," Reuser in view of Van Hove would have rendered claim 9 obvious. BioMarin contends that both of its experts testified that the highly purified active precursor form should be administered to patients, and the art disclosed purification of the 110 kD precursor form of hGAA. Thus, it would have been obvious to use only the active precursor form.

Because we have modified the construction of "precursor," we do not have the benefit of the Board's considered analysis whether claim 9 would have been obvious under the correct construction. Although the Board found that both Reuser and Van Hove disclose precursor rhGAA, *Board Decision*, 2015 Pat. App. LEXIS 2305, 2015 WL 1009196, at *15-16, the Board did not determine whether they teach or suggest administering exclusively a precursor of rhGAA produced in CHO cell cultures. Before the Board, the parties certainly disputed whether claim 9 would have been obvious. For example, BioMarin offered expert testimony to support its contention that Reuser teaches or suggests administration of exclusively a precursor of rhGAA that has been produced in CHO cell cultures. *See, e.g.*, J.A. 561 (Reuser "confirms what was already reported in the literature, i.e., that when GAA is produced for a therapeutic use, either in CHO cells or in the milk of a recombinant mammal, the enzyme should be produced in the precursor form with proper glycosylation/

phosphorylation of mannose residues."); J.A. 641 ("[T]he rhGAA described by [Reuser] for therapeutic use would be the 110kd precursor form."). Thus, we vacate the Board's obviousness conclusion with respect to claim 9 and remand for the Board to apply our claim construction of "precursor."

Duke also argues that there was no motivation to combine Reuser and Van Hove, there was no reasonable expectation of success from that combination, and its proffered objective indicia support a conclusion of nonobviousness. On remand, the Board is to consider these arguments and provide a meaningful discussion of its analysis of them.[2]

B. Dependent Claim 19

Duke argues that the Board's claim 19 obviousness determination is legally deficient and the underlying fact-finding is not supported by substantial evidence because it rests on cursory and conclusory expert testimony. Duke contends that combining Reuser, Van Hove, and Brady would not have yielded the invention of claim 19 because none of the references discloses prophylactically administering an immunosuppressant prior to any administration of enzyme replacement therapy. Duke asserts that the Board's finding that "prophylactically administering an immunosuppressant would have been a 'predictable variation of the [after-the-fact] use of

2. Notably, Duke's objections to the Board's treatment of its evidence of objective indicia of non-obviousness—including its failure to apply a presumption of nexus—appear well taken.

immunosuppressant disclosed in Brady'" was neither supported by any record evidence nor argued by BioMarin. Appellant's Br. 64 (quoting *Rehearing Decision*, 2015 WL 4467381, at *8). Duke also contends that the record lacks a motivation to combine these references and that a skilled artisan would not have had a reasonable expectation of success. Duke further argues that BioMarin's common-sense theory lacks record support and ignores known risks and side effects.

BioMarin responds that prophylactic administration of immunosuppressants was a common sense solution to expected immune responses, informed by experience with other therapeutic proteins, e.g., Gaucher disease, discussed in Brady. BioMarin asserts that the Board properly relied on BioMarin's expert's testimony that a skilled artisan would reasonably have predicted that an adverse immune reaction may occur and would have been motivated to prevent that adverse immune reaction.

We agree with Duke that the Board erred in concluding that claim 19 was unpatentable as obvious. Substantial evidence does not support the Board's finding that "the prophylactic administration of an immunosuppressant would have been a predictable variation of the use of immunosuppressant disclosed in Brady." *Id.* at *8. It is undisputed that the Board correctly found that "Brady does not disclose administering immunosuppressant prior to any and all administration of hGAA, as required by claim 19." *Rehearing Decision*, 2015 WL 4467381, at *4. The expert testimony relied on by the Board to bridge the gap between the disclosure in Brady and claim 19 falls

short of what would have rendered the subject matter of claim 9 obvious.

> BioMarin's expert testified, *inter alia*, that:
>
> > [I]t would not be surprising if a proportion of patients treated with recombinant GAA protein developed an immune response to the recombinant enzyme. In patients with high titers of antibodies against the enzyme, particularly those with neutralizing antibodies, administering an immunosuppressant prior to, with or immediately after the therapeutic enzyme would be considered to mitigate the presence of antibodies and its negative impact. For example, Brady et al. discuss . . . efforts to "immunosuppress" the patient. . . . *If there is a high incidence of patients developing high antibody titers, an immunosuppressant could be administered prophylactically* prior to any administration of the recombinant enzyme begins to minimize the potential adverse effects of such.
>
> J.A. 575-76 (internal citations omitted) (emphasis added).

That testimony falls short because it does not address what an ordinary artisan would have done or understood regarding prophylactic administration of immunosuppressants in the context of GAA enzyme replacement therapy prior to the priority date of the '712 Patent. It merely suggests what "could be" done "if there is a high incidence" of antibody response. *Id.*

Moreover, there was no evidence that "a high incidence of patients" developed, or were expected to develop, "high antibody titers" to GAA enzyme replacement therapy. BioMarin submitted no evidence regarding the incidence of high antibody titers in patients receiving GAA before the '712 Patent. Furthermore, Brady teaches that "[v]ery few patients with Gaucher disease who are treated with [enzyme replacement therapy] develop a neutralizing antibody to the exogenous enzyme" and refers to this phenomenon as "rare." J.A. 526. Brady suggests that its "technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals)," *id.*, but Brady's technique did not involve prophylactic administration of immunosuppressants, *Rehearing Decision*, 2015 WL 4467381, at *4, *9 (APJ Bonilla, dissenting). Thus, the evidence of record does not establish the conditions precedent (a high incidence of patients with high antibody titers to the enzyme) to the prophylactic administration of immunosuppressants according to the expert's testimony. Such conclusory expert testimony cannot support an obviousness conclusion. *See In re Magnum Oil Tools*, 829 F.3d at 1380 ("To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness."). The evidence thus fails to render claim 19 obvious.

Appendix C

Conclusion

We have considered the parties' remaining arguments, but conclude that they are without merit. For the reasons set forth above, we reverse the Board's obviousness determination with respect to claim 19, vacate its obviousness determination with respect to claim 9, reverse its anticipation finding with respect to claim 9, and affirm in all other respects. We remand for proceedings consistent with this opinion.

AFFIRMED IN PART, REVERSED IN PART, VACATED IN PART, AND REMANDED

Costs

No costs.

APPENDIX D — DECISION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, DATED JULY 14, 2015

UNITED STATES PATENT
AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL
AND APPEAL BOARD

Case IPR2013-00535
Patent 7,056,712 B2

BIOMARIN PHARMACEUTICAL INC.,

Petitioner,

v.

DUKE UNIVERSITY,

Patent Owner.

Before LORA M. GREEN, JACQUELINE WRIGHT BONILLA, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

Opinion for the Board filed by *Administrative Patent Judge* SNEDDEN.

Opinion concurring-in-part and dissenting-in-part filed by *Administrative Patent Judge* BONILLA.

SNEDDEN, *Administrative Patent Judge.*

Appendix D

DECISION
Request for Rehearing
37 C.F.R. § 42.71(d)

I. INTRODUCTION

Duke University ("Patent Owner") filed a Request for Rehearing (Paper 87, "Req. Reh'g" or "Request") of our Final Decision (Paper 86, "Final Dec."). Petitioner filed an opposition to Patent Owner's Request. Paper 88. Patent Owner filed a reply in support of its Request. Paper 89 ("PO Reply").

In our Final Decision, we concluded that Petitioner demonstrated by a preponderance of the evidence that claims 1–9, 11, 12, 15, and 18–21 of U.S. Patent No. 7,056,712 B2 (Ex. 1001, "the '712 patent") were unpatentable. Final Dec. 40, 42. Patent Owner requests a rehearing as to our holding that Petitioner demonstrated by a preponderance of the evidence that claim 19 of the '712 patent would have been obvious over Reuser '771 (Ex. 1004)[1] in view of Van Hove 1997 (Ex. 1007)[2] and Brady (Ex. 1012)[3] under 35 U.S.C. § 103. Req. Reh'g 1.

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1. Reuser et al., WO 97/05771, published Feb. 20, 1997.

2. Van Hove et al., *Purification of recombinant human precursor acid α-glucosidase*, 43(3) Biochemistry & Molecular Biology Int'l 613–623 (1997).

3. Brady et al., *Management of Neutralizing Antibody to Ceredase in a Patient With Type 3 Gaucher Disease*, 100(6) Pediatrics e11 (1997).

For the reasons discussed below, we grant Patent Owner's Request for Rehearing to reconsider the teachings of Brady in relation to the subject matter of claim 19. We modify our analysis in determining that Petitioner has demonstrated by a preponderance of the evidence that claim 19 of the '712 patent would have been obvious over Reuser '771 in view of Van Hove 1997 and Brady.

II. ANALYSIS

A. Decision on Rehearing Request

In a request for rehearing, a dissatisfied party "must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d).

In its Request, Patent Owner agrees with our construction of claim 19 that the phrase "immunosuppressant is administered prior to any administration" of hGAA refers to administering an immunosuppressant prior to the first administration of hGAA to the individual. Req. Reh'g 2–3 (citing Final Dec. 7, 37). Patent Owner also contends, however, that we overlooked that neither Brady, nor the other two cited references, "recognized the problem addressed by claim 19," i.e., "that patients may have an immune response to GAA produced in Chinese hamster ovary ('CHO') cell cultures." Req. Reh'g 4–5. According to Patent Owner, "the '712 patent contains the first report of an immune response to the administration of hGAA produced in CHO cell cultures." *Id.* at 4

Even if no cited reference discloses that an immune response occurs upon administering GAA produced in CHO cell cultures in particular, that is not the end of our analysis. Brady discusses Gaucher disease, a disorder caused by a lysosomal protein deficiency, similarly at issue in the disease recited in claim 19, and treating a patient with enzyme replacement therapy using an exogenous enzyme, as similarly recited in claim 19. Ex. 1012, 1; Final Dec. 4, 34–35. In that context, Brady discloses that some patients developed "a neutralizing antibody to the exogenous enzyme" used in the study. Ex. 1012, 1, Abstract.

As explained in our Final Decision, Brady discusses the use of the immunosuppressant cyclophosphamide to manage enzyme neutralizing antibodies when treating Gaucher's disease patients with the exogenous enzyme glucocerebrosidase. Final Dec. 34–35. Brady also expressly discloses that "[i]t is also likely that this technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals)." Ex. 1012, 1, Abstract; Final Dec. 35. Thus, Brady describes an unwanted immune response when administering an exogenous enzyme, a method for reducing that immune response by administering an immunosuppressant, and suggests that its method would be helpful in reducing a similar reaction when administering enzyme replacement therapy in patients having other enzyme-deficiency disorders. Thus, we remain persuaded that a preponderance of the evidence establishes that an ordinary artisan would have known

about the "problem" of a potential unwanted immune response when administering an exogenous enzyme (such as GAA from any source) and also would have understood that administering an immunosuppressant would likely help reduce the unwanted response.

In its Request, Patent Owner further contends, however, that we misapprehended Brady by assuming that "Day 1" in that reference referred to the very first day of enzyme administration. Req. Reh'g 5–6. Specifically, Patent Owner argues that Brady discloses that "'Day 1' refers to the first day of the clinical protocol that includes the immunosuppressant—not the very first day of therapy by administration of the replacement enzyme glucocerebrosidase." *Id.* at 6 (citing Paper 59, 50–51 ("PO Resp." or "Patent Owner Response"); Ex. 2019 ¶ 111). Thus, according to Patent Owner, Brady "does not disclose a method of preventing an immune reaction before it occurs." *Id.* at 6.

As discussed in our Final Decision, and acknowledged by Patent Owner in its Response, Brady teaches administering both enzyme and immunosuppressant on "Day 1," as disclosed in a particular paragraph in Brady. Final Dec. 37; PO Resp. 54; Ex. 1012, 3, Table 1. In that paragraph, Brady states that the patient "received one intravenous infusion of 15 mg of cyclophosphamide per kilogram of body weight *on the first day of treatment*, and he was given a daily oral dose of 2 mg/kg of cyclophosphamide from days 2 to 10." Ex. 1012, 3 (emphasis added).

In relation to that disclosure, Patent Owner argued in its Response that because Brady "does not disclose when on Day 1 the immunosuppressant is administered, Brady does not disclose that the immunosuppressant is administered prior to the first administration of the enzyme within the particular administration interval that begins on and includes Day 1." PO Resp. 54.

Based on the above-mentioned disclosure in Brady, arguments and cited evidence by Patent Owner in its Response, as well as testimony by Dr. Gregory Pastores cited by Petitioner, we determined that "an ordinary artisan would have had reason to administer an immunosuppressant, for example on Day 1 of treatment, prior to any administration of enzyme therapy, such as rhGAA." Final Dec. 37–38 (citing Paper 5 ("Pet."), 52; Ex. 1020 ¶ 95).

As noted above, Patent Owner contends in its Request that "Day 1" in Brady "refers to the first day of the clinical protocol that includes the immunosuppressant—not the very first day of therapy by administration of the replacement enzyme glucocerebrosidase." Req. Reh'g 6. Patent Owner points us to its earlier Response (PO Resp. 50–51) and cited testimony by Dr. Wasserstein (Ex. 2019 ¶ 111), to identify where it previously raised this contention. Req. Reh'g 6. In the cited portion of its Response, Patent Owner stated that an "immunosuppressant (cyclophosphamide) was administered to address the immune response that had already occurred—not to prevent such a response from occurring in the first place, as in claim 19." PO Resp. 51 (citing Ex. 2019 ¶ 111). Dr.

Wasserstein similarly testified that Brady administered an immunosuppressant "to address the immune response that had already occurred—not to prevent such a response from occurring in the first place." Ex. 2019 ¶ 111.

In relation to Patent Owner's contentions in this regard, we grant a rehearing to reconsider the teachings of Brady in relation to "Day 1." Taking a closer look at the reference as a whole, we see that Brady discloses, in the paragraph discussed above, that "[t]he effort to immunosuppress the patient was initiated on July 26, 1993." Ex. 1012, 3. Reading the entire paragraph, it is clear that July 26, 1993, corresponds to "Day 1" as presented in Table 1, i.e., the first day that the patient received both an immunosuppressant and enzyme therapy. *Id.*

Earlier in the reference, Brady states that the "patient was admitted to NIH for periodic evaluation on January 21, 1992, 6 months after the initiation of enzyme replacement therapy." *Id.* at 2 (under the heading "Clinical Course"). The reference also states that "[o]n March 19, 1993, 1 day after routine intravenous infusion of Ceredase, the patient experienced severe pain in his left shoulder . . . ." *Id.* Thus, we are persuaded by Patent Owner's contentions that Brady does not disclose administering immunosuppressant prior to any and all administration of hGAA, as required by claim 19. Req. Reh'g 6. Accordingly, we now reconsider the arguments and evidence, including the aspects of Brady discussed above, and address the question of whether claim 19 is obvious over the combination of Reuser '771, Van Hove 1997, and Brady.

Appendix D

B. Obviousness of Claim 19 Over Reuser '771, Van Hove 1997, and Brady

1. Construction of the Phrase "prior to any administration"

Including the limitations of the claims on which it depends, claim 19 recites:

> 19. [A method of treating glycogen storage disease type II in a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures, wherein the human acid α-glucosidase is administered in conjunction with an immunosuppressant, and] wherein the immunosuppressant is administered *prior to any administration* of human acid α-glucosidase.

PO Resp. 53 (emphasis added).

In our Final Decision, we recognized that the Specification of the '712 patent states that "[i]n a particularly preferred embodiment, the immunosuppressive or immunotherapeutic regimen is begun prior to the first administration of GAA, in order to minimize the possibility of production of anti-GAA antibodies." Ex. 1001, 5:55–59.

In view of the claim language itself, including the term "any," as well as the above-mentioned description in the Specification, we construed "administered prior to any administration" of hGAA in claim 19 to refer to administering an immunosuppressant prior to the first administration of hGAA to the individual. We maintain our claim construction.

2. Obviousness Analysis

a. Summary of Issue Presented

In its Petition, Petitioner contends that Reuser '771, in view of Van Hove 1997 and Brady, discloses or suggests every element of dependent claim 19. Pet. 51, 45–46. Brady, in particular, is relied on by Petitioner for the contention that the administration of immunosuppressant prior to any administration of human acid α-glucosidase, as recited in claim 19, is obvious. Pet. 45–46, 52. Petitioner contends that Brady discusses the use of the immunosuppressant cyclophosphamide in conjunction with enzyme replacement therapy in Gaucher's disease, and that such a strategy is likely to be helpful in enzyme replacement therapy in other disorders where a genetic mutation abrogates the production of the protein. *Id.* at 45–46.

Petitioner relies also on the Declaration of Dr. Gregory Pastores (Ex. 1020, "Pastores Dec.") as evidence to support its contention that it would have been obvious to administer an immunosuppressant in conjunction with enzyme replacement therapy to treat GSD-II "to alleviate unwanted immune responses." Pet. 46 (citing Pastores

Dec. ¶ 95). Petitioner contends that it was "well known in the art to administer the immunosuppressant prior to administering the enzyme replacement protein." *Id.* at 45–46, 52 (citing Pastores Dec. ¶ 95); Paper 67 ("Pet. Reply"), 13 (citing Pastores Dec. ¶¶ 93–95; Ex 1165, Abstract).

Patent Owner contends that an ordinary artisan would have had no reason to combine the cited references, arguing that an ordinary artisan "interested in treating GSD-II with hGAA from CHO cells would have had no reason to also administer an immunosuppressant." PO Resp. 47–51. Patent Owner contends also that a person of ordinary skill in the art would not have considered Brady "relating to treating a single patient with Gaucher's disease who had experienced a rare and severe immunological response to administration of Ceredase isolated from human placenta relevant to a treatment regimen for treating GSD-II with hGAA produced in CHO cell cultures." *Id.* at 49 (citing Ex. 2020, ¶ 154; Ex. 2019 ¶ 105).

Patent Owner further relies on the Declaration of Dr. Wasserstein (Ex. 2019, "Wasserstein Dec."). Patent Owner contends, citing testimony by Dr. Wasserstein, that "immunological risks to GSD-II patients would be different than the immunological risks to patients with Gaucher's disease," and that "Brady concerns administering an immunosuppressant in response to an immunological reaction to exogenous enzyme, not for the purpose of preventing production of anti-GAA antibodies." PO Resp. at 50 (citing Wasserstein Dec. ¶¶ 107, 111–112). Patent Owner further contends that Brady does not disclose

administration of immunosuppressant prior to the first administration of the enzyme within an administration interval, as required in claim 19. *Id*. at 53–55.

In its Reply to Patent Owner's Response, Petitioner rebuts Patent Owner's contention that a person of ordinary skill in the art could not have predicted that an immunosuppressant could be useful when the active precursor form of CHO GAA is used to treat Pompe patients. Pet. Reply 12 (citing PO Resp. 48). Petitioner contends that the problem of immune responses was known for many approved protein therapeutics, and that Dr. Wasserstein acknowledged that an adverse immunological reaction due to enzyme replacement therapy would have been treated similarly to any other adverse immunological reaction. *Id.* at 12–13 (citing Exs. 1162, 1163; Ex 2085, 137:10–13, 139:12–140:10).

b. Discussion

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim." *KSR Int'l Co. v. Teleflex, Inc*., 550 U.S. 398, 418 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417. In this case, the preponderance of evidence on record shows that it was known to use an immunosuppressant in conjunction with Gaucher disease, when treating with an enzyme replacement therapy. Exs. 1111, 1112, 1165; Pastores Dec. ¶¶ 93–95; Wasserstein Dec. ¶¶ 107, 111–112 (stating that Brady describes "[a]n immunosuppressant…given, along with other aspects of

the intervention, to address the immune response that had already occurred – not to prevent such a response from occurring in the first place, as taught by the '712 Patent and claimed in claim 19"). In particular, Brady discloses the use of an immunosuppressant, cyclophosphamide, to manage neutralizing antibodies directed against a treatment enzyme, Ceredase, in patients with Gaucher disease, a lysosomal protein deficiency disease. Ex. 1012, 1. Brady expressly states that its "technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein." *Id.* Such teachings would have suggested to an ordinary artisan to use an immunosuppressant similarly when administering enzyme replacement therapy, such as rhGAA produced in CHO cells, to at least some patients when treating a different lysosomal protein deficiency, such as Pompe disease, even assuming one understood that a severe neutralizing antibody response would have been rare. Pastores Dec. ¶¶ 93–95.

As the Patent Owner notes, however, Brady does not disclose prophylactically administering immunosuppressant for the purposes of minimizing any potential adverse effects from administration of the replacement enzyme. Req. Reh'g 6 (citing PO Resp., 50–51; Wasserstein Dec. ¶ 111). Rather, only those patients who developed an adverse immunological reaction were treated with immunosuppressant in conjunction with subsequent administrations of enzyme. Ex. 1012, 3.

Accordingly, the question before us now is whether it would have been obvious to administer an immunosuppressant as a prophylactic, before any sign of an adverse immunological reaction. In this regard, Dr. Pastores testifies as follows:

> Patients generally tolerate the infusions and have a high compliance rate with [enzyme replacement therapy], although some have had immune reactions either to the replacement enzyme or some component of the formulation containing the enzyme. With administration of protein therapies, it would not be unusual to use, as a precaution, premedications such as antihistamines and antipyretics to prevent or mitigate any potential reactions to intravenous protein administration until it was established that the patient is safely tolerating the treatment.
>
> . . . it would not be surprising if a proportion of patients treated with a recombinant GAA protein developed an immune response to the recombinant enzyme.
>
> In patients with high titers of antibodies against the enzyme, particularly those with neutralizing antibodies, administering an immunosuppressant prior to, with or immediately after the therapeutic enzyme would be considered to mitigate the presence of antibodies and its negative impact (Brady

> et al., *Pediatrics*, 100(6):E11, 1997, Ex 1012). For example, Brady et al. discuss on page 3 of 4, beginning at left column, final paragraph, efforts to "immunosuppress" the patient. Similarly Grabowski reports that hypersensitivity to the replacement enzyme may be addressed by pretreatment with antihistamines or the widely used immunosuppressant, corticosteroids. (Grabowski et al., *Blood Reviews*, 12:115(1998), Ex 1011; p 130, left column, first paragraph) If there is a high incidence of patients developing high antibody titers, an immunosuppressant could be administered prophylactically prior to any administration of the recombinant enzyme begins to minimize the potential adverse effects of such.

Pastores Dec. ¶¶ 93–95 (emphasis omitted).

Patent Owner does not directly rebut Dr. Pastores's testimony that the use of premedications in protein therapies "would not be unusual," or that the development of an immune response from the administration of a foreign protein would not be surprising. Rather, Patent Owner argues that "[p]rior to 2000, there were no reports of an immunological response in patients with GSD-II to whom exogenous hGAA was administered." PO Resp. 48. Patent Owner further argues that "[t]he desirability of also administering an immunosuppressant while administering hGAA from CHO cells, either in response to an undesirable immunological response or to prevent the formation of anti-GAA antibodies associated with such

a response became apparent only during the clinical trial reported in the '712 Patent." *Id.* at 49 (citing Wasserstein Dec. ¶ 106 ("The '712 Patent contains the first report of any immune response to ERT treatment of GSD-II with exogenous GAA, as well as the first teaching of methods to treat and/or prevent such reactions.")).

We agree with Patent Owner that Brady does not teach prophylactically administering an immunosuppressant under our construction of claim 19. We determine, however, that the preponderance of evidence shows that the prophylactic administration of an immunosuppressant would have been a predictable variation of the use of immunosuppressant disclosed in Brady. Brady teaches administering the immunosuppressant in an "effort to immunosuppress the patient" and to reduce neutralizing antibodies in the individual. Ex. 1012, 3 (including sections titled "Intervention" and "Reduction of Neutralizing Antibody Titer"). Dr. Pastores testifies that administration of foreign protein could lead to an immune response (Pastores Dec. ¶ 94), such as the adverse immune response seen in Brady, and that hypersensitivity to replacement enzyme may be addressed by pretreatment with antihistamines or widely used immunosuppressants such as corticosteroids (Dr. Pastores ¶ 95 (citing Ex 1011, 130)).

In *KSR*, the Court offered guidance on when a combination might be obvious under § 103:

> When a work is available in one field, design incentives and other market forces can prompt

> variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

550 U.S. at 401. Under *KSR*, we conclude that Petitioner's proposed combination of elements from Reuser '771, Van Hove 1997, and Brady would have been obvious to a person of ordinary skill in the art. The choice of administering immunosuppressant before an adverse immune response develops in a patient, or after a patient has experienced an adverse immune response, are predictable variations producing the same result—prevention of an adverse immune response to foreign protein. There is no evidence of record demonstrating that the prophylactic treatment of an adverse immune response in response to GAA administration was uniquely challenging or difficult for one of ordinary skill in the art. *See Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) (alleged invention obvious in view of what "common sense" would tell the skilled artisan); *KSR*, 550 U.S. at 417 ("predictable variations" are not patentable).

III. CONCLUSION

We grant Patent Owner's Request for Rehearing. We modify our analysis in determining that Petitioner has demonstrated by a preponderance of the evidence that claim 19 of the '712 patent would have been obvious over Reuser '771 in view of Van Hove 1997 and Brady. We also clarify that Petitioner did not challenge claim 19 on an anticipation ground (Pet. 3–4, 20–37).

IV. ORDER

For the reasons given, it is

ORDERED that Patent Owner's Request for Rehearing is *granted*;

FURTHER ORDERED that a preponderance of the evidence of record supports the conclusion that claim 19 of the '712 patent is unpatentable; and

FURTHER ORDERED that the Final Decision is modified to include our analysis herein regarding whether claim 19 would have been obvious over Reuser '771 in view of Van Hove 1997 and Brady.

BONILLA, *Administrative Patent Judge,* concurring-in-part and dissenting-in-part.

I agree with my colleagues that we should grant Patent Owner's Request for Rehearing to reconsider the teachings of Brady in relation to the subject matter of claim 19. I agree we should reconsider the teachings of Brady in relation to "Day 1" described in that reference. Upon reconsideration, like my colleagues, I am persuaded by Patent Owner's contentions that Brady does not disclose administering immunosuppressant prior to any and all administration of hGAA, as required by claim 19. Req. Reh'g 6.

On rehearing, therefore, we now must reconsider whether Petitioner has shown by a preponderance of the evidence that claim 19 of the '712 patent is unpatentable as obvious over the combination of Reuser '771, Van Hove 1997, and Brady, with the current understanding of what Brady discloses. In this regard, I would determine that the Petition, as it relates to claim 19 in particular, provides or relies upon only cursory analysis and conclusory statements in support, while Petitioner's Reply provides no relevant analysis as it relates to claim 19 in particular.

Specifically, in its Petition, in the portion addressing claim 18 (which depends from claim 1) and claim 19 (which depends from claim 18) in a relevant ground (Ground 11), Petitioner refers to arguments it made pertaining to a different ground (Ground 7). Pet. 52–53 (referring to Pet. 45–46, Ground 7, arguing claims 18 and 19 are unpatentable over Synpac (Ex. 1002) in view of Grabowski

(Ex. 1011) or Brady). In Ground 7, regarding claim 18, Petitioner argues that "it was well known at the time of the invention of the '712 patent to use immunosuppressants in conjunction with administration of the administered enzyme replacement protein," citing Dr. Pastores' Declaration. Pet. 45–46 (citing Ex. 1020 ¶ 95). In relation to claim 19, however, the Petition states, in its entirety, citing to no evidence: "It was further well known in the art to administer the immunosuppressant prior to administering the enzyme replacement protein." Pet. 46.

Likewise in Ground 11 (at issue here), with regard to claim 18, Petitioner contends that "it was well known at the time of the invention of the '712 patent to use immunosuppressants 'in conjunction with' (claim 18) an enzyme in ERT." Pet. 51–52. Regarding claim 19, however, Petitioner states only, in its entirety, citing one paragraph in Dr. Pastores' Declaration: "It was further well known in the art to administer the immunosuppressant 'prior to any administration of' (claim 19) the enzyme if immune responses had been observed in a significant number of patients during clinical trials." Pet. 52 (citing Ex 1020 ¶ 0095).

In its Reply to Patent Owner's Response, Petitioner responds to Patent Owner's assertions regarding whether an ordinary artisan would have predicted that "an immunosuppressant could be useful when the active precursor form of CHO GAA is used to treat Pompe patients." Pet. Reply 12–13. In other words, Petitioner argued only that one would have been motivated to administer an immunosuppressant with GAA in GSD-

II patients generally, and not just in Gaucher's patients receiving the enzyme Ceredase. While this point may have been relevant to claim 18, Petitioner's Reply did not address the issue at hand here in relation to claim 19, which recites administering the immunosuppressant "prior to any administration" of human GAA to an individual.

Like my colleagues, as relevant to claim 18 (upon which claim 19 depends), I remain persuaded that Petitioner has established by a preponderance of the evidence that an ordinary artisan would have understood that administering an immunosuppressant likely would have helped reduce an unwanted immune response when administering an exogenous enzyme (such as GAA from any source).

I respectfully disagree with my colleagues, however, that Petitioner has established by a preponderance of the evidence, as presented in its Petition or Petitioner's Reply, that claim 19 would have been obvious over the combination of Reuser '771, Van Hove 1997, and Brady. Specifically, in its Petition and Reply, Petitioner does not explain, nor establish adequately, how Reuser '771, Van Hove 1997, or Brady, either individually or in combination, teach or suggest administering an immunosuppressant to a patient before the patient has exhibited any sign of an adverse reaction to the enzyme therapy.

As noted above, in relation to Ground 7 and claim 19, the Petition merely argues, in a conclusory manner, without any citation to the record, that it was well known in the art to administer the immunosuppressant prior to

administering an enzyme replacement protein. Pet. 45–46. In relation to Ground 11 and claim 19, the Petition merely argues, again in a conclusory manner, that was it was well known in the art to administer the immunosuppressant "prior to any administration of" (claim 19) the enzyme if immune responses had been observed in a significant number of patients during clinical trials, citing only paragraph 95 of Dr. Pastores' Declaration (Ex 1020 ¶ 95). Pet. 52.

In paragraph 95 of his Declaration, Dr. Pastores discusses Brady and Grabowski only. As discussed in the majority opinion above, Brady teaches administering an immunosuppressant to address an antibody reaction resulting from enzyme replacement therapy. Maj. Op. 3–4. Like Brady, Grabowski discusses administering an immunosuppressant to patients to address "[h]ypersensitivity (antibody related) and non-allergic adverse events," which occurred "in ~15% of patients" treated with the exogenous enzymes discussed in that reference. Ex. 1011, 129. In this context, Grabowski teaches that such events "are treated conservatively by slowing of the infusion rate (extending the infusion time to 3 or more hours) and/or by pretreatment with antihistamines. A few patients have needed corticosteroids." Ex 1011, 130.

Like Brady, however, Grabowski does not teach administering an immunosuppressant (e.g., corticosteroid) prior to treatment with any exogenous enzyme in the first instance in a patient. Rather, at most, Grabowski suggests, as Brady does, that once an adverse event is identified in a patient undergoing enzyme therapy, the

"hypersensitivity or non-allergic adverse events are treated" by administering an immunosuppressant (or antihistamine) prior to the next enzyme administration interval. *Id*. Consistently, in its Reply to Patent Owner's Response, Petitioner contended that both Drs. Wasserstein and Pastores testified that it was well known "that patients receiving protein therapeutics (including ERT for Gaucher's disease) often have an immune response that requires appropriate treatment." Pet. Reply 12–13.

Neither Petitioner in its Petition or Reply, nor Dr. Pastores in his cited testimony, adequately explains, however, how Brady (or Grabowski) teaches or suggests administering an immunosuppressant to a patient before the patient has exhibited any sign of an adverse reaction to the enzyme therapy. At most, Dr. Pastores testifies that "[i]f there is a high incidence of patients developing high antibody titers, an immunosuppressant could be administered prophylactically prior to any administration of the recombinant enzyme begins to minimize the potential adverse effects of such." Ex. 1020 ¶ 95; *see also id.* ¶ 93 (stating that "it would not be unusual to use, as a precaution, premedications such as antihistamines and antipyretics to prevent or mitigate any potential reactions," not referring to immunosuppressants).

While Dr. Pastores conclusory statements may indicate what "could be" done if "there is a high incidence" of antibody response, he does not explain, nor provide evidence showing, what an ordinary artisan *would have done* in this regard prior to the filing date of the '712 patent, or what one *would have understood* in relation

to incidents of "high antibody titers" in response to exogenous enzyme therapy. On this last point, I note that Brady, for example, teaches that an adverse neutralizing antibody response to glucocerebrosidase occurs only in "rare instances" in "[v]ery few patients." Ex. 1012, 1, Abstract. Thus, Brady again suggested to an ordinary artisan to wait and see if the rare adverse reaction of "high antibody titers" (as referenced in Ex. 1020 ¶ 95) actually occurred in a patient receiving enzyme therapy before administering an immunosuppressant, entirely consistent with express teachings in both Brady and Grabowski, as discussed above.

Thus, in its Petition and Reply, I conclude that Petitioner fails to point us to a preponderance of the evidence establishing that an ordinary artisan would have understood Brady, or any of the cited prior art references, to teach or suggest administering an immunosuppressant "prior to any administration" of an exogenous enzyme, as recited in claim 19.

By statute, the burden is on Petitioner to establish its case in an *inter partes* review. 35 U.S.C. § 316(e) (stating that, in an *inter partes* review, "the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence"). The majority relies on paragraphs 93 and 94 in Dr. Pastores' Declaration when stating that "Patent Owner does not directly rebut Dr. Pastores' testimony that the use of premedications in protein therapies 'would not be unusual,' or that the development of an immune response from the administration of a foreign protein would not

be surprising." Maj. Op. 10–12. Notably, Petitioner does not cite paragraphs 93 and 94 in its Petition in relation to claims 18 or 19 (Pet. 45–46, 51–52), nor in its Reply in relation to claim 19 (Pet. Reply 12–13 (addressing the subject matter of claim 18, i.e., whether an ordinary artisan would have been motivated to administer hGAA "in conjunction" with an immunosuppressant)).

Moreover, Petitioner never asserts or suggests that the "choice of administering immunosuppressant before an adverse immune response develops in a patient or after a patient has experienced an adverse immune response are predictable variations producing the same result—prevention of an adverse immune response to foreign protein," as the majority discusses above. Maj. Op. 12–13 (citing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 401 (2007)). I would not expect Patent Owner to respond to arguments that Petitioner never made in the appropriate papers, nor require Patent Owner to show via "evidence of record . . . that the prophylactic treatment of an adverse immune response in response to GAA administration was uniquely challenging or difficult for one of ordinary skill in the art." *Id.* at 13.

For the reason discussed above, I would grant Patent Owner's Request for Rehearing and modify our Final Decision to reflect that Petitioner has not demonstrated by a preponderance of the evidence that claim 19 of the '712 patent would have been obvious over Reuser '771 in view of Van Hove 1997 and Brady.

APPENDIX E — OPINION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE , PATENT TRIAL AND APPEAL BOARD, DATED FEBRUARY 23, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2013-00535
Patent 7,056,712 B2

BIOMARIN PHARMACEUTICAL INC.,

Petitioner,

v.

DUKE UNIVERSITY,

Patent Owner.

Before LORA M. GREEN, JACQUELINE WRIGHT BONILLA, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

BONILLA, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Appendix E

I INTRODUCTION

Petitioner, BioMarin Pharmaceutical Inc. ("Petitioner"), filed a Petition (Paper 5, "Pet.") requesting *inter partes* review of claims 1–9, 11, 12, 15, and 18–21 of U.S. Patent No. 7,056,712 B2 (Ex. 1001, "the '712 patent"). 35 U.S.C. § 311. Patent Owner Duke University ("Patent Owner") filed a Preliminary Response (Paper 13, "Prelim. Resp."). We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–9, 11, 12, 15, and 18–21 of the '712 patent as unpatentable. Paper 16 ("Dec. to Inst."), 23.

We instituted this proceeding to review whether claims 1–9, 11, 12, 15, and 18–21 are unpatentable on the following grounds.

Reference(s)	Basis	Claims challenged
van Bree '410 (Ex. 1005)[1]	§ 102	1–9, 11, 12, 15, 20, and 21
Reuser '771 (Ex. 1004)[2] in view of Van Hove 1997 (Ex. 1007)[3]	§ 103	1–9, 15, and 20

1. van Bree et al., U.S. Patent No. 7,351,410 B2, issued Apr. 1, 2008 (Ex. 1005).

2. Reuser et al., WO 97/05771, published Feb. 20, 1997 (Ex. 1004).

3. Van Hove et al., *Purification of recombinant human precursor acid α-glucosidase*, 43(3) Biochemistry & Molecular Biology Int'l 613–623 (1997) (Ex. 1007)

Appendix E

Reference(s)	Basis	Claims challenged
Reuser '771 in view of Van Hove 1997, van der Ploeg (Ex. 1014),[4] and Bembi (Ex. 1008)[5]	§ 103	11, 12, and 21
Reuser '771 in view of Van Hove 1997 and Brady (Ex. 1012)[6]	§ 103	18 and 19

Dec. to Inst. 23.

After institution of trial, Patent Owner filed a Patent Owner Response. Paper 59 ("PO Resp."). Petitioner subsequently filed a Reply to the Response. Paper 67 ("Reply").

In addition, Petitioner filed a Motion to Exclude seeking to exclude certain evidence. Paper 73. Patent Owner filed an Opposition to Petitioner's Motion to Exclude (Paper 76), and Petitioner filed a Reply (Paper 80). Likewise, Patent Owner filed a Motion to Exclude seeking to exclude certain evidence. Paper 72. Petitioner filed an Opposition to Patent Owner's Motion to Exclude (Paper 77), and Patent Owner filed a Reply (Paper 81).

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4. van der Ploeg et al., *Receptor-Mediated Uptake of Acid α-Glucosidase Corrects Lysosomal Glycogen Storage in Cultured Skeletal Muscle*, 24(1) PEDIATRIC RES. 90–94 (1988) (Ex. 1014).

5. Bembi et al., *Enzyme Replacement Therapy in Type 1 and Type 3 Gaucher's Disease*, 344 LANCET 1679-1682 (1994) (Ex. 1008).

6. Brady et al., *Management of Neutralizing Antibody to Ceredase in a Patient With Type 3 Gaucher Disease*, 100(6) PEDIATRICS e11 (1997) (Ex. 1012).

An oral hearing was held on October 3, 2014. A transcript of the hearing has been entered into the record. Paper 85 ("Tr.").

We have statutory authority under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a). Petitioner has shown by a preponderance of the evidence that claims 1–9, 11, 12, 15, and 18–21 of the '712 patent are unpatentable. Patent Owner's Motion to Exclude is dismissed as moot, and Petitioner's Motion to Exclude is denied-in-part and dismissed-in-part.

A. Related Proceedings

The parties indicate that are no other related judicial or administrative matters. Pet. 1, Paper 11, 3. On the same day Petitioner filed its Petition in this proceeding, however, it also filed two other Petitions seeking *inter partes* review of U.S. Patent No. 7,351,410 ("van Bree '410") (IPR2013-00534) and U.S. Patent No. 7,655,226 ("the '226 patent") (IPR2013-00537), respectively. Although the '712 patent is not related to van Bree '410 (Ex. 1005, in this proceeding) or the '226 patent, all three patents relate to similar subject matter, i.e., methods of treating Pompe disease.

B. The '712 Patent

The '712 patent relates to methods of treating glycogen storage disease type II ("GSD-II"). Ex. 1001, Abstract. Glycogen storage disease type II, also known as Pompe disease or acid maltase deficiency, is a genetic muscle disorder caused by a deficiency of acid α-glucosidase ("GAA"), a glycogen degrading lysosomal enzyme.

Id. at 1:12–15. The disclosed methods involve enzyme replacement therapy ("ERT"), including administering to an individual a therapeutically effective amount of GAA. *Id.* at 1:62–66; 2:20–27. In a preferred embodiment, the method uses recombinant human acid α-glucosidase ("rhGAA"), such as a recombinant human GAA precursor form, produced in Chinese hamster ovary ("CHO") cell cultures. *Id.* at 3:57–4:4. In certain embodiments, the method involves administering GAA in conjunction with other agents, such as immunosuppressants. *Id.* at 5:29–33.

Independent claims 1 and 20, reproduced below, are illustrative of the claimed subject matter:

> 1. A method of treating glycogen storage disease type II in a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures.
>
> 20. A method of treating cardiomyopathy associated with glycogen storage disease type II in an human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in Chinese hamster ovary cell culture.

Claims 2–9, 11, 12, 15, 18, 19, and 21 depend from claim 1.

II. ANALYSIS

A. Claim Construction

Consistent with the statute and legislative history of the America Invents Act, the Board interprets claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also* Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012). There is a "heavy presumption" that a claim term carries its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) (citations omitted).

1. Claim Phrases Construed in the Decision to Institute

In our Decision to Institute, we construed the phrase "produced in chinese hamster ovary cell cultures" recited in claims 1, 8, 9, and 20. Dec. to Inst. 6–7. We did not construe the phrase as a product-by-process limitation, as urged by Petitioner. *Id*. at 7. We agreed with Patent Owner that this claim language more closely identifies the protein source, rather than a product defined by a process that allows one to claim "an otherwise patentable product that resists definition by other than the process by which it is made." *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006) (quoting *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985)). Dec. to Inst. 7. Thus, we concluded that "produced in chinese hamster ovary cell

cultures" in relation to the recited hGAA[7] corresponded to a limitation of the challenged claims. *Id*. at 12.

In addition, in our Decision to Institute, we construed other phrases of the challenged claims, as reproduced in the table below.

Claim(s)	Claim Phrase	Claim Construction
1 and 20	administering "periodically at an administration interval"	administering "at regular intervals" or "from time to time," which "need not be a fixed interval, but can be varied over time, depending on the needs of the individual," and includes "monthly, bimonthly, weekly, twice weekly, daily," as distinguished from a "one-time dose"

7. The acronym "hGAA" used herein refers to "human acid α-glucosidase" as recited in the challenged claims.

Appendix E

Claim(s)	Claim Phrase	Claim Construction
1, 5–7, and 20	"therapeutically effective amount" of hGAA	"an amount of hGAA administered at an interval that ameliorates, or lessens the severity or frequency of, symptoms of glycogen storage disease type II," including amounts such as "15 mg, about 1–10 mg, or about 5 mg hGAA per kilogram body weight of the individual"
18	hGAA administered "in conjunction with"	administered "at about the same time" as hGAA, which includes "within a short time frame (e.g., within 24 hours) of administration of the GAA"

Id. at 8–9.

Patent Owner does not propose alternative claim constructions for the above-mentioned claim phrases in its Patent Owner Response, nor does Petitioner challenge our constructions in its Reply. *See, e.g.*, PO Resp. 15–16 (proposing construction of other terms). We discern no reason to alter the above-mentioned claim constructions in any respect for this Final Written Decision.

Claim 19, which depends from claims 1 and 18, recites that "the immunosuppressant is administered prior to any administration" of hGAA to the individual. In our Decision to Institute, we interpreted this phrase to refer to administering an immunosuppressant before the first administration of any hGAA within a particular administration interval. Dec. to Inst. 9. After considering the entire record before us now, the Specification of the '712 patent, and Patent Owner's contentions in its Response, we reevaluate that claim construction. *See, e.g.*, PO Resp. 54 (discussing Ex. 1012).

Most relevant to the language of claim 19, the Specification of the '712 patent states that "[i]n a particularly preferred embodiment, the immunosuppressive or immunotherapeutic regimen is begun prior to the first administration of GAA, in order to minimize the possibility of production of anti-GAA antibodies." Ex. 1001, 5:55–59. In view of the claim language itself, including the term "any," as well as the above-mentioned description in the Specification, we construe "administered prior to any administration" of hGAA in claim 19 to refer to administering an immunosuppressant prior to the first administration of hGAA to the individual.

2. "Precursor" of rhGAA

In its Patent Owner Response, Patent Owner proposes that the term "precursor" in claim 9 means "any precursor of recombinant hGAA (e.g. a 110-kD form)" that is "exclusively . . . produced in CHO cell cultures." PO Resp. 15, 22–24. Petitioner does not propose an alternative claim construction in its Reply. Reply 5.

We agree that Patent Owner's proposed claim construction is the broadest reasonable reading in view of the Specification and language in claim 9 itself. We clarify, however, that claim 1, upon which claim 9 depends, recites a method *comprising* administering hGAA. Neither claim 1 nor claim 9 precludes administering a non-precursor form of hGAA or rhGAA, even if claim 9 requires administering a precursor of recombinant hGAA that has been produced in CHO cell cultures. Claims 1 and 9 encompass administering both precursor and non-precursor forms at the same time, and are not limited to administering exclusively a precursor form and no other form.

3. "Bimonthly" administration interval

Patent Owner proposes that the term "bimonthly" in claim 11 means "every other week." PO Resp. 15, 25–26. Petitioner does not propose an alternative claim construction in its Reply. Reply 5–6. We agree that Patent Owner's proposed claim construction is the broadest reasonable reading of the term in view of the Specification. *See, e.g.*, Ex. 1001, 1:52–2:13 (describing administration "monthly, bimonthly, weekly, twice weekly, daily").

B. Anticipation by van Bree '410

Petitioner contends that van Bree '410 anticipates claims 1–9, 11, 12, 15, 20, and 21 of the '712 patent. Pet. 33–37. BioMarin provides a claim chart to explain how van Bree '410 allegedly discloses the claimed subject matter, and relies upon the Declaration of Dr. Gregory Pastores

("Pastores Declaration") (Ex. 1020), and the Declaration of Dr. Matthew Croughan ("Croughan Declaration") (Ex. 1021), to support its positions. *Id*. at Appendix 2; *see also id*. at 34, 36–37.

1. van Bree '410 (Ex. 1005)

Van Bree '410 describes "methods of treating Pompe's disease using human acid alpha glucosidase," where a "preferred treatment regime comprises administering greater than 10 mg/kg body weight per week to a patient." Ex. 1005, Abstract. Claim 1 in van Bree '410 recites a "method of treating a human patient with Pompe's disease, comprising intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase . . . ." *Id*. at 29:8–12. In examples, van Bree '410 describes the use of rhGAA isolated from the milk of transgenic mice, including for use in human clinical trials. *Id*. at 16:17–20:48; 24:10–25:20. For instance, Example 5 in the reference describes a human clinical trial conducted in healthy male volunteers involving intravenous infusion "administered two weeks apart." *Id*. at 24:10–38.

When describing its "Therapeutic Methods" generally, van Bree '410 discloses that "an alternative way to produce human acid α-glucosidase is to transfect the acid α-glucosidase gene into a stable eukaryotic cell line (e.g., CHO) as a cDNA or genomic construct operably linked to a suitable promoter," but states that such an approach is "more laborious to produce the large amounts . . . for clinical therapy . . . ." *Id*. at 13:39, 58–64.

In the same "Therapeutic Methods" section, van Bree '410 discloses that "'therapeutically []' . . . effective doses will depend on the severity of the condition and on the general state of the patient's health." *Id.* at 14:12–15. Van Bree '410 also discloses that hGAA "is usually administered at a dosage of 10 mg/kg patient body weight or more per week to a patient," and describes a preferred embodiment where "10 mg/kg, 15 mg/kg . . . is administered once, twice or three times weekly." *Id.* at 14:16–27. In addition, "[t]reatment is typically continued for at least 4 weeks, sometimes 24 weeks, and sometimes for the life of the patient." *Id.* at 14:27–29. One example of "a maintenance dose is at least about 5 to at least about 10 mg/kg patient body weight per week . . . ." *Id.* at 14:40–42. Van Bree '410 also teaches that, "[t]ypically, the intravenous infusion occurs over a period of several hours (e.g., 1–10 hours and preferably 2–8 hours, more preferably 3–6 hours), and the rate of infusion is increased at intervals during the period of administration." *Id.* at 14:52–55. Van Bree '410 further discloses the "methods are effective on patients with both early onset (infantile) and late onset (juvenile and adult) Pompe's disease." *Id.* at 15:10–14.

In another section titled "Conforma[t]ion of Lysosomal Proteins," van Bree '410 states that "[r]ecombinant lysosomal proteins are preferably processed to have the same or similar structure as naturally occurring lysosomal proteins." *Id.* at 5:36–38. The reference describes that "[l]ysosomal proteins are glycoproteins that are synthesized on ribosomes bound to the endoplasmic reticulum (RER)." *Id.* at 5:38–40. The reference explains that "N-linked glycosylation process starts in the RER"

with the transfer of "precursor Glc3Man9GlcNAc2." *Id.* at 5:42–45. Thereafter, in the RER and Golgi apparatus, phosphorylation occurs through "a two-step procedure" involving a cleavage that "exposes mannose 6-phosphate as a recognition marker and ligand for the mannose 6-phosphate receptor mediating transport of most lysosomal proteins to the lysosomes." *Id.* at 5:45–58.

In that same section, van Bree '410 describes that "[i]n addition to carbohydrate chain modification, most lysosomal proteins undergo proteolytic processing," and describes details of the proteolytic processing. *Id.* at 5:59–6:11. That process produces, as main species, "a 110/100 kD precursor, a 95 kD intermediate and 76 kD and 70 kD mature forms." *Id.* at 6:6–8.

Thereafter, in the same section, van Bree '410 states that "post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." *Id.* at 6:11–16. The reference also describes that "[a]uthentic processing to generate lysosomal proteins phosphorylated at the 6' position of the mannose group can be tested." *Id.* at 6:17–21.

In Example 3, which describes analyzing acid α-glucosidase produced in the milk of transgenic mice, van Bree '410 states that "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α-glucosidase purified from bovine testis, human urine and

medium of transfected CHO cells." *Id*. at 20:32–37. The example describes also describes that "the N-terminal amino acid sequence of the recombinant α-glucosidase produced in the milk of mice was shown to be the same as that of α-glucosidase precursor from human urine." *Id*. at 20:41–48.

2. Analysis—Claims 1–8, 12, 15 and 20

Petitioner contends that van Bree '410 discloses every element of challenged claims 1 and 20, as well as dependent claims 2–9, 11, 12, 15, and 21, citing a claim chart and supporting evidence. Pet. 33–37, Appendix 2. For example, regarding "administering to the individual a therapeutically effective amount of human acid α-glucosidase," recited in claims 1 and 20, as well as specific amounts recited in claims 5–7, Petitioner points to where van Bree '410 describes "that a dose is usually 10 mg/kg," a dose used in the disclosed clinical trials, and that "preferred regimes are 10, 15, 20, 30 or 40 mg/kg, 1–3 times per week." Pet. 35. Petitioner also contends that van Bree '410 teaches a maintenance dose of 5mg/kg, as recited in claim 7. *Id*; Ex. 1005, 14:40–42.

Petitioner contends also that van Bree '410 describes using "recombinant" hGAA produced in CHO cells in its methods, as recited in claims 1, 8, and 20. Pet. 33–35 (citing Ex. 1005, 5:36–38, 6:12–16, 10:57–11:42, 19:50–20:47), Appendix 2. Petitioner contends further that van Bree '410 describes treating an infantile, juvenile, and adult-onset form of GSD-II, as recited in claims 2–4. *Id*. at Appendix A (citing Ex. 1005, 15:12–14). Petitioner contends that

van Bree '410 discloses administering hGAA bimonthly, weekly, at an interval varied over time, and intravenously, as recited in claims 11, 12, 15, and 21. *Id.* at 36, Appendix 2 (citing Ex. 1005, 24:23; 14:26–43).

In its Response, Patent Owner contends that the section in van Bree '410 titled "Therapeutic Methods" (discussed above), relied upon by Petitioner, "does not disclose therapeutically effective amounts and administration intervals for use specifically with hGAA produced in CHO cell cultures." PO Resp. 19. Specifically, according to Patent Owner, van Bree '410 does not disclose the combination of: "(i) administering a therapeutically effective amount of hGAA; (ii) produced in CHO cell cultures; *and* (iii) periodically at an administration interval arranged as recited in claims 1 and 20." *Id.*

In addition, Patent Owner contends that an ordinary artisan would have known that "the therapeutically effective amounts and administration intervals disclosed for the hGAA genus [in van Bree '410] were not applicable to hGAA produced in CHO cell cultures for several reasons," citing Declarations by Dr. Melissa Wasserstein (Ex. 2019) and Dr. Richard Cummings (Ex. 2020). PO Resp. 20 (citing Ex. 2019 ¶ 64; Ex. 2020 ¶ 103). Patent Owner argues that an ordinary artisan "knew that the characteristics of hGAA including glycosylation and phosphorylation patterns vary significantly depending upon the source." *Id.* (citing Ex. 2019 ¶ 66; Ex. 2020 ¶¶ 105–107). After noting the importance of hGAA having at least one mannose-6-phosphate group, Patent Owner contends that U.S. Patent No. 6,537,785 ("Canfield") (Ex.

2016) discloses "that less than 1% of hGAA produced in CHO cell cultures bear the critical mannose-6-phosphate group." *Id.* (citing Ex. 2016, 20:29–31).

Thus, according to Patent Owner, "given the difference in properties of hGAA produced in transgenic animals and hGAA produced in CHO cells," an ordinary artisan would have understood that the administration amounts and intervals disclosed in van Bree '410 (regarding administration of hGAA produced in milk of transgenic mice) would not be applicable to hGAA produced in CHO cells culture. PO Resp. 20–21 (citing Ex. 2019 ¶¶ 66–67; Ex. 2020 ¶ 107). Patent Owner also contends that van Bree '410 only discloses the *possibility* of using CHO cells as a source, and discloses that such use "was expressly not preferred because it was more laborious to produce large amounts" as needed for treatment in humans. *Id.* at 21.

As pointed out by Patent Owner, Canfield (Ex. 2016) states that "production and secretion of human acid α-glucosidase by CHO cells has been reported" in Van Hove 1996 (Ex. 1016).[8] Ex. 2016, 20:21–27. Canfield states that the "carbohydrate structures of this preparation were not characterized" in Van Hove 1996, and contends that "this preparation was obtained and analyzed." *Id.* at 20:27–29. Canfield states that its own results "showed that less than 1% of the oligosaccharides contained

8. Van Hove et al., *High Level Production of Recombinant Human Lysosomal Acid α-glucosidase in Chinese Hamster Ovary Cells Which Targets to Heart Muscle and Corrects Glycogen Accumulation in Fibroblasts from Patients with Pompe Disease*, 93 Proc. Natl. Acad. Sci. USA 65–70 (1996) (Ex. 1016).

any M6P," and data "show that known preparations of recombinant lysosomal enzymes contain no more than 5.2% phosphorylated oligosaccharides." *Id.* at 20:29–39. Patent Owner relies on this disclosure in Canfield to support its contention that ordinary artisans would have known that the administration amounts and intervals disclosed in van Bree '410 in relation to hGAA produced in transgenic animals would not have been applicable to hGAA produced in CHO cell cultures.

Van Hove 1996 teaches methods for the "[h]igh-level production" of rhGAA in CHO cells "which targets to heart muscle and corrects glycogen accumulation in fibroblasts from patients with Pompe disease." Ex. 1016, title. Van Hove 1996 indicates that addition of its hGAA produced in CHO cell cultures, including the precursor 110 kDa form, caused fibroblasts from two patients to uptake the enzyme "as seen in normal fibroblasts" in *in vitro* studies. *Id.* at 67, 2nd col., 68, ¶ spanning 1st and 2nd cols. In addition, hGAA produced in CHO cells demonstrated "acid α- glucosidase activity [that] was strikingly higher in the liver and in the heart" in *in vivo* animal studies, as compared to control animals. *Id.* at 68, 2nd col.

Similarly to Van Hove 1996, Canfield (Ex. 2016) describes methods for producing "high mannose lysosomal hydrolases," and methods for treating "lysosomal storage diseases by administering a disease treating amount of the highly phosphorylated lysosomal hydrolases of the present invention to a patient." Ex. 2016, 21:38–22:62. In that context, Canfield describes that "[i]n a preferred embodiment, recombinant human acid alpha glucosidase

('rh-GAA') is prepared by culturing CHO cells secreting rh-GAA in Iscove's Media modified by the addition of an alpha 1,2-mannosidase inhibitor." *Id.* at 22:23–27. In relation to its own hGAA produced in CHO cell cultures, Canfield describes that "74% of the rh-GAA oligosaccharides were phosphorylated," and "[s]ince each molecule of rh-GAA contains 7 N-linked oligosaccharides, 100% of the rh-GAA molecules are likely to contain the mannose-phosphate modification." *Id.* at 22:40–48.

Based on the above-mentioned disclosures, we are not persuaded that Canfield indicates that an ordinary artisan would have known that the administration amounts and intervals disclosed in van Bree '410 would have been inapplicable to hGAA produced in CHO cell cultures. For example, Van Hove 1996 indicates that its hGAA produced in CHO cells were taken up by heart cells in *in vivo* animal studies, and Canfield teaches that its own hGAA produced in CHO cell cultures were phosphorylated at a high level. Absent data or information in Van Hove 1996 itself regarding glycosylation and phosphorylation of its own hGAA produced in CHO cells, as used in those studies, we do not know the glycosylation and phosphorylation status of Van Hove's preparation. Furthermore, we do not know from the record what exact "preparation was obtained" by Dr. Canfield. Ex. 2016, 20:21–29.

In any event, as pointed out by Petitioner, van Bree '410 itself indicates hGAA produced in CHO cells would have similar characteristics as hGAA produced in transgenic mice, including glycosylation and phosphorylation patterns. Pet. 33–35. When describing its "Therapeutic

Methods" generally, van Bree '410 discloses that "an alternative way" to produce hGAA is to transfect the gene "into a stable eukaryotic cell line (e.g., CHO)." Van Bree '410 describes further that "[r]ecombinant lysosomal proteins are preferably processed to have the same or similar structure as naturally occurring lysosomal proteins." *Id.* at 5:36–38. The reference describes that a glycosylation process that involves phosphorylation, which leads to the addition of manose-6-phosphate on the protein. *Id.* at 5:42–58.

Moreover, van Bree '410 describes that "[i]n addition to carbohydrate chain modification, most lysosomal proteins undergo proteolytic processing." *Id.* at 5:59–6:11. In that context, van Bree '410 states that "post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." *Id.* at 6:11–16. Furthermore, when describing its analysis of hGAA produced in transgenic mice, van Bree '410 states that "[r]estoration of the endogenous acid α-glucosidase activity . . . was as efficient as restoration by acid α-glucosidase purified from . . . medium of transfected CHO cells." *Id.* at 20:32–37.

Based on such disclosures in van Bree '410 itself, we conclude that Petitioner has established by a preponderance of the evidence that this reference describes administering hGAA produced in CHO cell cultures to patients in the same manner, i.e., using the same amounts and dosage intervals, as described for hGAA produced in transgenic animals.

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The Declarations of Dr. Wasserstein (Ex. 2019) and Dr. Cummings (Ex. 2020), cited by Patent Owner, do not persuade us otherwise. PO Resp. 19–21 (citing Ex. 2019 ¶¶ 64–67; Ex. 2020 ¶¶ 101–107). For example, Dr. Cumming refers to where van Bree '410 says "it is *possible* that other sources of [hGAA], such as resulting from cellular expression systems, can also be used," but "it is more laborious to produce the large amounts" hGAA produced in stable eukaryotic cell lines, such as CHO cells, as "needed for clinical therapy." Ex. 1005, 13:53–64 (emphasis added); Ex. 2020 ¶ 101 (citing Ex. 1005, 13:53–64); *see also* Ex. 2020 ¶¶ 102–104, 106–111 (discussing van Bree '410). Dr. Wasserstein similarly cites van Bree '410. Ex. 2019 ¶¶ 66–67. As discussed above, however, other portions of van Bree '410 indicate that hGAA produced in CHO cells would work upon administration as it would work for hGAA produced in transgenic mice, even assuming producing hGAA in CHO cells would be "more laborious."

Dr. Cumming and Dr. Wasserstein also refer to Canfield (Ex. 2016). Ex. 2020 ¶ 102, Ex. 2019 ¶ 66. As discussed above, we are not persuaded that Canfield indicates that an ordinary artisan would have known that the administration amounts and intervals disclosed in van Bree '410 would have been inapplicable to hGAA produced in CHO cell cultures. Moreover, we find that Canfield indicates that hGAA produced in CHO cells would work in methods for treating lysosomal storage diseases, as does Van Hove 1996 in relation to Pompe disease in particular.

In addition, we are not persuaded by Dr. Cummings' and Dr. Wasserstein's citation to a conference poster

indicating what was "later confirmed" in 2003, i.e., after the filing date of '712 patent. Ex. 2020 ¶¶ 105, 112, 113 (citing "McVie-Wylie Poster," Ex. 2047); Ex. 2019 ¶ 66 (also relying on Dr. Cumming Declaration). We note that the McVie-Wylie Poster itself discloses that both hGAA produced in transgenic rabbits and rhGAA produced in CHO cells worked to "clear glycogen" in mice, and that the "reduction in glycogen was more significant in mice treated with the rhGAA produced in CHO cells." Ex. 2047. Such disclosures do not indicate that descriptions in van Bree '410 regarding administration amounts and intervals would apply only to hGAA produced in transgenic mice, but not hGAA produced in CHO cell cultures, especially when van Bree '410 itself discusses how hGAA produced from both sources are similar, as discussed above.

Based on the record before us, we conclude that Petitioner has established by a preponderance of the evidence that van Bree '410 describes every element of claims 1 and 20, as well as dependent claims 2–8, 12, and 15 of the '712 patent.

3. Analysis—claim 9

As noted above, Petitioner contends that van Bree '410 describes a "precursor" form of recombinant hGAA produced in CHO cells cultures, as recited in claim 9. Pet. 33–35 (citing Ex. 1005, 5:36–38, 6:12–16, 20:41–47, 19:50–20:11); Appendix 2. For example, van Bree '410, in a section titled "Conforma[t]ion of Lysosomal Proteins," states that the "main species recognized" of post translational hGAA "are a 110/100 kD precursor, a 95 kD intermediate and 76

kD and 70 kD mature forms," and that "post translational processing of natural" hGAA and rhGAA "as expressed in cultured mammalian cells like . . . CHO cells is similar." Ex. 1005, 6:1–16.

In its Response, Patent Owner contends that administering a "precursor" in claim 9 refers to "administering *exclusively* a precursor of recombinant hGAA that has been produced in CHO cell cultures." PO Resp. 22–23 (emphasis added). Patent Owner further contends that the rhGAA precursor disclosed in van Bree is only a precursor obtained from the milk of transgenic mammals. *Id.* at 23. According to Patent Owner, van Bree '410 "does not disclose administering exclusively any precursor of recombinant hGAA, let alone a precursor of recombinant hGAA produced in CHO cell cultures." *Id.* at 23–25.

As noted above, we construe "precursor" in claim 9, and the rest of claims 1 and 9, as encompassing administering both precursor and non-precursor forms of rhGAA at the same time, and not limited to administering exclusively a precursor form and no other form. Thus, we are not persuaded by Patent Owner's position that van Bree '410 does not disclose administering exclusively any precursor of rhGAA. In addition, for the reasons discussed above in relation to claims 1 and 20, we also conclude that van Bree '410 describes administering a precursor of recombinant hGAA produced in CHO cell cultures, even assuming the reference teaches administering a "mixture which 'is preferably predominantly (i.e., >50%) in the precursor form of about 100-110 kD.'" PO Resp. 23 (quoting Ex. 1005, 13:46–50).

Petitioner has established by a preponderance of the evidence that van Bree '410 describes every element of claim 9 of the '712 patent.

4 Analysis—claim 11

Petitioner contends that van Bree '410 describes administering rhGAA produced in CHO cell cultures, where the administration interval is bimonthly, as recited in claim 11. Pet. 26, Appendix 2 (citing Ex. 1005, 24:23 (Example 5)); Reply 5–6.

Patent Owner responds that van Bree '410 does not disclose administering hGAA to a human individual that has GSD-II every other week, i.e., bimonthly. PO Resp. 26–27. Patent Owner points out that Petitioner relies on Example 5 in van Bree '410, "which describes a phase I study involving *administering hGAA to healthy male volunteers,*" i.e., a study that only assessed "the tolerability of different doses of hGAA." *Id.* at 27.

We agree with Patent Owner. While van Bree '410 describes administering hGAA produced in CHO cells to GSD-II patients "once, twice or three times weekly" for the reasons discussed above, the reference does not describe administering hGAA less frequently except in Example 5, which describes administering hGAA to healthy volunteers. Ex. 1005, 14:12–55. Petitioner has not established by a preponderance of the evidence that van Bree '410 expressly or inherently describes *treating* GSD-II in a human by administering rhGAA bimonthly, as required in claim 11.

5 Analysis—claim 21

Petitioner contends that van Bree '410 describes administering rhGAA produced in CHO cell cultures, where the administration interval is varied over time, as recited in claim 21. Pet. 36 (citing Ex. 1005, 14:35–43). The passage in van Bree '410 cited by Petitioner describes that hGAA "is administered at an initially 'high' dose (i.e., a 'loading dose')," such as "at least about 40 mg/kg patient body weight 1 to 3 times per week," followed by "administration of a lower doses (i.e., a 'maintenance dose')," such as "at least about 5 to at least about 10 mg/kg patient body weight per week." Ex. 1005, 14:35–43.

Patent Owner contends that this cited passage "*does not disclose administering an amount of hGAA that is varied over time depending on the needs of the individual*," but rather is "regimented on a weekly or multiple times per week basis without any variance from time to time." PO Resp. 28–29 (citing Ex. 2019, ¶¶ 76, 80, 81). Patent Owner also contends that the "the initial loading dose would not be understood" by an ordinary artisan "to be *a therapeutically effective amount* of hGAA." *Id.* at 29 (citing Ex. 2019, ¶ 80)

We disagree. Claim 21 requires, in relation to the method of claim 1, that the administration interval is varied over time. In the context of a section on "Therapeutic Methods," van Bree '410 describes administering rhGAA at a certain dosages twice or three times a week "(e.g., for 1, 2, or 3 weeks)", and thereafter at different dosages less often, i.e., once per week. Ex. 1005, 14:35–43. The reference also describes monitoring hGAA following

treatment, and that "a further dosage is administered when detected levels fall substantially below (e.g., less than 20%) of values in normal persons." *Id.* at 14:30–34.

Based on those descriptions, and for the reasons discussed above regarding claim 1, Petitioner has established by a preponderance of the evidence that van Bree '410 discloses every element of claim 21. We are not persuaded otherwise by Dr. Wasserstein's testimony that an ordinary artisan would have appreciated that the described loading dose in van Bree '410 would not have corresponded to a therapeutic dose. Ex. 2019, ¶ 80 (lacking evidence in support for this proposition).

C. Obviousness Over Reuser '771 and Van Hove 1997

Petitioner contends that claims 1–9, 15, and 20 of the '712 patent would have been obvious over Reuser '771 in view of Van Hove 1997. Pet. 26–33, 48–51. Petitioner provides a claim chart to explain how the references allegedly disclose or suggest claimed subject matter, and relies upon the Pastores Declaration (Ex. 1020) and Croughan Declaration (Ex. 1021), to support its positions. *Id.* at Appendix 2; *see also id.* at 26–33, 48–51.

1. Reuser '771 (Ex. 1004)

Reuser '771 relates generally to the production of lysosomal proteins, such as GAA, in the milk of transgenic animals. Ex. 1004, 1:11–2:15. Reuser '771 describes "[g]lycogen storage disease type II (GSD II; Pompe

disease; acid maltase deficiency) . . .” as having three clinical forms, infantile, juvenile and adult. *Id.* at 2:13–22. Reuser ’771 states that “attempts have been made to treat patients having lysosomal storage diseases by (intravenous) administration of the missing enzyme, i.e., enzyme therapy,” and describes prior animal testing involving “intravenously administering purified acid α-glucosidase in phosphorylated and unphosphorylated forms to mice.” *Id.* at 2:32–3:4.

In this context, Reuser ’771 describes isolating lysosomal enzymes from human and animal sources, and states that an “alternative way to produce human acid α-glucosidase is to transfect the acid α-glucosidase gene into a stable eukaryotic cell line (e.g., CHO) as a cDNA or genomic construct operably linked to a suitable promoter.” *Id.* at 3:15–18. Because such production methods can be expensive, however, Reuser ’771 describes another approach of using recombinant proteins produced in the milk of a transgenic animal. *Id.* at 3:19–27.

Reuser ’771 teaches that “[t]he proteolytic processing of acid α-glucosidase is complex,” and the “main species recognized are a 110/100 kDa precursor, a 95 kDa intermediate and 76 kDa and 70 kDa mature forms.” *Id.* at 9:19–26. Reuser ’771 teaches further that “post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar.” *Id.* at 9:29–34.

Regarding uses of such recombinant proteins in enzyme replacement therapy in patients, Reuser '771 describes a "typical composition for intravenous" administration. *Id.* at 18:11–14; 19:34–37. According to Reuser '771, a "therapeutically-" or "prophylactically-effective dose" "will depend on the severity of the condition and on the general state of the patient's health, but will generally range from about 0.1 to 10 mg of purified enzyme per kilogram of body weight." *Id.* at 20:24–28.

Examples in Reuser '771 describe constructing transgenic mice that express human GAA, as well as analyzing the activity of hGAA produced in the milk of transgenic mouse lines. *Id.* at 21:14–28:24. In Example 3, recombinant "[a]cid α-glucosidase purified from the milk was [] tested for phosphorylation by administrating the enzyme to cultured fibroblasts from patients with GSD II (deficient in endogenous acid α-glucosidase)." *Id.* at 27:29–32. As also described in this example, "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α-glucosidase purified from bovine testis, human urine and medium of transfected CHO cells." *Id.* at 28:10–14. In addition, "the N-terminal amino acid sequence of the recombinant α-glucosidase produced in the milk of mice was shown to be the same as that of α-glucosidase precursor from human urine." *Id.* at 28:20–23.

2. Van Hove 1997 (Ex. 1007)

Van Hove 1997 describes a method for purifying recombinant hGAA expressed in CHO cells. Ex. 1007,

613–614. This reference states that "[l]arge quantities of recombinant acid α-glucosidase are needed for in vivo experimentation of enzyme replacement therapy in Pompe disease," and "eventually for use in medicine." *Id.* It also states that the disclosed method "is amenable to scale up, and has increased speed, and improved reproducibility with similar high yield and purification efficiency when compared to previous methods." *Id.* at 613. It describes producing "large quantities" of recombinant hGAA in CHO cells, including recombinant "precursor" GAA. *Id.* at 613–614, 617.

When discussing Pompe disease, Van Hove 1997 further states that "[p]atients with the most common infantile form present with a progressive myopathy and hypertropic cardiomyopathy leading to death before age two years." *Id.* at 613.

3. Analysis

Petitioner contends that Reuser '771, either alone or in view of Van Hove 1997, discloses or suggests every element of claims 1 and 20, as well as dependent claims 2–9 and 15, citing a claim chart and supporting evidence. Pet. 26–33, 48–51; Appendix 2. For example, regarding "administering to the individual a therapeutically effective amount of human acid α-glucosidase" recited in claims 1 and 20, as well as specific amounts recited in claims 5–7, Petitioner points to teachings in Reuser '771 that disclose administering to a GSD-II patient "from about *0.1* to *10 mg* of purified enzyme per kilogram of body weight." Pet. 29–30; Appendix 2; Ex. 1004, 20:9–28. We note that

the '712 patent itself similarly describes a "preferred" therapeutically effective amount "in the range of about 1–10 mg enzyme/kg body weight." Ex. 1001, 6:11–17.

Petitioner indicates also where Reuser '771 describes other recited elements, such as "recombinant" hGAA, including "a precursor" form, as recited in claims 8 and 9. Pet. 30–31 (citing Ex. 1004, 9:30–34; 8:53–54; 9:24–25; 28:19–24; Ex. 1020 ¶ 57; Ex. 1021 ¶¶ 90–94). Petitioner identifies where Reuser '771 teaches that the main species of GAA include a 110/100 kDa precursor, and that post translational processing of natural hGAA is similar to that of recombinant hGAA expressed in CHO cells. Ex. 1004, 9:19–34. Regarding claims 2–4, Petitioner further points to where Reuser '771 teaches that glycogen storage disease type II has three clinical forms, infantile, juvenile and adult. *Id*. at 29, Appendix 2; Ex. 1004, 2:15–22. Petitioner also identifies where Reuser '771 teaches administering hGAA intravenously, as recited in claim 15. Pet. 31, Appendix 2; Ex. 1004, 20:9–10.

In addition, Petitioner contends that Reuser '771 describes, or at least suggests, the suitability of using CHO cells to produce recombinant hGAA for use in treating GSD-II, even if the reference also teaches that such production might be more expensive than production in the milk of transgenic animals. Pet. 27; Ex. 1021 ¶ 0094; Ex. 1004, 3:15–25; 11:29–34; 28:10–14. Petitioner further contends that Van Hove 1997 "relates to the production of recombinant human acid α-glucosidase in CHO cells, particularly large scale production and purification for producing a protein for enzyme replacement therapy." Pet. 50.

Regarding independent claim 20, Petitioner contends that treating cardiomyopathy is inherent in the teaching of Reuser '771, which describes treating GSD-II with GAA. *Id.* at 31 (citing Ex. 1020 ¶ 99). Petitioner relies on the testimony of Dr. Pastores, who indicates, consistent with the claim language itself, that cardiomyopathy is associated with, i.e., a symptom of, GSD-II (Pompe disease). Ex. 1020 ¶ 99. Also consistently, as noted above, when discussing Pompe disease, Van Hove 1997 states that "[p]atients with the most common infantile form present with a progressive myopathy and hypertropic cardiomyopathy leading to death before age two years." Ex. 1007, 613.

Petitioner contends that the only element in challenged claims 1 and 20 that is not mentioned expressly in Reuser '771 is administering hGAA "periodically at an administration interval." Pet. 28. Petitioner also contends, however, relying on testimony by Dr. Pastores, that a person of ordinary skill would have understood "that ERT [enzyme replacement therapy] for GSD-II is not a one shot cure but would require repeated and spaced administrations for the rest of the patient's life." *Id.* (citing Ex. 1020 ¶¶ 60, 61, 84–87, 90, 98).

In its Preliminary Response, Patent Owner contends that BioMarin's "argument, at best, demonstrates that Reuser '771 discloses the feature 'at regular intervals' and maybe 'from time to time.'" Prelim. Resp. 28. As discussed in our Decision to Institute and above, however, we construe "periodically at an administration interval" in claims 1 and 20 to encompass such administration.

Appendix E

In its Response after institution, Patent Owner contends that an ordinary artisan would not have "combined Reuser and Van Hove, i.e., replaced the hGAA produced in transgenic animals described in Reuser with the hGAA produced in CHO cells described in Van Hove," relying on Declarations by Dr. Cummings (Ex. 2020) and Dr. Wasserstein (Ex. 2019). PO Resp. 30–31. We conclude that a preponderance of the evidence establishes otherwise.

We find that Reuser '771 suggests using, in its methods, rhGAA from sources other than milk of transgenic mice, including as produced in CHO cell culture. For example, Reuser teaches that "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α-glucosidase purified from bovine testis, human urine and medium of transfected CHO cells." Ex 1004, 28:10–18. In addition, Van Hove 1997 describes methods for making large quantities of rhGAA in CHO cells, and at least suggests using such rhGAA for the treatment of Pompe disease. Ex. 1007, 613–614. In light of disclosures in the two references, both discussing rhGAA produced in CHO cells and methods of treating Pompe disease, we find that one would have had reason to combine teachings of those references.

Patent Owner acknowledges that the above-mentioned statement in Reuser '771 (PO Resp. 31; Ex 1004, 28:10–18), but contends that an ordinary artisan reading the reference would not have thought that hGAA from transgenic mice and CHO cells shared similarities because

Reuser '771 "cites only previous *in vitro* studies," and no *in vivo* data, in support. PO Resp. 31–32. That contention assumes, however, that one would have understood that statements in Reuser '771, indicating that hGAA from both sources (transgenic mice and CHO cells) would work to restore endogenous GAA activity, were affirmatively incorrect in the absence of *in vivo* data. A showing of obviousness here does not require *in vivo* data as "proof" that an otherwise clear statement in Reuser '771 is correct, when it is reasonably based on *in vitro* studies and other information discussed in the reference.

As the Supreme Court has explained:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 402–403 (2007). Here, Reuser '771 identified rhGAA produced in CHO cells, in particular, and, especially in view of Van Hove 1997, provided "good reason to pursue the known options within his or her technical grasp" using such rhGAA for the treatment of Pompe disease, as taught by Reuser '771, including at the administration doses and intervals disclosed in Reuser '771.

In its Response, Patent Owner also acknowledges that Reuser '771 teaches that "post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." *Id.* at 32; Ex 1004, 9:29–34. Patent Owner contends that this statement in Reuser '771 relates to processing of the amino acid sequence of hGAA, but not glycosylation or phosphorylation of hGAA. PO Resp. 32 (citing Ex. 2020 ¶ 136).

Patent Owner's contention in this regard suffers the same shortcomings discussed above in relation similar contentions by Patent Owner regarding van Bree '410. Similarly to van Bree '410, Reuser '771 includes a section titled "Conformation of Lysosomal Proteins" discussing post translational processing of GAA, which includes glycosylation, phosphorylation, and proteolysis. Ex. 1004, 8:25–10:3. It is in relation to "post translational processing," not just proteolytic processing, that Reuser '771 states that the processing is similar for natural GAA and rhGAA expressed in cultured mammalian cells, such as CHO cells.

Patent Owner also contends that an ordinary artisan reading Van Hove 1997, as well as Van Hove 1996 and Canfield (discussed above), would have understood "the relative inferiority of CHO cells as a source for GAA." PO Resp. 33–35. For example, Patent Owner contends that Reuser '771 describes that transgenic animals were capable of secreting lysosomal proteins "at high levels of at least 10, 50, 100, 500, 1000, 2000, 5000 or 10,000 μg/ml,"

while "Van Hove 1997 described the production of GAA using CHO cells in concentrations of up to only 90 μg/ml." *Id*. at 33 (citing Ex. 2020 ¶ 130 (citing Ex. 1004, 17:16–17; Ex. 1007, 613)).

We disagree that Van Hove 1997 describes production in concentrations of up to only 90 μg/ml. Rather, Patent Owner points to where Van Hove 1997 refers to earlier work by others, including Van Hove 1996, producing GAA in such quantities. PO Resp. 33; Ex. 1007, 613. In any event, Van Hove 1997 expressly teaches how to produce rhGAA in CHO cells, and Van Hove 1997 and Reuser '771 both provided the motivation to use such rhGAA in the methods described Reuser '771.

Relying on Van Hove 1996 and Canfield, Patent Owner also contends that an ordinary artisan would have had no reason to use hGAA produced in CHO cell cultures in the methods of Reuser '771, and no reasonable expectation of success that rhGAA produced in CHO cells, as taught by Van Hove 1997, would have worked in the methods disclosed in Reuser '771. PO Resp. 34–38. Patent Owner again relies on alleged teaching in Van Hove 1996 that rhGAA produced in CHO cells were "undesirably taken up by the liver," as well as Canfield's alleged teaching that rhGAA in Van Hove 1996 were not sufficiently phosphorylated. *Id*. at 34–35, 37. For the reasons discussed above, we do not agree with Patent Owner's characterization of those references. For example, as noted above, Van Hove 1996 teaches that its rhGAA produced in CHO cells exhibited "strikingly increased enzyme levels in the heart following intravenous injection" in animal *in vivo* studies. Ex. 1016, 69, 2nd col.; Reply 9.

Petitioner has established by a preponderance of the evidence that an ordinary artisan reading Reuser '771, in view of Van Hove 1997, with knowledge of Van Hove 1996, Canfield and other references discussed herein, would have had reason to use rhGAA produced in CHO cells, as taught by Van Hove 1997, in the methods disclosed in Reuser '771, and would have had a reasonable expectation of success in doing so, in view of those references. Petitioner has established by a preponderance of the evidence that claims 1–9, 15, and 20 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997.

D. Obviousness Over Reuser '771, Van Hove 1997, van der Ploeg, and Bembi

Petitioner contends that claims 11, 12, and 21 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997, van der Ploeg, and Bembi, among other references. Pet. 51, 43–44. We discuss Reuser '771 and Van Hove 1997 above.

1. van der Ploeg (Ex. 1014)

Van der Ploeg describes cellular uptake of different species of hGAA by muscle cells, including by a 110 kD precursor form of GAA purified from human urine. Ex. 1014, 90, Abstract, 91, 1st col., 93, 2nd col. Van der Ploeg teaches that the "half-life of endocytosed acid α-glucosidase varied between 6 and 9 days in different experiments." *Id.* at 91, 2nd col.

2. Bembi (Ex. 1008)

Bembi describes a protocol for enzyme replacement treatment in patients with Gaucher's disease. Ex. 1008, Summary. In this clinical study, "infusion frequency was weekly during the first 6-9 months and biweekly afterwards." *Id.* at 1679, 2nd col, 1680, Table 1. Bembi discloses that such enzyme replacement therapy can be effective with "a 2-week interval between infusions." *Id.* at 1679, 1st col.

3. Analysis

Petitioner contends that Reuser '771, in view of Van Hove 1997, van der Ploeg, and Bembi, discloses or suggests every element of dependent claims 11, 12, and 21, relying on arguments and evidence discussed above in relation to claim 1, as well as testimony in the Pastores Declaration. Pet. 51, 43–44. Petitioner contends that van der Ploeg "states that the tissue half-life of GAA is known to be 6-9 days." *Id.* at 44. Petitioner relies on testimony by Dr. Pastores to support the contention that, based on that known half-life, it would have been obvious to a clinician to choose a dosing interval of once weekly or bimonthly, as recited in claims 11 and 12. *Id.* Likewise, Petitioner contends that it would have been obvious to vary the administration interval over time, as recited in claim 21. *Id.* In that regard, Petitioner cites testimony by Dr. Pastores indicating that it would have been obvious to vary an administration interval over time after observing patient response to the enzyme. *Id.* (citing Ex. 1020 ¶ 86 (citing Ex. 1008, 1679, 2nd col.)).

Patent Owner contends that Petitioner has not established a reason to combine the four references. PO Resp. 38–41. Patent Owner contends that "van der Ploeg describes an *in vitro* experiment in which muscle cell cultures from an infantile GSD-II patient were treated with hGAA purified from human urine." *Id*. at 39. Patent Owner argues that "[g]iven the known differences in glycosylation and phosphorylation of hGAA from different sources," an ordinary artisan would have had no reason to combine teachings in van der Ploeg to those in references disclosing hGAA produced in CHO cell cultures or transgenic animals. *d*. at 39–40 (citing Ex. 2019 ¶¶ 97–100; Ex. 2020 ¶¶ 145–146). In addition, according to Patent Owner, an ordinary artisan would not have considered the *in vitro* half-life of hGAA from van der Ploeg to be relevant to an *in vivo* half-life because of "the body's sophisticated clearance mechanisms" and prior studies showing that the "majority of hGAA, regardless of source, was taken up by the liver." *Id*. at 40 (citing Ex. 2019 ¶ 98).

Patent Owner contends also that an ordinary artisan would have had no reasonable expectation of success "of obtaining the claimed inventions by combining Reuser, Van Hove, van der Ploeg and Bembi," relying on testimony by Dr. Wasserstein (Ex. 2019) and Dr. Cummings (Ex. 2020). *Id*. at 41–44. For instance, Patent Owner relies on testimony by Dr. Wasserstein stating that no data demonstrated that "hGAA produced in CHO cell cultures could reach muscle cells or be taken up by the lysosomes *in vivo*." *Id*. at 42 (citing Ex. 2019 ¶ 99). In addition, Patent Owner again points out that van der Ploeg discusses the half-life of hGAA *in vitro*, and again refers to "known

differences in glycosylation and phosphorylation of hGAA from different sources." *Id.* at 43–44. Patent Owner also contends that because Bembi relates to treating Gaucher's disease with a different enzyme, rather than GSD-II with hGAA produced in CHO cells, relying on Bembi to suggest administration intervals in relation to treating GSD-II is "unsound." *Id.* at 44 (citing Ex. 2019, ¶¶ 93–94).

As discussed above, Reuser '771 suggests that "natural" hGAA (e.g., purified from urine) and hGAA produced in CHO cells or in transgenic animals exhibit similar post translational processing, including glycosylation, phosphorylation, and proteolysis, and similarly restore endogenous GAA activity in cultured fibroblasts from patients with GSD-II. Ex. 1004, 8:25–10:3; 27:29–28:14. While van der Ploeg describes studies conducted in culture cells *in vitro*, and the half-life of GAA in that context, Dr. Pastores' testimony persuades us that such teachings regarding the enzyme half-life would have suggested optimization of therapy (as discussed ahead) to obtain a dosing interval of rhGAA of once weekly or bimonthly, as recited in claims 11 and 12. Ex. 1020 ¶¶ 86–92. We are also persuaded that Bembi suggests administration intervals of weekly and bimonthly, and varying administration intervals over time, when treating patients with enzyme therapy to treat a lysosomal protein deficiency. Ex. 1008, 1679.

In relation to *in vivo* treatment in humans, a preponderance of the evidence establishes that an ordinary artisan would have engaged in routine optimization when selecting doses and dosing intervals

generally when practicing the enzyme therapy disclosed in Reuser '771 (Ex. 1005, 18:36–20:28), and such optimization was achievable through the use of standard clinical trial procedures. Ex. 1020 ¶¶ 74–92; Pet. 44, 51. The record before us establishes sufficiently that the experimentation needed to achieve the dosing intervals in claims 11, 12, and 21 was "'nothing more than routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan], not of an inventor.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (quoting *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006)*; see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art."). The motivation to optimize the therapy disclose in Reuser "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

A reasonable expectation of success does not require absolute predictability. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). While we recognize that there would have been some degree of unpredictability for the successful treatment of Pompe disease from the administration of GAA, the preponderance of evidence of record indicates

all that remained to be achieved over the prior art was the determination that a suggested dose and dosing schedule would have been safe and effective for the treatment of human patients. This is not a case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006). Reuser '771 discloses specific methods and doses for enzyme replacement therapy in patients using rhGAA (Ex. 1004, 18:11–20:28), and suggests the use of rhGAA produced in CHO cell culture in particular (*id.* at 3:15–25; 9:29–34, 28:8–14), while Van Hove 1997 expressly discloses methods for producing rhGAA in CHO cell culture with "high yield and purification efficiency" (Ex. 1007, 613, summary).

This is also not a case where there were "numerous parameters" to try. *Pfizer*, 480 F.3d at 1364 (citing *Medichem*, 437 F.3d at 1165 ("to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.") (internal quotations omitted)). Rather, we are persuaded by Dr. Pastores' testimony that the knowledge in the art regarding the treatment of Pompe disease with human GAA would have provided the motivation to select a suitable dose and dosing schedule (Ex. 1020 ¶¶ 77–82),

would have been informed by the clinical experience with Gaucher's disease (*id.* at ¶ 86 (citing Ex. 1009, 1052,)), and that, because "it was well known that any enzyme replacement therapy for Pompe disease would be required for the rest of a patient's life, . . . repeated spaced administration of GAA to patients would be immediately understood upon reading Reuser '771" (Ex. 1020 ¶ 60).

Patent Owner's contention that Bembi focuses on the use of β-glucocerebrosidase to treat Gaucher's disease, and not hGAA to treat Pompe disease, does not persuade us otherwise. PO Resp. 40–41. Bembi provides evidence of dosing intervals that an ordinary artisan would have considered when routinely optimizing the therapy disclosed in Reuser '771, which similarly related to enzyme therapy to treat a lysosomal protein deficiency.

Petitioner has established by a preponderance of the evidence that claims 11, 12, and 21 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997.

E. Obviousness Over Reuser '771, Van Hove 1997, and Brady

Petitioner contends that claims 18 and 19 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997 and Brady. Pet. 51, 45–46. We discuss Reuser '771 and Van Hove 1997 above.

Appendix E

1. Brady (Ex. 1012)

Brady discloses a clinical protocol to manage enzyme neutralizing antibodies in patients during treatment of Gaucher's disease with the enzyme glucocerebrosidase. Ex. 1012, 1. Brady states that "the strategy we have used (plasma exchange, cyclophosphamide, intravenous IgG, and large doses of enzyme) may provide benefit to such individuals." *Id.* at Abstract. Brady further discloses that "[i]t is also likely that this technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals)." *Id.* In the protocol, in an "effort to immunosuppress the patient," Brady teaches administering cyclophosphamide (an immunosuppressant) on the same day as glucocerebrosidase enzyme, and in some cases before administering the enzyme on a following day. *Id.* at 3, ¶ spanning 1st and 2nd cols., Table 1.

2. Analysis

Petitioner contends that Reuser '771, in view of Van Hove 1997 and Brady, discloses or suggests every element of dependent claims 18 and 19, relying on arguments and evidence discussed above in relation to claim 1, as well as testimony in the Pastores Declaration. Pet. 51, 45–46. Petitioner contends that Brady discusses the use of the immunosuppressant cyclophosphamide in conjunction with enzyme replacement therapy in Gaucher's disease, and that such a strategy is likely to be helpful in enzyme replacement therapy in other disorders where a genetic

mutation abrogates the production of the protein. *Id.* at 45–46. Petitioner relies also on testimony by Dr. Pastores to support the contention that it would have been obvious to administer an immunosuppressant in conjunction with enzyme replacement therapy to treat GSD-II "to alleviate unwanted immune responses." *Id.* at 46 (citing Ex. 1020 ¶ 95).

Patent Owner contends that an ordinary artisan would have had no reason to combine the cited references, arguing that an ordinary artisan "interested in treating GSD-II with hGAA from CHO cells would have had no reason to also administer an immunosuppressant." PO Resp. 47–51. Patent Owner contends also that an ordinary would not have considered Brady "relating to treating a single patient with Gaucher's disease who had experienced a rare and severe immunological response to administration of Ceredase isolated from human placenta relevant to a treatment regimen for treating GSD-II with hGAA produced in CHO cell cultures." *Id.* at 49 (citing Ex. 2020, ¶ 154; Ex. 2019 ¶ 105). Patent Owner also contends, citing testimony by Dr. Wasserstein, that "immunological risks to GSD-II patients would be different than the immunological risks to patients with Gaucher's disease," and that "Brady concerns administering an immunosuppressant in response to an immunological reaction to exogenous enzyme, not for the purpose of preventing production of anti-GAA antibodies." *Id.* at 50 (citing Ex. 2019 ¶¶ 107, 111–112). Patent Owner further contends that Brady does not disclose administration of immunosuppressant prior to the first administration of the enzyme within an administration interval, as required in claim 19. *Id.* at 53–55.

We conclude that Dr. Pastores' testimony in this regard is more persuasive. Ex. 1020 ¶¶ 93–95. Brady discloses the use of an immunosuppressant, cyclophosphamide, to manage neutralizing antibodies directed against a treatment enzyme, Ceredase, in patients with Gaucher disease, a lysosomal protein deficiency disease. Ex. 1012, 1. Brady expressly states that its "technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein." *Id*. Such teachings would have suggested to an ordinary artisan to use an immunosuppressant similarly when administering enzyme replacement therapy, such as rhGAA produced in CHO cells, to least some patients when treating a different lysosomal protein deficiency, such as Pompe disease, even assuming one understood that a severe neutralizing antibody response would have been rare. Ex. 1020, ¶¶ 93–95.

Brady likewise would have suggested that after a neutralizing antibody response occurred, an ordinary artisan would have had reason to administer enzyme therapy, such as rhGAA produced in CHO cells, in conjunction with an immunosuppressant (i.e., within a short time frame of each other, as required in claim 18), and before the first administration of rhGAA in a next administration interval. *See, e.g.*, Ex. 1012, 3, ¶ spanning 1st and 2nd cols., Table 1 (describing administering enzyme therapy ("GC") and immunosuppressant cyclophosphamide ("CTX")).

Regarding claim 19, as discussed above, we construe the phrase "immunosuppressant is administered

prior to any administration" of hGAA to refer to administering an immunosuppressant prior to the first administration of hGAA to the individual. As noted by Patent Owner, Brady teaches administering both enzyme and immunosuppressant on "Day 1," i.e., the first day of treatment in the individual. PO Resp. 54; Ex. 1012, 3, ¶ spanning 1st and 2nd cols., Table 1. Brady further teaches administering the immunosuppressant (cyclophosphamide or "CTX") again prior to subsequent administrations of the enzyme. *Id.*

Brady teaches administering the immunosuppressant in this fashion in an "effort to immunosuppress the patient" and reduce neutralizing antibodies in the individual. *Id.* at 3. (including sections titled "Intervention" and "Reduction of Neutralizing Antibody Titer"). Based on such teachings in Brady and the record before us, we are persuaded that an ordinary artisan would have had reason to administer an immunosuppressant, for example on Day 1 of treatment, prior to any administration of enzyme therapy, such as rhGAA. *See also* Pet. 52 (citing Ex. 1020 ¶ 95 (testimony of Dr. Pastores stating that "[i]f there is a high incidence of patients developing high antibody titers, an immunosuppressant could be administered prophylactically prior to any administration of the recombinant enzyme begins to minimize the potential adverse effects of such.")).

Petitioner has established by a preponderance of the evidence that claims 18 and 19 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997 and Brady.

F. Secondary Considerations

We recognize that factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–1472 (Fed. Cir. 1984). Such a conclusion, however, requires the finding of a nexus to establish that the evidence relied upon traces its basis to a novel element in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). All types of objective evidence of non-obviousness must be shown to have nexus. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) (praise); *Stamps.com Inc. v. Endicia, Inc.*, 437 F. App'x 897, 905 (Fed. Cir. 2011) (skepticism).

Patent Owner contends that several lines of objective evidence (or "secondary considerations") demonstrate the non-obviousness of the challenged claims. PO Resp. 55–58. In particular, Patent Owner argues long-felt need

and failure by others (*id.* at 56), unexpected results (*id.* at 56–57), licensing (*id.* at 57), commercial success (*id.* at 57–58), and praise and industry acceptance (*id.* at 58).

All of the challenged claims recite a method of treating GSD-II disease by administering hGAA produced in a CHO cell culture. Patent Owner's arguments with regard to each of the secondary considerations, however, fail to establish a nexus between those recited methods and the asserted objective evidence of non-obviousness.

For example, Patent Owner does not explain adequately why the "successful therapeutic treatment for Pompe disease with hGAA produced in CHO cell cultures" as disclosed in the '712 patent would have been unexpected upon reading Reuser '771, in view of Van Hove 1997 and other references, or how the subject matter of '712 patent overcame a "failure of others." *Id.* at 56–57. For instance, Patent Owner provides no evidence that the method taught in Reuser '771 (Ex. 1004, 18:11–20:28), using rhGAA produced in CHO cells as suggested in Reuser '771 and Van Hove 1997, would not, or did not, work in human patients.

Moreover, in relation to licensing, as noted by Petitioner, Patent Owner does not discuss or address whether other patents or intellectual property might have been involved in the "two significant rights transfers" mentioned by Patent Owner. *Id.* at 57. Likewise, Patent Owner does not show adequately a nexus between what is recited in the challenged claims of the '712 patent in particular and the commercial success of Myozyme/

Lumizyme or the asserted praise and industry acceptance. *Id*. at 57–58 (citing Ex. 2021 ¶ 57, 36), 58. For instance, although Patent Owner points us to a Declaration by Mr. Phillip Green discussing Myozyme/Lumizyme sales and royalty rates, Patent Owner does not explain adequately, or point us to where Declaration addresses, the required nexus. *Id*.

Accordingly, the objective evidence does not persuade us that the challenged claims would have been non-obvious. When we balance Petitioner's evidence of obviousness against Patent Owner's asserted objective evidence of non-obviousness, we determine that a preponderance of the evidence supports Petitioner's position that challenged claims would have been obvious over the cited references.

G. Conclusion

In view of the above, we conclude that Petitioner has demonstrated by a preponderance of the evidence that van Bree '410 anticipates claims 1–9, 12, 15, and 18–21 of the '712 patent, and that claims 1–9, 11, 12, 15, and 18–21 would have been obvious over Reuser '771 in view of Van Hove 1997, and van der Ploeg, Bembi, and/or Brady

III. MOTIONS TO EXCLUDE

A. Patent Owner's Motion to Exclude Evidence

Patent Owner moves to exclude Petitioner's Exhibit 1157 (a deposition transcript of Dr. William Canfield), as well as Exhibits 1117, 1118, 1121, 1127, 1131, 1132, 1136,

1137, and 1161–1165, for different reasons. Paper 72. Because we do not rely on any of these exhibits in reaching the Final Written Decision, we dismiss Petitioner's motion as moot.

B. Petitioner's Motion to Exclude Evidence

Petitioner moves to exclude the Declaration of Mr. Philip Green (Ex. 2021), portions of Dr. Cummings' Declaration discussing Mr. Green's testimony (Ex. 2020 ¶¶ 14, 155–160), as well as Exhibit 2070, which is a "Technology Assignment Agreement," and Exhibit C to a larger 2000 Agreement between Synpac and Genzyme. Paper 73, 1.

Because we do not rely on paragraphs 14 and 155–160 of Dr. Cummings' Declaration (Ex. 2020), nor Exhibit 2070, in reaching the Final Written Decision, we dismiss the portion of Petitioner's Motion to Exclude relating to those exhibits as moot.

As discussed above, however, we consider Mr. Green's Declaration when analyzing Patent Owner's contentions regarding objective evidence of non-obviousness. Petitioner argues that we should exclude this Declaration because: (1) it "assumes that Myozyme and Lumizyme are the same product described and claimed" in the '712 patent; (2) Mr. Green has no "firsthand knowledge of the chemical identity" of Myozyme and Lumizyme or whether the method clamed in the '712 patent is used to make Myozyme and Lumizyme; (3) "Mr. Green testified that he did not know whether the cell line that was the subject of

the 1996 Assignment Agreement . . . (Ex 2070) was the same cell line used by Genzyme to create Myozyme and Lumizyme"; and (4) paragraphs 16–18 and 47–49 of Mr. Phillip's Declaration mention a 2000 "Agreement" that is not of record in this proceeding. Paper 73, 4–8 (citing Federal Rules of Evidence 702 and 703).

We have reviewed the cited portions of the testimony provided by Mr. Green and see no basis on which they would warrant the extreme remedy of exclusion. Patent Owner's above-mentioned contentions go to the weight and sufficiency of Mr. Green's testimony, rather than its admissibility. We are capable of discerning from the testimony, and the evidence presented, whether the witness' testimony should be entitled to any weight, either as a whole or with regard to specific issues. We deny Petitioner's Motion to Exclude in relation to the Declaration of Mr. Philip Green (Ex. 2021).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–9, 11, 12, 15, and 18–21 of the '712 patent are determined to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

APPENDIX F — DECISION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD, DATED FEBRUARY 24, 2014

UNITED STATES PATENT
AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL
AND APPEAL BOARD

BIOMARIN PHARMACEUTICAL INC.,

Petitioner,

v.

DUKE UNIVERSITY,

Patent Owner.

Case IPR2013-00535
Patent 7,056,712 B2

Before LORA M. GREEN, JACQUELINE WRIGHT BONILLA, and SHERIDAN K. SNEDDEN,
Administrative Patent Judges.

BONILLA, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

Appendix F

I. INTRODUCTION

Petitioner BioMarin Pharmaceutical Inc. ("BioMarin") filed a petition (Paper 5, "Pet.") requesting *inter partes* review of claims 1-9, 11, 12, 15, and 18-21 of U.S. Patent No. 7,056,712 B2 (Ex. 1001, "the '712 patent"). 35 U.S.C. § 311. Duke University ("Duke") filed a timely preliminary response (Paper 13, "Prelim. Resp."). Based on the record presented, we conclude that BioMarin has shown that, under 35 U.S.C. § 314(a), there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims.

A. Related Proceedings

BioMarin indicates that are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Pet. 1. On the same day, BioMarin filed its petition in this proceeding, however, it also filed two other petitions seeking *inter partes* review of U.S. Patent No. 7,351,410 ("van Bree '410") (IPR2013-00534) and U.S. Patent No. 7,655,226 ("the '226 patent") (IPR2013-00537), respectively. Although the '712 patent is not related to van Bree '410 (Ex. 1005, in this proceeding) or the '226 patent, all three patents relate to similar subject matter, i.e., methods of treating Pompe's disease.

B. The '712 Patent

The '712 patent relates to methods of treating glycogen storage disease type II ("GSD-II"). Ex. 1001, Abstract. Glycogen storage disease type II, also known as Pompe's

disease or acid maltase deficiency, is a genetic muscle disorder caused by a deficiency of acid α-glucosidase ("GAA"), a glycogen degrading lysosomal enzyme. *Id*. at 1:12-15. The disclosed methods involve enzyme replacement therapy ("ERT"), including administering to an individual a therapeutically effective amount of GAA. *Id*. at 1:62-66; 2:20-27. In a preferred embodiment, the method uses recombinant human acid α-glucosidase ("rhGAA"), such as a recombinant human GAA precursor form, produced in Chinese hamster ovary ("CHO") cell cultures. *Id*. at 3:57-4:4. In certain embodiments, the method involves administering GAA in conjunction with other agents, such as immunosuppressants. *Id*. at 5:29-33.

Independent claims 1 and 20, reproduced below, are illustrative of the claimed subject matter:

> 1. A method of treating glycogen storage disease type II in a human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of human acid α- glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell cultures.
>
> 20. A method of treating cardiomyopathy associated with glycogen storage disease type II in an human individual having glycogen storage disease type II, comprising administering to the individual a therapeutically effective amount of

> human acid α-glucosidase periodically at an administration interval, wherein the human acid α-glucosidase was produced in chinese hamster ovary cell culture.

Claims 2-9, 11, 12, 15, 18, 19, and 21 depend on claim 1.

C. Asserted Grounds

BioMarin contends that the challenged claims are unpatentable under 35 U.S.C. §§ 102 or 103 based on the following twelve grounds (Pet. 3-5, 20-52, Appendix 2):

Reference(s)	Basis	Claims challenged
Synpac (Ex. 1002),[1] including as evidenced by Genzyme General (Ex. 1003)[2]	§ 102	1-4, 8, 9, 15, and 20
Reuser '771 (Ex. 1004)[3]	§ 102 or § 103	1-9, 15, and 20[4]

1. Synpac Pharmaceuticals Limited, "Duke University Starts Clinical Trials for Pompe's Disease," press release, June 30, 1999 (Ex. 1002); *see also* http://www.amda-pompe.org/index.php/main/news/duke_university_starts_clinical_trials_for_pompes_disease (accessed Dec. 16, 2013).

2. Acid Maltase Deficiency Association, Genzyme General, "Genzyme General Obtains Rights to Pompe Disease Therapy from Synpac . . . ," press release, April 20, 2000 (Ex. 1003).

3. Reuser et al., WO 97/05771, published Feb. 20, 1997 (Ex. 1004).

4. Pet. 26.

Appendix F

Reference(s)	Basis	Claims challenged
van Bree '410 (Ex. 1005)[5]	§ 102 or § 103	1-9, 11, 12, 15, 20, and 21
Synpac and Reuser '771	§ 103	1-4, 8, 9, 15, and 20
Synpac and Kikuchi (Ex. 1006),[6] and/or Van Hove 1996 (Ex. 1016)[7]	§ 103	5-7
Synpac and van der Ploeg (Ex. 1014),[8] Barton (Ex. 1009),[9] or	§ 103	11, 12, and 21

5. van Bree et al., U.S. Patent No. 7,351,410 B2, issued Apr. 1, 2008 (Ex. 1005).

6. Tateki Kikuchi et al., "Clinical and Metabolic Correction of Pompe Disease by Enzyme Therapy in Acid Maltase-deficient Quail," J. Clin. Invest., 101(4):827-833 (1998) (Ex. 1006).

7. Johan L. K. Van Hove et al., "High level production of recombinant human lysosomal acid α-glucosidase in Chinese hamster ovary cells which targets to heart muscle and corrects glycogen accumulation in fibroblasts from patients with Pompe disease," Proc. Natl. Acad. Sci. USA, 93:65-70 (1996) (Ex. 1016).

8. Ans T. van der Ploeg et al., "Receptor-Mediated Uptake of Acid α-Glucosidase Corrects Lysosomal Glycogen Storage in Cultured Skeletal Muscle," Pediatric Research, 24(1):90-94 (1988) (Ex. 1014).

9 Norman W. Barton et al., "Replacement Therapy for Inherited Enzyme Deficiency –Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease," N. Eng. J. Med., 324(21):1464-1470 (1991) (Ex. 1009).

Appendix F

Reference(s)	Basis	Claims challenged
Bembi (Ex. 1008)[10]		
Synpac and Grabowski (Ex. 1011)[11] or Brady (Ex. 1012)[12]	§ 103	18 and 19
Synpac and Hers (Ex. 1019)[13]	§ 103	20
Reuser '771 and Synpac, van der Ploeg, Fuller (Ex. 1015),[14] and/or Van Hove 1997 (Ex. 1007)[15]	§ 103	1-9, 15, and 20[16]

10. B. Bembi et al., "Enzyme replacement therapy in type 1 and type 3 Gaucher's disease," The Lancet, 344:1679-1682 (1994) (Ex. 1008).

11. G. A. Grabowski et al., "Enzyme therapy for Gaucher disease: the first 5 years," Blood Reviews, 12:115-133 (1998) (Ex. 1011).

12. Roscoe O. Brady et al. "Management of Neutralizing Antibody to Ceredase in a Patient With Type 3 Gaucher Disease," Pediatrics, 100(6):e11 (1997) (Ex. 1012).

13. H. G. Hers, "α-Glucosidase Deficiency in Generalized Glycogen-Storage Disease (Pompe's Disease)," Biochem. J., 86:11-16 (1963) (Ex. 1019).

14. Maria Fuller et al., "Isolation and characterisation of a recombinant, precursor form of lysosomal acid α-glucosidase," Eur. J. Biochem., 234:903-909 (1995) (Ex. 1015).

15. Johan L. K. Van Hove et al., "Purification of recombinant human precursor acid α-glucosidase," Biochemistry and Molecular Biology International, 43(3):613-623 (1997) (Ex. 1007).

Appendix F

Reference(s)	Basis	Claims challenged
Reuser '771 and Synpac, Fuller, and/or Van Hove 1997, and van der Ploeg, Barton, or Bembi	§ 103	11, 12, and 21
Reuser '771 and Synpac, Fuller, and/or Van Hove 1997, and Grabowski or Brady	§ 103	18 and 19
Reuser '771 and Synpac, Fuller, and/or Van Hove 1997, and Hers	§ 103	20

II. ANALYSIS

A. Claim Construction

Consistent with the statute and legislative history of the America Invents Act, the Board interprets claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also* Office Patent Trial Practice Guide ("Practice Guide"), 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012). There is a "heavy presumption" that a claim term carries its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) (citations omitted).

16. Pet. 48.

Appendix F

1. "Produced in Chinese Hamster Ovary Cell Cultures"

According to BioMarin, "produced in chinese hamster ovary cell cultures," as recited in independent claims 1 and 20, is a product-by-process limitation. BioMarin contends that human GAA (hGAA) "produced in chinese hamster ovary cell cultures" is drawn to a product, and the hGAA product is defined in the claims by the process by which it is produced, i.e., in CHO cell culture. Pet. 17-18. BioMarin argues further that "the product-by-process limitation does not give patentable weight to the claim if the product used in the claimed method 'is the same as or obvious from a product of the prior art'." Pet. 19 (citing *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006)).

Duke, on the other hand, contends that this language "describes human acid α-glucosidase from chinese hamster ovary cell cultures," i.e., the source of the hGAA, and is not a product-by-process limitation. Prelim. Resp. 6-7, 9. Duke refers to *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) as:

> holding that the limitation "purified from mammalian cells grown in culture" "clearly limits the *source* of the [protein]" (emphasis added)); *id.* at 1330, n.5 (claim limitations, including "purified from mammalian cells grown in culture" "mean just what they say. Accordingly they limit only the *source* from which the [protein] is obtained, not the method by which it is *produced*." (emphasis added)).

Prelim. Resp. 6-7.

On the record before us, we do not construe "produced in chinese hamster ovary cell cultures" in relation to the recited hGAA as a product-by-process limitation. A product-by-process claim is "one in which the product is defined at least in part in terms of the method or process by which it is made." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 158 n.* (1989) (citation omitted). Here, we agree with Duke that the claim language more closely identifies the protein source, rather than a product that is defined by a process that allows one to claim "an otherwise patentable product that resists definition by other than the process by which it is made." *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006) (quoting *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985)).

2. Administering "Periodically at an Administration Interval"

Duke contends that we should construe "periodically at an administrative interval" in claims 1 and 20 as the Board interpreted the phrase in an earlier 2005 decision. Prelim. Resp. 19 (citing *Ex parte Chen*, No. 2005-0410 (BPAI 2005), Ex. 1028, 4-6). We agree. To clarify, however, as stated in the Board's 2005 decision, and consistent with the Specification of the '712 patent, we construe this phrase to refer to administering hGAA "at regular intervals" or "from time to time," which "need not be a fixed interval, but can be varied over time, depending on the needs of the individual." Ex. 1028, 5-6; Ex. 1001, 6:

18-22. That includes, but is not limited to, administering hGAA "monthly, bimonthly, weekly, twice weekly, daily." Ex. 1001; 2:9-10; 6:27-30 (distinguishing "periodically" from a "one-time dose").

3. "Therapeutically Effective Amount" of hGAA

Claims 1, 5-7, and 20 recite a "therapeutically effective amount" of hGAA. The '712 patent Specification defines "therapeutically effective amount" as "a dosage amount that, when administered at regular intervals, is sufficient to treat the disease, such as by ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease." *Id.* at 5:60-66. In certain embodiments, that amount is less than about 15 mg enzyme/kg body weight of the individual, in the range of about 1-10 mg enzyme/kg body weight, about 10 mg enzyme/kg body weight, or about 5 mg enzyme/kg body weight, administered at a regular interval (e.g., monthly, bimonthly, weekly, twice weekly, daily). *Id.* at 2:62-3:4; 6:12-17.

Consistent with those disclosures, we construe "therapeutically effective amount" to be an amount of hGAA administered at an interval that ameliorates, or lessens the severity or frequency of, symptoms of glycogen storage disease type II. Such amounts include about 15 mg, about 1-10 mg, or about 5 mg hGAA per kilogram body weight of the individual, as recited in dependent claims 5-7.

4. "In Conjunction with" and "Prior To Any Administration"

Dependent claim 18 recites that the hGAA is administered "in conjunction with" an immunosuppressant. BioMarin argues that this language means that the immunosuppressant is administered "at about the same time" as hGAA. Pet. 19 (citing Ex. 1001, 5:33-35). We agree with that construction. We note further that the '712 patent discloses that "in conjunction with" means "that the agent is administered at about the same time as the GAA," which may include administering an immunosuppressant separately, but "within a short time frame (e.g., within 24 hours) of administration of the GAA." Ex. 1001, 5:33-44. Thus, we construe "in conjunction with" to refer to administering hGAA and an immunosuppressant at about the same time, i.e., within 24 hours of each other.

Claim 19, which depends on claim 18, recites that the immunosuppressant is administered "prior to any administration" of hGAA to the individual. Consistent with the ordinary meaning of phrases in both claims 18 and 19, as well as teachings in the Specification, we construe this language to refer to administering an immunosuppressant before the first administration of any hGAA within a particular administration interval. *See* Ex. 1001, 6:24-39 (regarding "interval").

B. Anticipation by van Bree '410

BioMarin contends that van Bree '410 anticipates claims 1-9, 11, 12, 15, 20, and 21 of the '712 patent. Pet.

33-37. BioMarin provides a claim chart to explain how van Bree '410 allegedly discloses the claimed subject matter, and relies upon the Declaration of Dr. Gregory Pastores ("Pastores Declaration") (Ex. 1020), and the Declaration of Dr. Matthew Croughan ("Croughan Declaration") (Ex. 1021), to support its positions. *Id*. at Appendix 2; *see also id*. at 34, 36-37.

1. van Bree '410 (Ex. 1005)

Van Bree '410 describes "methods of treating Pompe's disease using human acid alpha glucosidase," where a "preferred treatment regime comprises administering greater than 10 mg/kg body weight per week to a patient." Ex. 1005, Abstract. Claim 1 in van Bree '410 recites a "method of treating a human patient with Pompe's disease, comprising intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase . . . ." *Id*. at 29:8-12; *see also id*. at 24:10-38 (Example 5, referring to intravenous infusion administered two weeks apart).

In examples, van Bree '410 describes the use of rhGAA isolated from the milk of transgenic mice, including for use in human clinical trials. *Id*. at 16:17-20:48; 24:10-25:20. When describing "Therapeutic Methods" generally, however, van Bree '410 discloses that "an alternative way to produce human acid α- glucosidase is to transfect the acid α-glucosidase gene into a stable eukaryotic cell line (e.g., CHO) as a cDNA or genomic construct operably linked to a suitable promoter," but states that such an approach is "more laborious to produce the large amounts . . . for clinical therapy . . . ." *Id*. at 13:39, 58-64.

Van Bree '410 discloses that hGAA "is usually administered at a dosage of 10 mg/kg patient body weight or more per week to a patient," and describes a preferred embodiment where "10 mg/kg, 15 mg/kg . . . is administered once, twice or three times weekly." *Id.* at 14:16-27. In addition, "[t]reatment is typically continued for at least 4 weeks, sometimes 24 weeks, and sometimes for the life of the patient." *Id.* at 14:27-29. One example of "a maintenance dose is at least about 5 to at least about 10 mg/kg patient body weight per week . . . ." *Id.* at 14:40-42. Van Bree '410 also teaches that, "[t]ypically, the intravenous infusion occurs over a period of several hours (e.g., 1-10 hours and preferably 2-8 hours, more preferably 3-6 hours), and the rate of infusion is increased at intervals during the period of administration." *Id.* at 14:52-55. Van Bree '410 further discloses the "methods are effective on patients with both early onset (infantile) and late onset (juvenile and adult) Pompe's disease." *Id.* at 15:10-14.

2. Analysis

BioMarin contends that van Bree '410 qualifies as prior art under 35 U.S.C. § 102(e). Pet. 33. Duke does not challenge this contention, but rather argues that van Bree '410 fails to describe certain elements of challenged claims. *See, e.g.*, Prelim. Resp. 2-3, 6-16, 32-34, 40-45. Thus, for purposes of this decision, we determine that van Bree '410 qualifies as prior art under § 102(e).

BioMarin contends that van Bree '410 discloses every element of claims 1 and 20, as well as dependent claims

2-9, 11, 12, 15, and 21, citing a claim chart and supporting evidence. Pet. 33-37; Appendix 2. For example, regarding "administering to the individual a therapeutically effective amount of human acid α-glucosidase," recited in claims 1 and 20, as well as specific amounts recited in claims 5-7, BioMarin points to where van Bree '410 describes "that a dose is usually 10 mg/kg," a dose used in the disclosed clinical trials, and that "preferred regimes are 10, 15, 20, 30 or 40 mg/kg, 1-3 times per week." Pet. 35. BioMarin also contends that van Bree '410 teaches a maintenance dose of 5mg/kg, as recited in claim 7. *Id*; Ex. 1005, 14:40-42.

BioMarin contends that van Bree '410 describes other recited elements, such as "recombinant" hGAA, including "a precursor" form, as recited in claims 8 and 9. Pet. 33-35 (citing Ex. 1005, 10:57-11:42; 19:50-20:11); *id*. at Appendix 2 (citing Ex. 1005, 20:42-47). BioMarin also contends that van Bree '410 describes treating an infantile, juvenile, and adult-onset form of GSD-II, as recited in claims 2-4. *Id*. at Appendix A (citing Ex. 1005, 15:12-14).

In addition, BioMarin points to where van Bree '410 discloses administering hGAA bimonthly, weekly, at an interval varied over time, and intravenously, as recited in claims 11, 12, 15, and 21. *Id*. at 36, Appendix 2 (citing Ex. 1005, 24:23; 14:26-43). Duke responds that van Bree '410 does not disclose administering "periodically at an administration interval" as recited in claims 1 and 20, based on an asserted claim construction. Prelim. Resp. 32-33. As noted above, however, we construe administering "periodically at an administration interval"

to encompass administering hGAA bimonthly, weekly, and at an interval varied over time, and BioMarin has demonstrated a reasonable likelihood that van Bree '410 provides such disclosure. Pet. 36, Appendix 2.

Duke also argues that van Bree '410 does not disclose treating GSD-II using hGAA that "was produced in chinese hamster ovary cell cultures," as required in the challenged claims. Prelim. Resp. 6-15, 40-42. Along these lines, Duke argues that this phrase is not a product-by-process limitation. *Id.* Duke also contends that van Bree '410 teaches the use of hGAA produced in milk of transgenic mice, and BioMarin "makes no attempt . . . to demonstrate that . . . Van Bree '410 Patent disclose[s] the treatment of GSD-II using human acid α-glucosidase that 'was produced in chinese hamster ovary cell cultures.'" *Id.* at 10.

As discussed above, we do not construe "produced in chinese hamster ovary cell cultures" to be a product-by-process limitation, and, therefore, we consider whether cited prior art teaches or suggests hGAA produced in CHO cell culture. BioMarin persuades us, however, that van Bree '410 describes relevant "Therapeutic Methods" involving the use of hGAA produced recombinantly in CHO cells, even if it also teaches that such production might be "more laborious" than production in milk of transgenic animals. Ex. 1005, 13:39, 58-64.

Thus, we are persuaded that there is a reasonable likelihood that BioMarin would prevail in showing that van Bree '410 anticipates claim 1, as well as dependent

claims 2-9, 11, 12, 15, and 21. Independent claim 20 is similar to claim 1, but recites a method of "treating cardiomyopathy associated with glycogen storage disease type II." BioMarin contends that van Bree '410 describes such treatment. Pet. 36 (citing Ex. 1005, 15:19-37). We are persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail on the ground that van Bree '410 anticipates claim 20.

C. Obviousness Over Reuser '771 and Van Hove 1997

BioMarin contends that claims 1-9, 15, and 20 of the '712 patent would have been obvious over Reuser '771, either alone or in view of Van Hove 1997, among other references. Pet. 26-33, 48-51. BioMarin provides a claim chart to explain how Reuser '771 allegedly discloses or suggests claimed subject matter, and relies upon the Pastores Declaration (Ex. 1020) and Croughan Declaration (Ex. 1021), to support its positions. *Id.* at Appendix 2; *see also id.* at 26-33, 48-51.

1. Reuser '771 (Ex. 1004)

Reuser '771 relates generally to the production of lysosomal proteins, such as GAA, in the milk of transgenic animals. Ex. 1004, 1:11-2:15. Reuser '771 describes "[g]lycogen storage disease type II (GSD II; Pompe disease; acid maltase deficiency) . . ." as having three clinical forms, infantile, juvenile and adult. *Id.* At 2:15-22. Reuser '771 states that "attempts have been made to treat patients having lysosomal storage diseases by

(intravenous) administration of the missing enzyme, i.e., enzyme therapy," and describes prior animal testing involving "intravenously administering purified acid α-glucosidase in phosphorylated and unphosphorylated forms to mice . . . ." *Id.* at 2:32-3:4.

In this context, Reuser '771 describes isolating lysosomal enzymes from human and animal sources, but states that an "alternative way to produce human acid α-glucosidase is to transfect the acid α-glucosidase gene into a stable eukaryotic cell line (e.g., CHO) as a cDNA or genomic construct operably linked to a suitable promoter." *Id.* at 3:15-18. Because such production methods can be expensive, however, Reuser '771 describes another approach of using recombinant proteins produced in the milk of a transgenic animal. *Id.* at 3:19-27.

Reuser '771 teaches that "[t]he proteolytic processing of acid α-glucosidase is complex," and the "main species recognized are a 110/100 kDa precursor, a 95 kDa intermediate and 76 kDa and 70 kDa mature forms." *Id.* at 9:19-26. Reuser '771 teaches further that "post translational processing of natural human acid α-glucosidase and of recombinant forms of human acid α-glucosidase as expressed in cultured mammalian cells like COS cells, BHK cells and CHO cells is similar." *Id.* at 9:29-34.

Regarding uses of such recombinant proteins in enzyme replacement therapy in patients, Reuser '771 describes a "typical composition for intravenous" administration. *Id.* at 18:11-14; 19:34-37. According to

Reuser '771, a "therapeutically-" or "prophylactically-effective dose" "will depend on the severity of the condition and on the general state of the patient's health, but will generally range from about 0.1 to 10 mg of purified enzyme per kilogram of body weight." *Id.* at 20:25-28.

Examples in Reuser '771 describe constructing transgenic mice that express human GAA, as well as analyzing the activity of hGAA produced in the milk of transgenic mouse lines. *Id.* at 21:14-28:24. In Example 3, recombinant "[a]cid α- glucosidase purified from the milk was [] tested for phosphorylation by administrating the enzyme to cultured fibroblasts from patients with GSD II (deficient in endogenous acid α-glucosidase)." *Id.* at 27:29-32. As also described in this example, "restoration of the endogenous acid α-glucosidase activity by acid α-glucosidase isolated from mouse milk was as efficient as restoration by acid α- glucosidase purified from bovine testis, human urine and medium of transfected CHO cells." *Id.* at 28:10-14. In addition, "the N-terminal amino acid sequence of the recombinant α-glucosidase produced in the milk of mice was shown to be the same as that of α-glucosidase precursor from human urine . . . ." *Id.* at 28:20-23.

2. Van Hove 1997 (Ex. 1007)

Van Hove 1997 describes a method for purifying recombinant hGAA expressed in CHO cells. Ex. 1007, 613-614. This reference states that "[l]arge quantities of recombinant acid α-glucosidase are needed for in vivo experimentation of enzyme replacement therapy in Pompe

disease," and "eventually for use in medicine." *Id.* It also states that the disclosed method "is amenable to scale up, and has increased speed, and improved reproducibility with similar high yield and purification efficiency when compared to previous methods." *Id.* at 613. It describes producing "large quantities" of recombinant hGAA in CHO cells, including recombinant "precursor" GAA. *Id.* at 613-614, 617.

When discussing Pompe's disease, Van Hove 1997 further states that "[p]atients with the most common infantile form present with a progressive myopathy and hypertropic cardiomyopathy leading to death before age two years." *Id.* at 613.

3. Analysis

BioMarin contends that Reuser '771, either alone or in view of Van Hove 1997, discloses or suggests every element of claims 1 and 20, as well as dependent claims 2-9 and 15, citing a claim chart and supporting evidence. Pet. 26-33, 48-51; Appendix 2. For example, regarding "administering to the individual a therapeutically effective amount of human acid α-glucosidase" recited in claims 1 and 20, as well as specific amounts recited in claims 5-7, BioMarin points to teachings in Reuser '771 that disclose administering to a GSD II patient "from about 0.1 to 10 mg of purified enzyme per kilogram of body weight." Pet. 29-30; Appendix 2; Ex. 1004; 20:9-28.

BioMarin also indicates where Reuser '771 describes other recited elements, such as "recombinant" hGAA,

including "a precursor" form, as recited in claims 8 and 9. Pet. 30-31 (citing Ex. 1004, 9:30-34; 8:53-54; 9:24-25; 28:19-24; Ex. 1020 [0057]; Ex. 1021 [0090]-[0094]). As noted above, Reuser '771 teaches that the main species of GAA include a 110/100 kDa precursor, and that post translational processing of natural hGAA is similar to that of recombinant hGAA expressed in CHO cells. Ex. 1004, 9:19-34.

BioMarin contends that the only element in the challenged independent claims that is not mentioned expressly in Reuser '771 is "periodically at an administration interval." Pet. 28. BioMarin also contends, however, relying on testimony by Dr. Pastores, that a person of ordinary skill would have understood "that ERT [enzyme replacement therapy] for GSD-II is not a one shot cure but would require repeated and spaced administrations for the rest of the patient's life." *Id.* (citing Ex. 1020 [0060], [0061], [0084]-[0087], [0090], [0098]). In response, Duke states that BioMarin's "argument, at best, demonstrates that Reuser '771 discloses the feature 'at regular intervals' and maybe 'from time to time.'" Prelim. Resp. 28. As discussed above, however, we construe "periodically at an administration interval" in claims 1 and 20 to encompass such administration.

Duke also argues that Reuser '771 does not disclose treating GSD-II using hGAA that "was produced in chinese hamster ovary cell cultures," as required in the challenged claims. Prelim. Resp. 6-15, 40-41. Along these lines, Duke again argues that this phrase is not a product-by-process limitation. *Id.* Duke also argues that

Reuser '771 teaches the use of hGAA produced in milk of transgenic mice, and BioMarin "makes no attempt . . . to demonstrate that the Reuser '771 . . . disclose[s] the treatment of GSD-II using human acid α-glucosidase that 'was produced in chinese hamster ovary cell cultures.'" *Id*. at 10.

BioMarin responds, however, that Reuser '771 describes, or at least suggests, the suitability of using CHO cells to produce recombinant hGAA for use in treating GSD-II, even if Reuser '771 also teaches that such production might be more expensive than production in the milk of transgenic animals. Pet. 27; Ex. 1021 ¶ 0094; Ex. 1004, 3:15-25; 11:29-34; 28:10-14. In addition, BioMarin also contends that Van Hove 1997 "relates to the production of recombinant human acid α-glucosidase in CHO cells, particularly large scale production and purification for producing a protein for enzyme replacement therapy." Pet. 50. We are persuaded that there is a reasonable likelihood that BioMarin would prevail in showing that Reuser '771, in view of Van Hove 1997, taught or suggested treating GSD-II using hGAA that "was produced in chinese hamster ovary cell cultures," as required in claims 1 and 20.

Regarding independent claim 20, BioMarin contends that treating cardiomyopathy is inherent in the teaching of Reuser '771, which describes treating GSD II with GAA. Pet. 31 (citing Ex. 1020 ¶ 0099). BioMarin relies on the testimony of Dr. Pastores, who indicates, consistent with the claim language itself, that cardiomyopathy is associated with, i.e., a symptom of, GSD II (Pompe's

disease). Ex. 1020 ¶ 0099. Also consistently, as noted above, when discussing Pompe's disease, Van Hove 1997 states that "[p]atients with the most common infantile form present with a progressive myopathy and hypertropic cardiomyopathy leading to death before age two years." Ex. 1007, 613. We are persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail on the ground that Reuser '771, in view of Van Hove 1997, would have rendered obvious claim 20.

We are also persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail on the ground that same references would have rendered obvious claims 2-9 and 15, which depend on claim 1. As discussed above, BioMarin contends where Reuser '771 describes or suggests the elements recited in claims 5-9. Pet. 29-31, Appendix 2. Regarding claims 2-4, BioMarin further contends where Reuser '771 teaches that glycogen storage disease type II has three clinical forms, infantile, juvenile and adult. *Id.* at 29, Appendix 2; Ex. 1004, 2:15-22. BioMarin also contends where Reuser '771 teaches administering hGAA intravenously, as recited in claim 15. Pet. 31, Appendix 2; Ex. 1004, 20:9-10.

D. Obviousness Over Reuser '771, Van Hove 1997, van der Ploeg, and Bembi

BioMarin contends that claims 11, 12, and 21 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997, van der Ploeg, and Bembi, among other references. Pet. 51, 43-44. We discuss Reuser '771 and Van Hove 1997 above.

Appendix F

1. van der Ploeg (Ex. 1014)

Van der Ploeg describes cellular uptake of different species of hGAA by muscle cells, including by a 110 kD precursor form of GAA purified from human urine. Ex. 1014, 90, Abstract, 91, 1st col., 93, 2nd col. Van der Ploeg teaches that the "half-life of endocytosed acid α-glucosidase varied between 6 and 9 days in different experiments. *Id.* at 91, 2nd col.

2. Bembi (Ex. 1008)

Bembi describes a protocol for enzyme replacement treatment in patients with Gaucher's disease. Ex. 1008, Summary. In this clinical study, "infusion frequency was weekly during the first 6-9 months and biweekly afterwards." *Id.* At 1679, 2nd col.

3. Analysis

BioMarin contends that Reuser '771, in view of Van Hove 1997, van der Ploeg, and Bembi, discloses or suggests every element of dependent claims 11, 12, and 21, relying on arguments and evidence discussed above in relation to claim 1, as well as testimony in the Pastores Declaration. Pet. 51, 43-44. BioMarin contends that van der Ploeg "states that the tissue half-life of GAA is known to be 6-9 days." *Id.* at 44. BioMarin relies on testimony by Dr. Pastores to support the contention that, based on that known half-life, that it would have been obvious to a clinician to choose a dosing interval of once weekly or once biweekly, as recited in claims 11 and 12. *Id.* Likewise,

BioMarin contends that it would have been obvious to vary the administration interval over time, as recited in claim 21. *Id.* In this regard, BioMarin cites testimony by Dr. Pastores indicating that it would have been obvious to vary an administration interval over time after observing patient response to the enzyme. *Id.* (citing Ex. 1020 ¶ 0086 (citing Ex. 1008, 1679, 2nd col.)).

We are persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail on the ground that Reuser '771, in view of Van Hove 1997, van der Ploeg, and Bembi, would have rendered obvious claims 11, 12, and 21 of the '712 patent.

E. Obviousness Over Reuser '771, Van Hove 1997, and Brady

BioMarin contend that claims 18 and 19 of the '712 patent would have been obvious over Reuser '771, in view of Van Hove 1997 and Brady, among other references. Pet. 51, 45-46. We discuss Reuser '771 and Van Hove 1997 above.

1. Brady (Ex. 1012)

Brady describes a clinical protocol to manage enzyme neutralizing antibodies in patients during treatment of Gaucher's disease with the enzyme glucocerebrosidase. Ex. 1012, 1. Brady states that "the strategy we have used (plasma exchange, cyclophosphamide, intravenous IgG, and large doses of enzyme) may provide benefit to such individuals." *Id.* at Abstract. Brady further

discloses that "[i]t is also likely that this technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals)." *Id.* In the protocol, in an "effort to immunosuppress the patient," Brady describes administering cyclophosphamide, in some cases before administering glucocerebrosidase enzyme on a following day. *Id.* at 3, ¶ spanning 1st and 2nd cols., Table 1.

2. Analysis

BioMarin contends that Reuser '771, in view of Van Hove 1997 and Brady, discloses or suggests every element of dependent claims 18 and 19, relying on arguments and evidence discussed above in relation to claim 1, as well as testimony in the Pastores Declaration. Pet. 51, 45-46. BioMarin contends that Brady discusses the use of the immunosuppressant cyclophosphamide in conjunction with enzyme replacement therapy in Gaucher's disease, and that such a strategy is likely to be helpful in enzyme replacement therapy in other disorders where a genetic mutation abrogates the production of the protein. *Id.* at 45-46. BioMarin also relies on testimony by Dr. Pastores to support the contention that it would have been obvious to administer an immunosuppressant in conjunction with enzyme replacement therapy to treat GSD-II "to alleviate unwanted immune responses." *Id.* at 46 (citing Ex. 1020 ¶ 0095).

We are persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail

on the ground that Reuser '771, in view of Van Hove 1997 and Brady, would have rendered obvious claims 18 and 19 of the '712 patent.

F. Other Anticipation Grounds

BioMarin contends that independent claims 1 and 20, and certain challenged dependent claims, are anticipated by Synpac or Reuser '771. Pet. 3-4, 20-37. We are not persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail on those anticipation grounds.

1. Synpac[17]

Synpac states that on May 24, 1999, Duke "announced the start of clinical trials to test the safety and efficacy of recombinant human acid alpha-glucosidase (rhGAA) for the treatment of glycogen storage disease type II (Pompe Disease)" in three infant patients, with plans to expand the trial to juveniles and adults. Ex. 1002, 1. Synpac further states that "[i]t is anticipated that if Pompe patients are treated with a manufactured version

17. The parties dispute whether Synpac qualifies as prior art under 35 U.S.C. § 102(b). The exhibit, on its face, indicates that the press statement "was released by Synpac (North Carolina), Inc., on June 30, 1999." Ex. 1002, 1. Duke contends, however, that BioMarin has not established adequately that Synpac was published, or otherwise accessible to the public, more than one year before the effective filing date of the '712 patent on July 18, 2000. Prelim. Resp. 3-6. Because we do not institute on a ground that relies on Synpac, we do not decide the issue at this time.

of acid alpha-glucosidase (rhGAA), the symptoms of Pompe disease may be alleviated." *Id.* It discloses that the "rhGAA will be administered intravenously," and that "[i]t is anticipated that patients will require life long therapy with rhGAA." *Id.* Synpac also describes manufacturing the rhGAA using a CHO cell line containing the human GAA gene. *Id.* at 2.

BioMarin contends that Synpac "discloses that '*effective dose*' and 'how frequently it will need to be administered' would be determined in the studies." Pet. 21 (citing Ex. 1002, 2). In other words, Synpac itself does not disclose any "therapeutically effective amounts" of rhGAA to be used in the clinical trials, as recited in independent claims 1 and 20. BioMarin does not contend how Synpac expressly or inherently discloses such amounts. Pet. 20-25. Thus, BioMarin does not establish a reasonable likelihood that it would prevail on the ground that Synpac anticipates the challenged claims.

2. Reuser '771

As discussed above, BioMarin concedes that Reuser '771 does not disclose expressly administering hGAA "periodically at an administration interval," as recited in claim 1 or 20. Pet. 28. BioMarin does not contend that this reference inherently (necessarily) discloses such administration. *Id.* at 28-29. Thus, BioMarin does not establish a reasonable likelihood that it would prevail on the ground that Reuser '771 anticipates the challenged claims.

G. Remaining Obviousness Grounds

In addition to the grounds of unpatentability discussed above, BioMarin also alleges other obviousness grounds with respect to the challenged claims. Upon review of such grounds, we conclude that they are redundant in light of the obviousness grounds on the basis of which we institute review.

III. CONCLUSION

For the foregoing reasons, we are persuaded that BioMarin has demonstrated that there is a reasonable likelihood that it would prevail regarding claims 1-9, 11, 12, 15, and 18-21 of the '712 patent. The Board has not made a final determination on the patentability of the challenged claims.

IV. ORDER

For the reasons given, it is

ORDERED that the Petition is *granted* as to claims 1-9, 11, 12, 15, and 18-21 of the'712 patent with respect to the following alleged grounds:

1. Claims 1-9, 11, 12, 15, 20, and 21 under 35 U.S.C. § 102 as anticipated by van Bree '410;

2. Claims 1-9, 15, and 20 under 35 U.S.C. § 103 as obvious over Reuser '771 in view of Van Hove 1997;

3. Claims 11, 12, and 21 under 35 U.S.C. § 103 as obvious over Reuser '771 in view of Van Hove 1997, van der Ploeg, and Bembi; and

4. Claims 18 and 19 under 35 U.S.C. § 103 as obvious over Reuser '771 in view of Van Hove 1997 and Brady;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '712 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that all other grounds presented in BioMarin's petition are *denied*, and no ground other than those specifically granted above is authorized for the *inter partes* review as to claims 1-9, 11, 12, 15, and 18-21; and

FURTHER ORDERED that an initial conference call with the Board is scheduled for 11:00 AM Eastern Time on March 17, 2014. The parties are directed to the Office Trial Practice Guide, 77 Fed. Reg. 48756, 48765-66 (Aug. 14, 2012) for guidance in preparing for the initial conference call, and should be prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

APPENDIX G — DENIAL OF REHEARING OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED FEBRUARY 4, 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1696

DUKE UNIVERSITY,

Appellant,

BIOMARIN PHARMACEUTICAL INC.,

Appellee.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00535.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, and STOLL, *Circuit Judges*.*

PER CURIAM.

* Circuit Judge Hughes did not participate.

Appendix G

CORRECTED ORDER

Appellant Duke University filed a petition for rehearing en banc. A response to the petition was invited by the court and filed by Appellee Biomarin Pharmaceutical Inc. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

It Is Ordered That:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on February 10, 2020.

For the Court

February 3, 2020
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court