Trials@uspto.gov
Tel: 571-272-7822

Paper 92
Entered: January 17, 2018

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

SNEDDEN, *Administrative Patent Judge.*

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" 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

[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).

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.

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).

*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.

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.*

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 post-translational 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 nonobviousness 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] long-standing 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 nonobviousness 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.

Case IPR2013-00535
Patent 7,056,712 B2

PETITIONER:

Gerald M. Murphy, Jr.
MaryAnne Armstrong, Ph.D
Eugene T. Perez
BIRCH, STEWART, KOLASCH & BIRCH, LLP
gmm@bskb.com
maa@bskb.com
etp@bskb.com

PATENT OWNER:

John White
Herman Yue
COOPER & DUNHAM LLP
DukeIPR@cooperdunham.com
SynpacIPR@pbwt.com

Trials@uspto.gov
Tel: 571-272-7822

Paper 90
Entered: July 14, 2015

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*.

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*.

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.

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

---

[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).

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.

*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.

Case IPR2013-00535
Patent 7,056,712 B2

PETITIONER:

Gerald M. Murphy, Jr.
MaryAnne Armstrong, Ph.D
Eugene T. Perez
BIRCH, STEWART, KOLASCH & BIRCH, LLP
mailroom@bskb.com
gmm@bskb.com
maa@bskb.com
etp@bskb.com

PATENT OWNER:

John White
COOPER & DUNHAM LLP
DukeIPR@cooperdunham.com
SynpacIPR@pbwt.com

Herman Yue
PATTERSON BELKNAP WEBB & TYLER LLP
SynpacIPR@pbwt.com

Trials@uspto.gov
Tel: 571-272-7822

Paper 86
Entered: February 23, 2015

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.*

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

## 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).

| 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).

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

[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).

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" |
| 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" |

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

| Claim(s) | Claim Phrase | Claim Construction |
|---|---|---|
| 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

[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*

"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 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."

---

*and Corrects Glycogen Accumulation in Fibroblasts from Patients with Pompe Disease*, 93 PROC. NATL. ACAD. SCI. USA 65–70 (1996) (Ex. 1016).

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.

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.

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.

*Id*. 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.

*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.

Case IPR2013-00535
Patent 7,056,712 B2

PETITIONER:

Gerald M. Murphy, Jr.
MaryAnne Armstrong, Ph.D
Eugene T. Perez
BIRCH, STEWART, KOLASCH & BIRCH, LLP
mailroom@bskb.com
gmm@bskb.com
maa@bskb.com
etp@bskb.com

PATENT OWNER:

John White
Herman Yue
COOPER & DUNHAM LLP
DukeIPR@cooperdunham.com
SynpacIPR@pbwt.com