NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

DUKE UNIVERSITY,
Appellant

v

BIOMARIN PHARMACEUTICAL INC.,
Appellee

2016-1106

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

Decided: April 25, 2017

STEVEN A. ZALESIN, Patterson Belknap Webb & Tyler LLP, New York, NY, argued for appellant. Also represented by CHARLENE CHOI, EUGENE M. GELERNTER, ZHIQIANG LIU, IRENA ROYZMAN; JOHN P. WHITE, Cooper & Dunham, LLP, New York, NY.

GERALD MYERS MURPHY, JR., Birch Stewart Kolasch & Birch, LLP, Falls Church, VA, argued for appellee. Also represented by MARYANNE ARMSTRONG, LYNDE FAUN HERZBACH, EUGENE PEREZ.

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

LOURIE, *Circuit Judge*.

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

BACKGROUND

I. The '712 Patent

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

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

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

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

The '712 patent teaches that GAA can be administered in conjunction with other agents, e.g., "immunosuppressants or other immunotherapeutic agents which counteract anti-GAA antibodies." *Id.* col. 5 ll. 29–33. It states that "[i]n a particularly preferred embodiment, the immunosuppressive or immunotherapeutic regime is begun prior to the first administration of GAA, in order to minimize the possibility of production of anti-GAA antibodies." *Id.* col. 5 ll. 55–59.

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

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

Id. col. 12 ll. 45–51.

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

Id. col. 14 ll. 13–19.

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

II. The Board's Final Written Decision

BioMarin Pharmaceutical Inc. ("BioMarin") filed a petition for IPR of claims 1–9, 11, 12, 15, and 18–21 of the '712 patent. The Board instituted review and ultimately

held that all of the challenged claims are unpatentable as anticipated by U.S. Patent 7,351,410 ("van Bree") and/or as obvious over PCT Publication WO 97/05771 ("Reuser") in view of Johan L.K. Van Hove et al., *Purification of Recombinant Human Precursor Acid a-Glucosidase*, 43(3) BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL 613–23 (1997) ("Van Hove") either alone or in combination with other references, including Roscoe O. Brady et al., *Management of Neutralizing Antibody to Ceredase in a Patient with Type 3 Gaucher Disease*, 100(6) PEDIATRICS e11 (1997) ("Brady").

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

A. The Prior Art

van Bree and Reuser disclose methods of producing rhGAA in transgenic mammals and its use in enzyme replacement therapy to treat Pompe disease. van Bree col. 2 ll. 33–36, col. 4 ll. 54–55; Reuser p. 4 ll. 14–37, p. 18 ll. 12–14. They both disclose that the main species of hGAA are a 110/100 kD precursor, a 95kD intermediate, and 76 kD and 70 kD mature forms. van Bree col. 6 ll. 6–8; Reuser p. 9 ll. 24–26. van Bree states that administration of GAA "is preferably predominantly (i.e., >50%) in the precursor form of about 100-110 kD." van Bree col. 13

ll. 48–50. van Bree and Reuser state that CHO cells are an alternative way to produce hGAA, but note disadvantages—labor and expense, respectively—with this approach. van Bree col. 13 ll. 58–64; Reuser p. 3 ll. 15–22.

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

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

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

B. The Rejections

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

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

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

The Board also concluded that claims 1–9, 11, 12, 15, and 18–21 were unpatentable as obvious over Reuser in view of Van Hove, either alone or in combination with other references, including Brady. The Board found that a skilled artisan would have had reason to combine the teachings of Reuser and Van Hove because "both discuss[] rhGAA produced in CHO cells and methods of treating Pompe disease." *Id.* at *18. The Board explained that "Reuser '771 identified rhGAA produced in CHO cells, in particular, and, especially in view of Van Hove 1997,

provided 'good reason to pursue the known options within his or her technical grasp' using such rhGAA for the treatment of Pompe disease, as taught by Reuser '771, including at the administration doses and intervals disclosed in Reuser '771." *Id.* (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 402–03 (2007)).

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

Regarding claim 9, the Board found that Reuser recites a precursor form of rhGAA and teaches that the main species of GAA include a 110/100 kDa precursor. *Id.* at *16. The Board did not discuss whether Reuser discloses administering exclusively a precursor of rhGAA.

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

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

III. The Board's Rehearing Decision

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

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

The dissenting APJ would have held that BioMarin failed to meet its burden with respect to claim 19. The APJ concluded that "[n]either [BioMarin] in its Petition or Reply, nor Dr. Pastores in his cited testimony adequately explains, however, how Brady (or Grabowski) teaches or suggests administering an immunosuppressant to a

patient before the patient has exhibited any sign of an adverse reaction to the enzyme therapy." *Id.* at *11 (APJ Bonilla, dissenting). The APJ explained that "[w]hile Dr. Pastores' conclusory statements may indicate what 'could be' done if 'there is a high incidence' of antibody response, he does not explain, nor provide evidence showing, what an ordinary artisan *would have done* in this regard prior to the filing date of the '712 patent, or what one *would have understood* in relation to incidents of 'high antibody titers' in response to exogenous enzyme therapy." *Id.* (APJ Bonilla, dissenting) (emphases in original).

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

DISCUSSION

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

I. Anticipation

We first address Duke's argument that the Board erred in finding that van Bree anticipated claims 1–9, 12, 15, 20, and 21 of the '712 patent. Anticipation is a question of fact that we review for substantial evidence. *In re Rambus, Inc.*, 753 F.3d 1253, 1256 (Fed. Cir. 2014). A prior art document may anticipate a claim if it describes every element of the claimed invention, either expressly or inherently. *Husky Injection Molding Sys. Ltd. v. Athena Automation Ltd.*, 838 F.3d 1236, 1248 (Fed. Cir. 2016). An anticipatory reference must be enabled, but "no 'actual creation or reduction to practice' is required." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting

Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1380–81 (Fed. Cir. 2003)).

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

A. Independent Claims 1 and 20

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

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

We agree with BioMarin that the Board's anticipation findings with respect to claims 1 and 20 were supported by substantial evidence. van Bree states that "the inven-

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

We conclude that the disclosure in van Bree supports the Board's finding that its teachings applied to GAA produced in CHO cell cultures. van Bree links its teachings to CHO cell cultures with respect to structure and post translational processing, including glycosylation and phosphorylation. *See id.* col. 5 l. 35–col. 6 l. 24. It explains that "post translational processing of natural [hGAA] and of recombinant forms of [hGAA] as expressed

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[1] We note that Duke has not raised an enablement challenge to van Bree and that, in any event, proof of efficacy or an actual reduction to practice using CHO cell cultures is not required for a reference to be an anticipation of the challenged method of treatment claims. *In re Gleave*, 560 F.3d at 1334; *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (explaining "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation").

in . . . CHO cells is similar." *Id.* col. 6 ll. 11–15. In the "Therapeutic Methods" section, van Bree teaches that a CHO cell line is "an alternative way to produce [hGAA]." *Id.* col. 13 ll. 58–60. In an example, van Bree reports that "restoration of the endogenous [GAA] activity by [GAA] isolated from mouse milk was as efficient as restoration by [GAA] purified from . . . CHO cells." *Id.* col. 20 ll. 32–36. Those statements constitute substantial evidence supporting the Board's finding that van Bree "describes administering hGAA produced in CHO cell cultures to patients in the same manner, i.e., using the same amounts and dosage intervals, as described for hGAA produced in transgenic animals." *Board Decision*, 2015 WL 1009196, at *11.

Expert testimony was not necessary to support the Board's anticipation determination. Here, the disclosures of van Bree alone were sufficiently clear and on point to constitute substantial evidence to support the Board's anticipation findings. Thus, the Board "could permissibly 'rely on its own reading of [van Bree]—supported by the Petition's observations about it'—to find that the [limitations] were disclosed." *In re NuVasive, Inc.*, 841 F.3d 966, 973 (Fed. Cir. 2016) (quoting *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1074 (Fed. Cir. 2015)).

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

BioMarin argued in the petition that van Bree anticipates the relevant claims and did not limit its arguments to the claim construction position rejected by the Board. *See* J.A. 146–50 (BioMarin's Petition). Duke had an opportunity to, and did in fact, respond to those arguments. *See* J.A. 263–75 (Duke's Patent Owner Response).

Thus, the Board properly "base[d] its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). That conclusion leaves no live issue as to Duke's challenge to the institution decision on the very same ground: that challenge is either unreviewable or, if reviewed, incorrect (for the reason just stated), and so could not benefit Duke.

B. Dependent Claim 9

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

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

BioMarin responds that the Board properly construed "precursor" as "any precursor of recombinant hGAA (e.g.,

a 110-kD form) that is exclusively produced in CHO cell cultures," and that under that construction van Bree anticipates claim 9. Appellee's Br. 56. BioMarin contends that the Board cited "*part* of" Duke's proposed construction, but "did not adopt the entirety" of it as "made clear by the use of ellipses and reinforced" by the Board's statements about the scope of the language. *Id.* (emphasis in original). BioMarin asserts that the record does not support limiting claim 9 to the administration of exclusively precursor and no other form of GAA.

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

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

precursor forms of rhGAA at the same time, and not limited to administering exclusively a precursor form and no other form.").

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

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

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

> *form* of human GAA that has been modified to contain motifs to allow efficient uptake of GAA, can be administered. In a particularly preferred embodiment, the GAA is the *precursor form* of recombinant human GAA.

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

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

II. Obviousness

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

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

A. Dependent Claim 9

Duke argues that under the correct construction of "precursor," Reuser in view of Van Hove does not render claim 9 unpatentable as obvious. Duke contends that neither reference teaches or suggests administering rhGAA produced from CHO cells exclusively in precursor form.

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

Because we have modified the construction of "precursor," we do not have the benefit of the Board's considered analysis whether claim 9 would have been obvious under the correct construction. Although the Board found that both Reuser and Van Hove disclose precursor rhGAA, *Board Decision*, 2015 WL 1009196, at *15–16, the Board did not determine whether they teach or suggest administering exclusively a precursor of rhGAA produced in CHO cell cultures. Before the Board, the parties certainly disputed whether claim 9 would have been obvious. For example, BioMarin offered expert testimony to support its contention that Reuser teaches or suggests administration of exclusively a precursor of rhGAA that has been

produced in CHO cell cultures. *See, e.g.*, J.A. 561 (Reuser "confirms what was already reported in the literature, i.e., that when GAA is produced for a therapeutic use, either in CHO cells or in the milk of a recombinant mammal, the enzyme should be produced in the precursor form with proper glycosylation/phosphorylation of mannose residues."); J.A. 641 ("[T]he rhGAA described by [Reuser] for therapeutic use would be the 110kd precursor form."). Thus, we vacate the Board's obviousness conclusion with respect to claim 9 and remand for the Board to apply our claim construction of "precursor."

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

B. Dependent Claim 19

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

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

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

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

We agree with Duke that the Board erred in concluding that claim 19 was unpatentable as obvious. Substantial evidence does not support the Board's finding that "the prophylactic administration of an immunosuppressant would have been a predictable variation of the use of immunosuppressant disclosed in Brady." *Id.* at *8. It is undisputed that the Board correctly found that "Brady does not disclose administering immunosuppressant prior to any and all administration of hGAA, as required by claim 19." *Rehearing Decision*, 2015 WL 4467381, at *4. The expert testimony relied on by the Board to bridge the gap between the disclosure in Brady and claim 19 falls short of what would have rendered the subject matter of claim 9 obvious.

BioMarin's expert testified, *inter alia*, that:

> [I]t would not be surprising if a proportion of patients treated with recombinant GAA protein de-

> veloped an immune response to the recombinant enzyme. In patients with high titers of antibodies against the enzyme, particularly those with neutralizing antibodies, administering an immunosuppressant prior to, with or immediately after the therapeutic enzyme would be considered to mitigate the presence of antibodies and its negative impact. For example, Brady et al. discuss . . . efforts to "immunosuppress" the patient. . . . *If there is a high incidence of patients developing high antibody titers, an immunosuppressant could be administered prophylactically* prior to any administration of the recombinant enzyme begins to minimize the potential adverse effects of such.

J.A. 575–76 (internal citations omitted) (emphasis added).

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

Moreover, there was no evidence that "a high incidence of patients" developed, or were expected to develop, "high antibody titers" to GAA enzyme replacement therapy. BioMarin submitted no evidence regarding the incidence of high antibody titers in patients receiving GAA before the '712 patent. Furthermore, Brady teaches that "[v]ery few patients with Gaucher disease who are treated with [enzyme replacement therapy] develop a neutralizing antibody to the exogenous enzyme" and refers to this phenomenon as "rare." J.A. 526. Brady suggests that its "technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals)," *id.*, but Brady's

technique did not involve prophylactic administration of immunosuppressants, *Rehearing Decision*, 2015 WL 4467381, at *4, *9 (APJ Bonilla, dissenting). Thus, the evidence of record does not establish the conditions precedent (a high incidence of patients with high antibody titers to the enzyme) to the prophylactic administration of immunosuppressants according to the expert's testimony. Such conclusory expert testimony cannot support an obviousness conclusion. *See In re Magnum Oil Tools*, 829 F.3d at 1380 ("To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness."). The evidence thus fails to render claim 19 obvious.

CONCLUSION

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

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

COSTS

No costs.