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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

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

[2] Van Hove et al., *Purification of recombinant human precursor acid α-glucosidase*, 43(3) BIOCHEMISTRY & MOLECULAR BIOLOGY INT'L 613–623 (1997).

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

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.

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