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Paper 14
Date: January 9, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RISEN (SUZHOU) PHARMA TECH. CO. LTD.,
Petitioner,

v.

ALZHEON, INC.,
Patent Owner.

IPR2022-01200
Patent No. 10,471,029 B2

Before SHERIDAN K. SNEDDEN, DEVON ZASTROW NEWMAN, and JAMIE T. WISZ, *Administrative Patent Judges.*

NEWMAN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. §§ 314, 325(d)

I. INTRODUCTION

A. Background and Summary

Risen (Suzhou) Pharma Tech. Co. Ltd., ("Petitioner") filed a Petition pursuant to 35 U.S.C. §§ 311–319 requesting an *inter partes* review of claims 1–14 ("the Challenged Claims") of U.S. Patent No. 10,471,029 (Ex. 1001, "the '029 patent"). Paper 1 ("Pet."). Alzheon, Inc., ("Patent Owner") filed a Patent Owner Preliminary Response ("Prelim. Resp."). Paper 12.

We have jurisdiction and authority to determine whether to institute trial pursuant to 35 U.S.C. § 6 (2011), 35 U.S.C. § 314(b) (2018); and 37 C.F.R. § 42.4(a) (2019). The standard for instituting an inter partes review is set forth in 35 U.S.C. § 314(a), which provides as follows:

> (a) THRESHOLD.—The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

(35 U.S.C. § 314(a)).

Petitioner challenges claims 1–14 as unpatentable under 35 U.S.C. § 103 in six grounds of unpatentability (Pet. 25). Generally, Patent Owner contends that the Petition should be denied as to all challenged claims (*see* Prelim. Resp.). We do not reach whether Petitioner has shown a reasonable likelihood of prevailing on at least one claim. For reasons discussed below, we discretionarily deny the Petition under 35 U.S.C. § 325(d).

B. Real Parties in Interest

Petitioner and Patent Owner identify themselves as the only real parties-in-interest involved in this case. Pet. 74, Paper 6, 1.

C. Related Matters

Petitioner and Patent Owner identify no related matters. Pet. 75; Paper 4, 1.

D. The '029 Patent

The '029 patent, titled "Methods for Treating Neurological Disorders" discloses "treatment of neurological disorders, particularly Alzheimer's disease in specific sub-populations that have one or more copies of the ApoE4 (or ε4) allele."[1] Ex. 1001, code (54), 1:48–51. Presence of the ApoE4 allele "is the strongest genetic risk factor for patients with late-onset [Alzheimer's Disease]." *Id.* at 5:5–6. The Specification discloses that "subjects with at least one ε4 allele account for 50%–60% of [Alzheimer's Disease] cases" and "subjects with two ε4 alleles account for 10%–14% of [Alzheimer's Disease] and exhibit an even more aggressive disease progression." *Id.* at 5:6–12. The "ε4 allele leads to an increased brain Aβ amyloid deposition . . . and faster cognitive decline. In addition, demented patients carrying one or two ε4 alleles of ApoE are more likely to have AD." *Id.* at 5:12–16.

The '029 patent discloses that tramiprosate is "a promising investigational product candidate for the treatment of Alzheimer's disease

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[1] "An allele is one of two or more versions of DNA sequence (a single base or a segment of bases) at a given genomic location. An individual inherits two alleles, one from each parent, for any given genomic location where such variation exists. If the two alleles are the same, the individual is homozygous for that allele. If the alleles are different, the individual is heterozygous." *See* definition of "allele" at https://www.genome.gov/genetics-glossary/Allele (last visited December 2, 2022). ApoE4 is one allele of the ApoE gene. Ex. 1009, 613 ("There are 3 different alleles for ApoE: ε2, ε3, and ε4."). Exhibit 3001.

that has undergone Phase III clinical trials[2] in North American and Europe." *Id.* at 5:31–34; 1:54–56. Tramiprosate "is believed to act by reducing the blocking amyloid aggregation, deposition and/or load of amyloid in the brain through its binding to soluble Aβ monomers." *Id.* at 5:36–39. The Specification discloses a specific compound, L-Valyl-3-aminopropanesulfonate (Val-APS), which is a prodrug of tramiprosate with "improved GI tolerability, reduced nausea & vomiting" compared to tramiprosate and additionally provides for once a day dosing. *Id.* at 1:56–61. In one study, Val-APS shows "improved accumulation in the brain" compared to tramiprosate. *Id.* at 20:55–57. Val-APS also shows an extended $T_{1/2}$ compared to tramiprosate, indicating the prodrug maintains a higher level of active drug in the bloodstream over time. *Id.* at 2:42–48; Fig. 7.

The Specification discloses:

> In certain embodiments, the efficacy of a compound may be determined through the ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive sub scale). ADAS was designed to measure the severity of the most important symptoms of Alzheimer's disease (AD). . . . The ADAS-Cog helps evaluate cognition and differentiates between normal cognitive functioning and impaired cognitive functioning. It is especially useful for determining the extent of cognitive decline and can help evaluate which stage of Alzheimer's disease a person is in, based on his answers and score. The ADAS-Cog can be used in clinical trials in order to determine incremental improvements

[2] Petitioner's declarant observes that data from the clinic trials, also referred to as the ALPHASE study, "was designed to investigate whether tramiprosate exerted certain therapeutic effects in patients with Alzheimer's disease." Ex. 1003 ¶ 89. The data study "generated the data reported in the '029 patent (as well as the data reported in EX1029 Gauthier, EX1004 Aisen, and EX1007 Caltagirone)" through "*post hoc*" analyses. *Id.* ¶ 90.

> or declines in cognitive functioning. An increased ADAS-Cog score compared to placebo demonstrates improved cognitive functioning.

Id. at 18:27–46.

Example 3 of the Specification discloses the results of a study in which AD patients who were administered tramiprosate were tested using the ADAS-Cog to assess any effect on cognitive functioning over time, and whether the effect could be correlated to a patient's ApoE4 genotype. *Id.* at 21:1–34. The data "established substantially improved AD As-cog scores vs placebo over time." *Id.* Figure 8, reproduced below, shows the effect of tramiprosate treatment on cognitive functioning over time as correlated to ApoE4+ genotype in general, as compared in three groups: 1) "ApoE4+/+", referring to patients homozygous for ApoE4 (i.e., patients having two ApoE4 alleles); 2) "ApoE4 all-comers" (i.e., patients having either one or two ApoE4 alleles; and 3) "Non-ApoE4 all-comers" (i.e., patients having no ApoE4 allele).

Figure 8: Effect of 3APS on Cognition in ApoE4 sub-populations

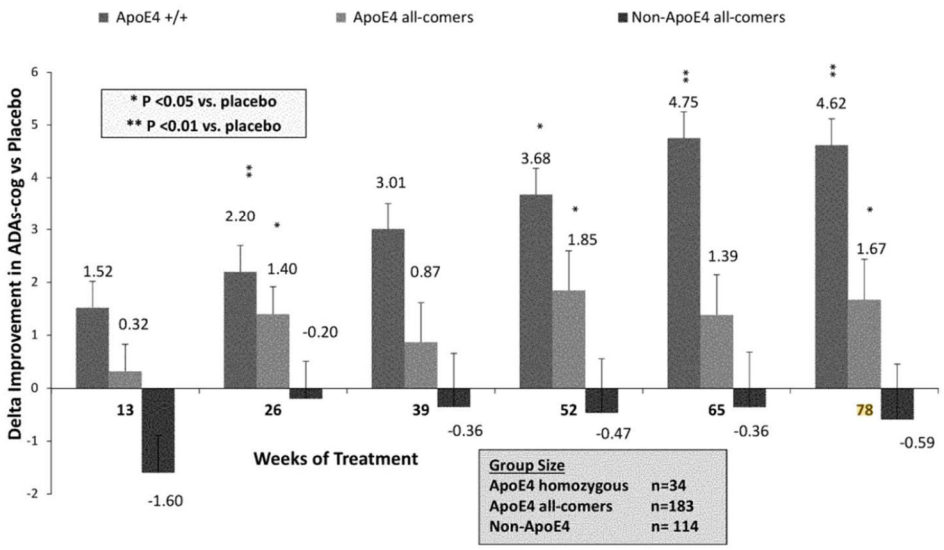


Figure 8, reproduced above:

> illustrates the advantageous effects of tramiprosate, the active agent of Val-APS, in certain sub-populations segregated based on Apo E4 status. The data established substantially improved ADAs-cog scores vs placebo over time. Data is presented at 13 weeks, 26 weeks, 39 weeks, 52 weeks, 65 weeks, and 78 weeks. The first column shows patients homozygous for ApoE4 ("ApoE4+/+"), the second column shows combined data from ApoE4 heterozygous and homozygous patients "ApoE4 all-comers" [i.e., ApoE4+/- and ApoE4+/+], the third column shows patients negative for ApoE4 (Non-ApoE4). ApoE4 prevalence correlates with improved cognition scores.

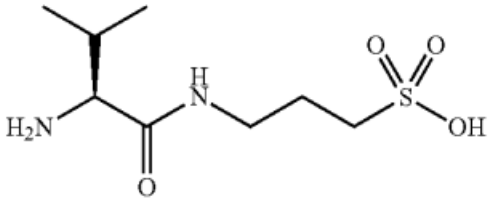
Id. at 2:48–59.

E. Illustrative Claim

Petitioner challenges claims 1–14 of the '029 patent. Pet. 25. Claims 1 and 3 are independent and claims 2 and 4–14 depend from the independent claims. Ex. 1001, 21:27–22:37. Claim 1 is illustrative of the claimed subject matter and is reproduced below.

> 1. A method of selecting and treating a patient suffering from Alzheimer's disease comprising the steps of:
>
> (a) selecting the patient as having a tramiprosate-sensitive form of Alzheimer's disease based on the presence of two ApoE4 alleles; and
>
> (b) administering to the selected patient tramiprosate in an amount effective to treat the disease.

Id. at 21:27–33. Claim 3 recites the method steps of claim 1 and administration of a specific compound, Val-APS, reproduced below to treat AD. *Id.* at 21:37–22:15.



Id.; *see also id.* at 2:1–10. Claims 2 and 4–14 are similar to the independent claims and recite additional limitations pertaining to administration of Val-APS and achievement of a reduction in cognitive decline in subjects. *Id.* at 21:34–36; 22:16–37.

F. Prior Art and Asserted Grounds

Petitioner asserts that the Challenged Claims are unpatentable based on the following grounds:

Ground	Claims Challenged	35 U.S.C. §	References
1	1, 2, 4	102[3]	Caltagirone[4]
2	1, 2, 4, 6, 7, 11, 12	102	Gervais[5]

[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the '029 patent claims priority to a provisional application filed after the effective date of these AIA amendments, we apply the AIA version of 35 U.S.C. § 102 and § 103.

[4] Carlo Caltagirone, et al., *The Potential Protective Effect of Tramiprosate (Homotaurine) Against Alzheimer's Disease: a Review*, AGING CLINICAL AND EXPERIMENTAL REASEARCH, 24(6):580–587 (2012) (Ex. 1007, "Caltagirone").

[5] Francine Gervais, et al., *Targeting Soluble Aβ Peptide with Tramiprosate for the Treatment of Brain Amyloidosis*, NEUROBIOLOGY OF AGING, 28:537–547 (2007) (Ex. 1028, "Gervais").

Ground	Claims Challenged	35 U.S.C. §	References
3	6, 7, 11, 12	103	Caltagirone, Aisen[6]
4	1–14	103	Babic,[7] Caltagirone, Aisen, Kong[8]
5	3, 5, 8–10, 13, 14	103	Caltagirone, Kong
6	3, 5, 8–10, 13, 14	103	Gervais, Kong

Pet. 25. Petitioner alleges all of the cited references qualify as prior art even if the earliest filing date is applied to the challenged claims and provides evidence of the public availability of these references. *Id.* at 4–14. Patent Owner does not challenge the prior art status of any asserted reference. *See generally* Prelim. Resp.

In support of the contentions in its Petition, Petitioner relies on the supporting Declaration of Dr. Robert Ruffolo, Jr., dated June 24, 2022. Ex. 1003.

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[6] Paul S. Aisen, et al., *Tramiprosate in Mild-to-moderate Alzheimer's Disease – a Randomized, Double-blind, Placebo-controlled, Multi-centre Study (the Alphase Study),* ARCHIVES OF MEDICAL SCIENCE, 7(1):102–111 (2011) (Ex. 1004, "Aisen").
[7] Tomislav Babic, et al., *ApoE Genotyping and Response to Galanthamine in Alzheimer's Disease – A Real Life Retrospective Study*, 28 COLL. ANTR. 199-204 (2004) (Ex. 1005, "Babic").
[8] Xianqi Kong, et al., U.S. Pat. No. US 8,748,656 B2, issued Jun. 10, 2014 (Ex. 1006, "Kong").

G. Pertinent Prosecution History

The ’029 patent issued November 12, 2019, from Application No. 15/127,565 (“the ’565 application), filed September 20, 2016. Ex. 1001, codes (21), (45), (54), (86).

During examination of the ’565 application, the Examiner issued multiple non-final rejections of the pending claims under 35 U.S.C. § 103 over Caltagirone and over Caltagirone in view of Kong. *See, e.g.*, Ex. 1002, 204–208. The Examiner cited Caltagirone’s teachings, which were based on post-hoc analysis of data obtained from the ALPHASE study. *Id*. Caltagirone’s analysis showed a positive and significant effect of homotaurine (tramiprosate) on certain patients, including “a reduction in global cognitive decline in APOE4 allele carriers, suggesting a disease modifying effect” that was “more prominent in a homogenous population of ApoE4 positive patients.” *Id.* at 205. The Examiner noted that Caltagirone did not select patients for treatment based on being ApoE4 positive, but that Caltagirone’s teachings suggest doing so based on the study results. *Id.*

The Examiner cited Kong’s disclosure that prodrugs of tramiprosate are “more readably absorbed tha[n] 3APS or were able to prevent first pass metabolism of 3APS,” had higher bioavailability and maintained a “2-fold increase in plasma concentration” compared to tramiprosate. *Id.* at 206–207. The Examiner found that the ordinarily skilled artisan would have been “motivated to administer the prodrug compound A2 because Kong et al. teach that compound A2 increased the bioavailability of tramiprosate and had improved pharmacokinetics compared to tramiprosate, such as relative bioavailability, increased plasma concentration and brain concentration.” *Id.* at 207.

After a final rejection in September 2016 in which the Examiner maintained these same rejections (*see id.* at 287–294), Applicant filed a response to the Final Office Action with additional arguments contesting the rejections (*see id.* at 303–312). When the Examiner issued an Advisory Action notifying Applicant that the Office would maintain its rejections (*id.* at 319–321), Applicant requested an Examiner interview, in which the Examiner and Applicant discussed:

> amending the independent claims to claim the patient population is ApoE4 +/+ [homozygous for the ApoE4 allele]. Applicant's argued that the Caltagirone reference does not teach the stratification of ApoE4 +/+ population. The Applicants discussed Fig. 8 in the specification that shows a significant difference in cognitive scores between the ApoE4 +/ and ApoE4 +/+. The Examiner stated that Caltagirone states the population is ApoE4 positive but does not teach if they are heterozygous and/or homozygous for the allele. The Examiner stated a new search is needed to investigate the population of Caltagirone and search the state of the art with respect to ApoE4 alleles and AD. Applicants stated that an RCE would be filed.

Id. at 322–325.

Applicant filed a Request for Continued Examination with amendments to the claims "to recite that the Alzheimer's patient is selected for treatment with tramiprosate or a prodrug thereof on the basis of <u>having two ApoE4 alleles</u> (*i.e.*, the patient is homozygous for the E4 allele)." *Id.* at 324–341. Applicant argued that the data of Figure 8 of the Specification "shows a substantial improvement in cognition in the ApoE4 homozygous group over the all ApoE4+ patient group (i.e., a greater than three-fold higher delta improvement in ADAs-cog versus placebo at 65 and 78 weeks)" and that this improvement was "surprising and unexpected in light of the

teachings of Caltagirone." *Id.* at 338. Applicant further argued that Caltagirone does not teach or suggest "patient stratification based on the presence of two ApoE4 alleles" or "limiting treatment to only those Alzheimer's patients who are ApoE4 homozygous and therefore not treating with tramiprosate those patients that are ApoE4 heterozygous" because Caltagirone makes no distinction between ApoE4 heterozygotes and homozygotes. *Id.* at 337. Applicant argued that the rejection of claims reciting treatment of homozygous ApoE4 patients with Val-APS was also patentable over the rejection based on Caltagirone and Kong for the same reasons. *Id.* at 339.

The Examiner allowed the claims in response to Applicant's amendments and remarks. *Id.* at 651–663. The Examiner's reasons for allowance addressed the teachings of Caltagirone, the "closest prior art," and noted that Caltagirone did not distinguish between ApoE4 heterozygotes and homozygotes or teach "step a) selecting the patient as having a tramiprosate sensitive form of AD based on the presence of two ApoE4 alleles and step b) administering to the selected patient a compound selected from tramiprosate or Val-APS, in an amount effective to treat the disease." *Id.* at 659. The Examiner noted that Applicants had "shown that ApoE4 homozygotes treated with tramiprosate showed a surprisingly greater cognitive benefit compared to all ApoE4 + patients (i.e. ApoE4 heterozygotes and homozygotes)," that the improvement was "unexpected in view of Caltagirone et al." and that the results could reasonably be expected to extrapolate to Val-APS. *Id.* at 660.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

"The level of skill in the art is a factual determination" that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc*., 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art ("skilled artisan") at the time of the invention would have had

> at least an M.D. or Ph.D. degree in a biomedical science or equivalent field. They would also have several years of clinical experience treating and/or conducting clinical trials of drugs for AD patients, or professional experience working in clinical trial design and execution related to drugs for AD or supervising such work.

Pet. 19 (citing Ex. 1003 ¶¶ 52–53). Patent Owner does not contest the characterization offered by Petitioner. Prelim. Resp. 14–15.

For purposes of this Decision, we adopt Petitioner's characterization as it is consistent with the level of skill in the art at the time of the invention as reflected by the '029 patent and the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Interpretation

Petitioner provides its interpretation of the plain and ordinary meaning of the following terms recited in independent claims 1 and 3: "selecting the

patient as having a tramiprosate-sensitive form of Alzheimer's disease based on the presence of two ApoE4 alleles" and "administering to the selected patient" tramiprosate (claim 1) or Val-APS (claim 3) "in an amount effective to treat the disease." Pet. 19–25. Petitioner argues that, because claim 1 recites the transitional phrase "comprising" and does not specify exclusion criteria for the method of treatment, claim 1 "does not exclude steps in addition to those recited" and thus "it is irrelevant whether additional patients are also selected for treatment based on factors other than being ApoE4 homozygotes." *Id.* at 20. Petitioner argues that, properly construed, the scope of claims 1 and 3 covers the treatment of ApoE4+ heterozygotes (i.e., patients having only a single ApoE4 allele) along with homozygotes (i.e., patients having two ApoE4 alleles). *Id.* at 23 (citing Ex. 1003 ¶¶ 205–208). In other words, Petitioner asserts that under a proper claim construction, the claims do not require that ApoE4 heterozygotes be selectively denied treatment. *Id.* at 20. Petitioner further asserts that during prosecution, Patent Owner argued that the challenged claims require treating only homozygotes and require denying treatment to heterozygotes. *Id.* (citing Ex. 1002, 337). Petitioner, however, argues that Patent Owner's claim construction arguments are meritless and should be rejected. In particular, Petitioner argues that Patent Owner's final amendments to these claims during prosecution did not amend their scope consistent with Patent Owner's accompanying representation that the claims recite selecting for treatment only patients having two ApoE4 alleles (e.g., the method recited treatment only to ApoE4+ homozygotes). *Id.* at 20–22. In addition to the purported ethical considerations of precluding treatment of ApoE4+ heterozygous patients having AD with tramiprosate, Petitioner argues that

there is no reason to preclude them when heterozygous patients benefit from such treatment and where the claims and the ’029 specification lack sufficient support for a negative limitation precluding their treatment. *Id.* at 22–23. Finally, Petitioner argues that the prosecution-based statements cannot be used to add a limitation not appearing in the claims. *Id.* at 24.

Patent Owner argues the preamble should be construed to limit the claims. *Id.* at 16–17. Patent Owner further offers a construction for “amount effective” in claims 1 and 3, arguing that its plain and ordinary meaning and express definition in the ’029’s specification supports construction as “an amount sufficient to treat a patient with Alzheimer’s disease.” *Id.* at 17 (citing Ex. 1001, 3:27–30). For purposes of determining whether to institute trial of the challenged claims, we determine it is not necessary to decide whether the preamble in limiting or to interpret “amount effective” or any other term not addressed by the parties. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs*. in the context of an AIA proceeding).

We apply the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp*., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic

evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc*., 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317.

The central issue for interpretation is whether claims 1 and 3 could include treatment of ApoE4+ heterozygous patients along with or in addition to the homozygous patients recited in these claims, as alleged by Petitioner (Pet. 22–23). As explained below, and as further discussed in our analysis of Patent Owner's argument for exercise of discretion to deny institution under 35 U.S.C. § 325(d), we conclude that claims 1 and 3 do not include treatment of ApoE4+ heterozygous patients because Applicant disclaimed treatment of populations containing ApoE4+ heterozygous patients in order to distinguish Caltagirone, as suggested by the Examiner. *See* Ex. 1002, 338–39.

While we acknowledge, as Petitioner argues (Pet. 24), that patent prosecution history cannot be used to add a limitation or restrict a claim that was not disclosed, we note that prosecution history "facilitates claim construction by revealing the intended meaning and scope of technical terms and may even trump the weight of specification language in some circumstances." *TDM Am., LLC v. U.S.*, 85 Fed. Cl. 774, 788 (2009) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 804 (Fed. Cir. 1999)). For example, "an applicant's amendment accompanied by explanatory remarks can define a claim term by demonstrating what the applicant meant by the amendment." *Personalized Media*, 952 F.3d at 1340.

Thus, "like the specification, the prosecution history can act like a dictionary." *Hemphill v. McNeil-PPC, Inc.*, 25 F. App'x 915, 918 (Fed. Cir. 2001) (non-precedential).

As explained above (*see* Section I.G.), the '029 Specification discloses that subjects with one ApoE4 allele are more likely to have AD, and when they do, show increased AD progression believed to be caused by failure to remove Aβ amyloid deposition in the brain. Ex. 1001, 5:12–16. Patients with two ApoE4 alleles account for a large percentage of AD patients with more aggressive disease progression. *Id.* at 5:6–12.

During prosecution, the Examiner rejected claims to treatment of an ApoE4+ patient with AD using tramiprosate over the Caltagirone reference, which disclosed treatment of ApoE4+ "all-comers" (containing at least one ApoE4 allele, either heterozygous or homozygous) with tramiprosate. *See, e.g.*, Ex. 1002, 204–208. When Patent Owner responded to the Examiner by highlighting data (i.e., Figure 8 of the specification giving rise to the '029 patent) showing a notable increase in cognitive function in patients with two ApoE4 alleles (homozygous) who were administered tramiprosate as compared to the ApoE4 "all-comers" (mixed homozygous/heterozygous population), the Examiner suggested narrowing the pending claims to treatment of ApoE4 homozygotes. Ex. 1002, 342. Patent Owner submitted amended claims requiring selection of patients for treatment who were homozygous for ApoE4, and argued:

> The presently amended claims . . . select only ApoE4 homozygotes for treatment with tramiprosate or a prodrug thereof, **necessarily omitting ApoE4 heterozygotes from such treatment**.
>
> . . .

> Caltagirone fails to teach or suggest a patient selection strategy that would limit tramiprosate treatment to patients having two ApoE4 alleles and, in fact, teaches away from such selection. Kong fails to contradict or overcome these deficiencies in Caltagirone. Kong does not refer to any patient selection strategy, much less one that would limit tramiprosate prodrug treatment to ApoE4 homozygotes. The Office's reliance on Kong is solely for its teaching of a tramiprosate prodrug. Thus, the combination of Caltagirone and Kong, taken under the Office's interpretation, suggests treatment of all ApoE4+ patients with a prodrug of tramiprosate. This falls far short of suggesting the presently claimed patient selection and treatment strategy which **selects only ApoE4 homozygotes for treatment and does not treat ApoE4 heterozygotes**.

Id. at 338–39 (emphasis added). The Examiner acknowledged the distinction over Caltagirone and allowed the claims, finding specifically that Caltagirone did not distinguish between homozygous and heterozygous populations or teach the method of selecting ApoE4 homozygotes for treatment, and noting that the treatment results for ApoE4 homozygotes were surprising and unexpected. Ex. 1002, 337, 342, 660.

Patent Owner's language accompanying its claim amendments makes clear that the amendments were meant to overcome Caltagirone's disclosure of treatment of ApoE4+ "all-comers" by defining its claimed method by the steps of "selecting" and "treating" ApoE4 homozygotes *alone*. *See Personalized Media*, 952 F.3d at 1340 (explaining relevance of an applicant's remarks accompanying claim amendments during prosecution to interpret "what the applicant meant by the amendment") In light of the amendment, we are not persuaded by Petitioner's argument that claims 1 and 3, which use the open transition "comprising," could be construed to include treatment of ApoE4 heterozygotes. While the claims do not affirmatively exclude treatment of heterozygotes, Patent Owner's amendment disclaimed

treatment of ApoE4 heterozygotes, as made clear from Patent Owner's statements during prosecution that the claims "select only ApoE4 homozygotes for treatment with tramiprosate or a prodrug thereof, necessarily omitting ApoE4 heterozygotes from such treatment" and "the presently claimed patient selection and treatment strategy . . . selects only ApoE4 homozygotes for treatment and does not treat ApoE4 heterozygotes." Ex. 1002, 339. *See Schriber–Schroth Co. v. Cleveland Trust Co.,* 311 U.S. 211, 220–21, 61 S.Ct. 235, 85 L.Ed. 132 (1940) ("It is a rule of patent construction consistently observed that a claim in a patent as allowed must be read and interpreted with reference to claims that have been cancelled or rejected, and the claims allowed cannot by construction be read to cover what was thus eliminated from the patent."); *cf. Graham v. John Deere Co*., 383 U.S. 1, 33, 86 S.Ct. 684 (1966) (ruling, in addressing the invalidity of the patents in suit, that "claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent"); see also *Omega Eng'g., Inc. v. Raytek Corp*., 334 F.3d 1314, 1325 (Fed. Cir. 2003) (noting that a prosecution history disclaimer requires a "clear disavowal" of claimed subject matter to attach). We interpret Patent Owner's characterizations of its patient selection and treatment strategy quoted above as a clear disavowal of treatment of ApoE4 heterozygotes.

We therefore construe the claimed treatment method to exclude treatment of ApoE4+ heterozygous patients. We find that additional steps that could fall within the claimed method would include those contemplated by the Specification (e.g., determining the efficacy of treatment through

evaluation by ADAS-cog testing, *see* Ex. 1001 18:27–46) or known to one of ordinary skill in the art, but not intentionally disclaimed subject matter.

We are further unpersuaded by Petitioner's arguments (Pet. 23–24) that the claims should be interpreted to include treatment of heterozygotes because they respond to the treatment and excluding them would be unethical, as neither argument relates to a law of claim construction or patentability.

We find claims 1 and 3, interpreted in light of the claim language, specification, and prosecution history, require selection and treatment of ApoE4+ homozygous patients for treatment and exclude ApoE4+ heterozygous patients from treatment. We conclude no more precise interpretation of the limitations to be necessary for purposes of deciding institution.

III. DISCRETIONARY DENIAL

A. 35 U.S.C. § 325(d)

Patent Owner contends we should exercise discretion under 35 U.S.C. § 325(d) because Petitioner "(1) presents the same or substantially the same art and arguments previously considered by the Office but (2) fails to demonstrate that the Office erred in a manner material to the patentability of the challenged claims." Prelim Resp. 17–18. Petitioner argues that the combination of references is materially different from and not cumulative to the art evaluated during prosecution, including because a new reference, Babic, is asserted in the challenge. Pet. 68–69. Petitioner further argues the Examiner erred by incorrectly construing the claims, allowing claims over the asserted references Caltagirone and Kong, and in misapplying or overlooking teachings of certain references. *Id.* at 70–71.

B. Legal Framework

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

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Within this two-part framework, the Board considers several non-exclusive factors as set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*"), which "provide useful insight into how to apply the framework" under § 325(d). *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 9 (PTAB Feb. 13, 2020) (designated precedential Mar. 24, 2020). These non-exclusive factors include:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18 (formatting added).

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office (*Advanced Bionics*, Paper 6 at 10). Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments (*Advanced Bionics*, Paper 6 at 10). Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office (*Advanced Bionics*, Paper 6 at 10). "At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown" (*Advanced Bionics*, Paper 6 at 9).

C. Analysis

1. The Parties' Contentions

Petitioner argues Babic was not before the Examiner during prosecution and that Aisen and Gervais were cited in an Information Disclosure Statement ("IDS") but were not evaluated during prosecution or relied on in any Office action. Pet. 68 (*citing Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486 Paper 10 at 15 (PTAB July 15, 2015)). Petitioner argues the combination of references is materially different and not cumulative of art cited during prosecution. Pet. 68–69. Petitioner argues Babic "teaches that there is a significant difference in drug

response in the ApoE4 homozygous compared to heterozygous and non-carrier subgroups." *Id.* (citing Ex. 1005, 202). Petitioner alleges "Babic's disclosure would provide the [person of ordinary skill in the art] a motivation to distinguish between the effects of an AD drug in heterozygous compared to homozygous ApoE4 carriers or non-carriers when evaluating drug efficacy." *Id.* at 69. Petitioner argues its application of the references was either not a focus of examination or presents an argument not previously addressed by the Examiner. In particular, Petitioner argues that under the claims as properly construed, treatment of heterozygotes is not excluded from the challenged claims and thus the teachings of Caltagirone and Gervais are anticipatory to tramiprosate and render use of Val-APS obvious. *Id.* at 70. Finally, Petitioner argues that the claims do not require superior performance of homozygotes to treatment with respect to heterozygotes, only effective treatment, which was not an argument addressed by the Examiner. *Id.*

Patent Owner argues that the Petition provides three categories of references: 1) Caltagirone and Kong, which were argued before the Examiner as a focus of examination; 2) Gervais and Aisen, which were submitted on an IDS but were not a focus of examination; and 3) Babic, which was not considered previously by the Examiner. Prelim. Resp. 18. Patent Owner argues that Babic is asserted in only one of six grounds, is combined with references that were previously considered, and is not more relevant than, and rather is cumulative to the teachings of those references, including Sleegers. *Id.* at 18, 30–31. Patent Owner provides a detailed application of the *Becton, Dickinson* factors to the current challenge to

support its argument that we should exercise discretion to deny review. *Id.* at 19–41.

2. Was the Same or Substantially the Same Art or Arguments Presented to the Office?

Turning to the first part of the *Advanced Bionics* framework, we consider whether the same or substantially the same art or arguments previously were presented to the Office. The parties do not dispute that Caltagirone and Kong formed the basis of rejections during Examination, and were thus previously presented to the Office. Pet. 70; Prelim Resp. 20. Gervais and Aisen were cited in two Information Disclosure Statements, but did not form the basis of a rejection. Ex. 1002, 684–85, 1137, 1148–49). On this record and in light of the guidance in *Advanced Bionics* that references considered in an IDS are considered presented to the Office, it is clear that Gervais and Aisen were also presented to the Office. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 7 (PTAB February 13, 2020) (precedential) (holding previously presented art includes "art made of record by the Examiner[9], and art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent.").

As discussed above in Section II.B., we have interpreted the claims to require selection and treatment of ApoE4 homozygous patients and to exclude treatment of ApoE4 heterozygous patients, and we disagree with

[9] Allegations that an Examiner failed to appreciate teachings in a reference is an issue of Examiner error related to the second part of the *Advanced Bionics* framework, and we address Petitioner's allegations in that regard in part two.

Petitioner's claim construction that extends the scope of the claims to treatment of ApoE4 heterozygous patients.[10]

We agree with Patent Owner (Prelim Resp. 22) that Gervais was considered by the Examiner and is a cumulative reference to Caltagirone. *See* Ex. 1073, 3:9–13; 25:20–24 (describing treatment using 3-amino-1-proanesulfonic acid (tramiprosate) of AD patients with a mutation in the ApoE gene, without specifying or otherwise selecting homozygous ApoE4+ patients). Petitioner has not persuasively explained why Gervais discloses selective treatment of ApoE4+ homozygous patients or otherwise discloses unique teachings.

We further agree with Patent Owner (Prelim. Resp. 23–24) that Aisen is cumulative to teachings in Caltagirone and Kong related to oral administration and dosage of tramisprosate or its prodrug. *See, e.g.*, Ex. 1002, 207–208 (Examiner citation of Kong for oral administration of tramiprosate prodrug in varying dosages). Petitioner has not persuasively explained why Aisen discloses selective treatment of ApoE4+ homozygous patients or otherwise discloses unique teachings.

Babic is the only reference asserted in this case that was not previously presented to the Office, and the only reference with which

[10] For this reason, we find Petitioner's arguments for Grounds 1 and 5, which assert a claim construction we have not adopted in arguing these grounds, to be no different from those issues addressed during examination in which the identical references disclosed treatment of populations of ApoE4 homozygotes along with heterozygotes. *See, e.g.*, Ex. 1002, 205–208 (Examiner citation of Caltagirone and Kong for treatment of AD in ApoE4+ "all-comer" patients and for oral administration of tramiprosate prodrug in varying dosages).

Petitioner argues a case for obviousness applying "the claim construction argument Patent Owner made during prosecution of the '029 patent—that the claims require ApoE4 heterozygotes to be selectively denied treatment." Pet. 40. Petitioner argues that "Babic correlates ApoE4 homozygous status with positive response to the AD drug candidate galantamine" and notes that the authors "specifically differentiated between ApoE4 homozygotes and heterozygotes in formulating the treatment groups and analyses." Pet. 40–41 (citing Ex. 1005, 202). With respect to why Ground 4 is a materially different combination than art previously considered by the Examiner, Petitioner argues that "Babic's disclosure would provide the POSA a motivation to distinguish between the effects of an AD drug in heterozygous compared to homozygous ApoE4 carriers or non-carriers when evaluating drug efficacy." *Id.*, at 69.

We turn to Petitioner's contentions in Ground 4 to test this statement. Petitioner alleges:

> Babic teaches that it "was undertaken to evaluate the efficacy and tolerability of galantamine at a dosage level of 30 mg/day during six month treatment of patients with various apoE genotypes who suffered from mild to moderate AD." (EX1005, 200). Babic further teaches that "[a]mong three subgroups of patients, apoE4 negative patients and apoE4 heterozygous patients deteriorated after 6 months of treatment" and "[o]nly the subgroup of apoE4 homozygous improved slightly after six months of treatment…The difference in responders rate among the genetic subgroups was significant ($\chi 2 = 6.89$; $p = 0.032$), suggesting that only apoE4 homozygous subgroup of patients with AD might be considered as responders on galantamine." (EX1005, 202; EX1003, ¶301).

Pet. 27.

Petitioner argues that Babic's disclosure that only ApoE4 patients responded to galantamine along with the teachings of Caltagirone and Kong

showing a response to tramiprosate in ApoE4 carriers "would have motivated a POSA to select homozygous ApoE4 carriers for treatment with any drug for which response has been correlated to ApoE4 carrier status." *Id.* at 41 (citing Ex. 1003 ¶¶ 73, 105–107). Petitioner further argues that the improved safety profile of tramiprosate over galantamine would have further motivated the ordinary artisan, and cites Aisen and Kong for motivation to administer in oral dosage form and to use Val-APS instead of tramiprosate. *Id.* at 42–43.

For the reasons discussed below, we determine that Babic is no more relevant than and is cumulative to Sleeger, which was previously presented to the Office. *See* Ex. 1002, 685, 1137. We agree with Petitioner that Babic discloses a statistically significant difference in the response[11] to administration of galantamine in ApoE4 homozygotes as compared to heterozygotes. The relevant data are the baseline and end-point characteristics of ApoE4 subgroups of patients, and are shown in Table 1 of Babic, with arrow annotations added, below:

[11] Babic discloses "Outcome measure was Mini Mental Status Examination (MMSE) and it was carried out by an independent neurologist who was not aware of the patient's ApoE status before the treatment and at 6 months." Ex. 1005, 8.

TABLE 1
BASELINE AND END-POINT CHARACTERISTICS OF APOE SUBGROUPS OF PATIENTS

Parameter	All	ApoE4 heterozygous	ApoE4 homozygous	ApoE4 negatives
All patients				
Number of patients: N (%)	126	62 (50.2%)	21 (16.7%)	43 (34.1%)
Age: X±SD (range)	68.5 ± 7.2 (51–89)	69.1 ± 6.9 (51–84)	70.7 ± 7.7 (51–85)	67.2 ± 7.4 (56–88)
Sex (M/F)	65/61	35/27	9/12	22/21
Duration of AD (years): X±SD (range)	3.0 ± 1.7 (1.2–8.0)	3.0 ± 1.6 (1.7–7.1)	3.2 ± 1.9 (1.1–6.4)	2.8 ± 1.8 (1.4–6.8)
Familial history of AD (N)	25	13	6	6
Baseline MMSE: X±SD (range)	18.0 ± 3.52 (12–24)	17.9 ± 3.54 (12–24)	18.1 ± 3.41 (12–23)	18.2 ± 3.58 (12–24)
Completes only				
Number of patients (N)	84	41 (49%)	14 (16%)	29 (35%)
Age: X±SD (range)	68.9 ± 7.1 (51–87)	69.4 ± 8.3 (53–84)	71.1 ± 6.7 (51–85)	67 ± 7.4 (57–87)
Sex (M/F)	42/42	23/18	5/9	14/15
Duration of AD (years): X±SD (range)	3.1 ± 1.8 (1.2–7.1)	3.0 ± 1.6 (1.7–7.1)	3.1 ± 2.1 (1.2–6.3)	3.0 ± 1.9 (1.8–6.6)
Familial history of AD (N)	17	9	3	5
Baseline MMSE: X±SD (range)	18.0 ± 3.73 (12–24)	17.7 ± 3.76 (12–24)	18.2 ± 3.14 (12–23)	18.2 ± 4.04 (13–24)
End-point MMSE: X±SD (range)	16.4 ± 5.61** (5–30)	15.9 ± 5.26 (8–27)	18.4 ± 4.43 (10–25)	16.2 ± 6.51 (5–30)
End-point responders (N)	34 (40%)	15 (37%)	10 (71%)	9 (31%)
		(χ^2 = 6.89; p = 0.032)		

** p < 0.01 (ANOVA model)

Ex. 1005, 9. Table 1 above shows the baseline and end-point characteristics of ApoE subgroups of patients treated with galantamine. The relevant lines are indicated by arrows to the right of the table.

We note that, while some improvement in measured characteristics is shown, Babic's disclosure characterizes the homozygous group results using tentative language:

> Only the subgroup of apoE4 homozygous improved *slightly* after six months of treatment . . . The difference in responders rate among the genetic subgroups was significant (x2 = 6.89; p = 0.032), suggesting that only apoE4 homozygous subgroup of

> patients with Alzheimer's disease *might be considered* as responders on galanthamine.[12]

Ex. 1005, 202 (emphasis added). The minimal increase in ApoE4 homozygous patients in Babic as compared to heterozygous patients is notable, but Babic's results are obtained using a different AD drug and are measured with a different test. Petitioner's evidence supporting its contentions of obviousness in Ground 4 (Pet. 41–42), including conclusions drawn from Babic's teachings, are Dr. Ruffalo's declaration and citations therein, and we examine those next.

Dr. Ruffalo claims that the ordinary artisan would have understood that heterozygotes and non-ApoE4 carriers "possess at least one functional ApoE2 or ApoE3 allele, which in some instances may be sufficient for functional transport of lipoproteins in the brain." Ex. 1003 ¶ 73 (citing Ex. 1004 ("Isaks")), 6 for support. Isaks states that, based on one study of brain imaging in ApoE4 populations, homozygous ApoE4 carriers had more white matter legions as compared to ApoE4 heterozygous and non-carrier brains. Ex. 1004, 6. Isaks states: "[t]hus, the presence of one other ApoE isoform may be sufficient for attaining normal development and maintenance of the brain." *Id.* Isaks continues with a paragraph addressing the limitations of the study and caveats as to interpretation of the results, concluding with "our findings should be interpreted with some caution." In

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[12] "Galanthamine" and "galantamine" as used herein and by the cited references refer to the same compound. *See* https://pubmed.ncbi.nlm.nih.gov/11060814/ (last visited January 5, 2023) ("Galanthamine (or galantamine, Reminyl) is a tertiary alkaloid acetylcholinesterase inhibitor (AChEI) which has been approved in several countries for the symptomatic treatment of senile dementia of the Alzheimer's type."). Exhibit 3002; *see also* Ex. 1003 FN 5.

addition, Ex. 1004 states in the Introduction that "[p]robably, [the increase in risk of AD in carriers] is caused by diverse pathogenic mechanisms as apolipoprotein E (ApoE) plays a role in various processes in the brain including the production and clearance of amyloid-β, and the maintenance and repair of synapses and neurons." *Id.* at 1. Because Isak's language indicating knowledge in this area at the time of publication is hypothesized and still unproven, we interpret with caution Dr. Ruffalo's statements regarding about what the ordinary artisan would have believed about the correlation of homozygous ApoE4 carriers and lipoprotein transport function.

Dr. Ruffalo continues in cited paragraphs 105–107 to observe that Babic ascertained that "different effects of a drug could be observed in different subpopulations of patients based on ApoE4 carrier status"" and that "drug effects in homozygous carriers could be greater than those in the heterozygous carriers and non-carriers who did not respond to the drug." Ex. 1003 ¶ 107. As stated, this testimony does not support Petitioner's contention that an ordinary artisan would have been motivated "to select homozygous ApoE4 carriers for treatment with *any drug* for which response has been correlated to ApoE4 carrier status." *See* Pet. 41 (emphasis added). In particular, we find an insufficient factual basis for Petitioner's contention that results obtained for galantamine, an acetylcholinesterase inhibitor (Ex. 1003 ¶ 105) would have motivated an ordinary artisan to replace the galantamine taught in Babic with tramiprosate (homotaurine), a GABA receptor agonist that works by a different mechanism (Ex. 1007, 582).

We have also considered Dr. Ruffalo's testimony that the ordinary artisan would have been motivated to replace Babic's galantamine with

tramiprosate as taught in Caltagirone or Val-APS as taught in Kong. Ex. 1003 ¶¶ 276–277. Dr. Ruffalo posits that Babic's disclosures would have motivated the ordinary artisan to analyze Caltagirone's data to ascertain if tramiprosate is more effective in homozygotes, and to replace galantamine with tramiprosate or Val-APS as taught in Kong because of their improved safety profiles as compared to galantamine, and because the replacement drugs target the underlying disease and not symptom amelioration as does galantamine. *Id*. Dr. Ruffalo also posits that the prior art would have imparted the following knowledge to the ordinary artisan:

> because the effect of tramiprosate was dependent on the required ApoE4 allele, homozygotes having the highest number of ApoE4 allele copies would derive, at the very least, as much benefit as from the drug as the heterozygotes having only one copy of the allele, and most likely the homozygotes would have the greatest therapeutic response to tramiprosate since they have the maximum number of copies of the required allele. Having done this simple assessment, A POSA would conclude that tramiprosate would be expected to exhibit a greater therapeutic effect in homozygotes and thus would have been motivated to treat homozygotes with tramiprosate, including in an oral dosage form as taught by Aisen.

Id. Dr. Ruffalo further posits that the skilled artisan would have had a reasonable expectation of success in administering tramiprosate to treat homozygous ApoE4 patients because they "would almost certainly have the greatest response to the drug." *Id.* ¶ 286.

Patent Owner argues that the Examiner previously examined the issue of whether ApoE4 genotypes in treatment decisions should be considered during prosecution, with respect to Caltagirone, where ApoE4 genotypes were included, and Sleegers (Ex. 1002, 685, 1137), where studies led away from such inclusion. Prelim. Resp. 30–31. We find Sleegers' disclosure

that the inclusion of ApoE4 genotype in other studies involving cholinesterase inhibitors, *as is tramiprosate*, to be more relevant than Babic's disclosure of results from a study regarding galanthamine, a drug that works by a different mechanism to target AD symptoms rather than the underlying disease and was reported using a different examination rubric. Were we to institute this case, we would have significant concerns regarding the sufficiency of Dr. Ruffalo's testimony regarding the ordinary artisan's motivation to substitute galantamine for tramiprosate based on safety profile and mechanism of action in light of other studies regarding cholinesterase inhibitors concluding differently. Thus, we find Babic is no more relevant than Sleegers, which was considered by the Examiner.

In sum, we find that Babic's disclosures and Petitioner's arguments regarding Babic provide minimal if any contribution to the extensive examination record of arguments before the Examiner. We therefore conclude that the art and arguments in the Petition are substantially the same as those previously presented to the office. Having determined so, we turn to the second part of the *Advanced Bionics* framework, which requires an assessment of whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

3. Did the Office Err in a Manner Material to the Patentability of Challenged Claims?

Petitioner argues the Examiner erred in the following ways: 1) incorrectly construing the claims; 2) improperly finding "unexpected" results; o; and 3) misapplying the teachings of Caltagirone and overlooking the teachings of Gervais, which include selectively treating ApoE4 homozygous patients as part of the ApoE4 carrier group. Pet. 71.

Petitioner argues the Examiner improperly construed claim elements 1(a) (selecting patient based on two ApoE4 alleles) and 1(b) (administering treatment in effective amount) by "adopt[ing] Applicant's argument that the claims require selectively denying treatment to ApoE4 heterozygotes." Pet. 72. Petitioner refers to its earlier arguments regarding claim construction for further detail. *Id*.

As addressed in Section II.B above, we find that claims 1 and 3, interpreted in light of the claim language, specification, and prosecution history, require selection and treatment of ApoE4+ homozygous patients for treatment and exclude ApoE4+ heterozygous patients from treatment. Accordingly, we find that Petitioner has not sufficiently demonstrated that the Examiner, who suggested amendment to require selection and treatment of ApoE4+ homozygous patients, erred in construing the claims as allowed to require this. Regarding Petitioner's allegation that the Examiner improperly found "unexpected" results and consequently misapplied the teachings of Caltagirone, Petitioner alleges the Examiner "erroneously placed weight on the Figure 8 data [from the '565 application] showing ApoE4 homozygotes respond to tramiprosate better than the combined ApoE4 carrier population, and on that basis found the claims "unexpected" and "surprising" for allowance." *Id.* at 72. Petitioner argues that the claims do not require that ApoE4 homozygotes respond better than heterozygotes to tramiprosate, but merely require that tramiprosate is "effective to treat the disease" in homozygotes "regardless of how other any other group responds. *Id.*

Patent Owner responds that unexpected results need not be recited in the claim, but must only be superior to results achieved by other articles.

Prelim. Resp. 37–38 (citing, *e.g.*, *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984)). Patent Owner argues that the unexpected results that gave rise to allowance of the claims was through isolation of homozygotes in relation to Caltagirone's teaching of ApoE4+ patients as a group. *Id.* at 38 (citing Ex. 1001, 21:5–25). Patent Owner further argues that Petitioner fails to explain the unexpected results themselves as shown by its own admissions and evidence. *Id.* (citing Pet. 11–13, summarizing wide variance in responses of ApoE4 populations to drugs).

Patent Owner has the better argument. The claims were allowed in response to Patent Owner's evidence that ApoE4 homozygotes showed unexpectedly significant increase in cognitive function after administration with tramiprosate. Ex. 1002, 651–663. This increase was not a limitation recited in the claim but was the basis for the selection of the homozygous population as the treatment subject. *Id.* Petitioner does not fault the data in Figure 8 nor explain why the significant increase in performance of ApoE4 homozygotes is not unexpected. Petitioner has not sufficiently explained through evidence or argument why the Examiner's allowance of the claims on that basis is error.

With regard to the third allegation of error, Petitioner alleges that the Examiner misapplied the teachings of Caltagirone and overlooked the teachings of Gervais, which include selectively treating ApoE4 homozygous patients as part of the ApoE4 carrier group. Pet. 71–73. As discussed above in Section II.B, we find that the claims require selection and treatment of ApoE4+ homozygous patients, which is not disclosed or suggested by Caltagirone or Gervais. Accordingly, we find Petitioner has not established that the Examiner erred in a manner material to patentability.

Finally, Petitioner argues against the exercise of discretion on the basis that "there is a reasonable likelihood that Petitioner will prevail on invalidity theories not previously addressed." Petitioner alleges Grounds 1–3, 5, and 6 assert the proper claim construction not addressed during prosecution. We have addressed this issue in Section II.B above.

Petitioner further alleges evidence not previously available during prosecution includes 1) Dr. Ruffolo's testimony "that the ApoE4 homozygote response to tramiprosate was not surprising or unexpected"; and 2) "materially different prior art including Babic which in combination with the other cited art renders the claims obvious." Pet. 73–74.

We have addressed Dr. Ruffalo's testimony regarding this issue above in Section III.C.2 and find it is not sufficiently factually supported by the evidence. We therefore do not find this testimonial evidence favors institution. We have also addressed Babic's disclosures and determined they are cumulative to other art in the examination record. We conclude the additional evidence does not establish error by the Office and is not a basis on which to institute *inter partes* review.

IV. CONCLUSION

As discussed above, Petitioner's challenges to the '029 patent's claims rely on Caltagirone, Kong, Gervais, Aisen, and Babic. Caltagirone and Kong were the subject of substantive examination during prosecution. Gervais and Aisen were cited in an IDS and are cumulative of Caltagirone. Babic was not considered during prosecution, but is cumulative of Gervais and pertains to a single ground that includes Caltagirone for the teaching of the aspect of asserted novelty. Petitioner has not sufficiently shown that the Examiner erred in allowing the claims. Taking a holistic view of the totality

of the circumstances presented, on this record, we exercise discretion under Section 325(d) and do not institute an *inter partes* review.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all challenged claims, and no trial is instituted.

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