

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

ALZHEON, INC.,  
Patent Owner.

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PGR2022-00051  
Patent No. 11,191,742 B2

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

WISZ, *Administrative Patent Judge*.

DECISION  
Denying Institution of Post-Grant Review  
35 U.S.C. § 324

## I. INTRODUCTION

Risen (Suzhou) Pharma Tech. Co. Ltd., (“Petitioner”) filed a Petition requesting a post-grant review of claims 1–19 (“the Challenged Claims”) of U.S. Patent No. 11,191,742 B2 (Ex. 1001, “the ’742 patent”). Paper 2 (“Pet.”). Alzheon, Inc., (“Patent Owner”) filed a Patent Owner Preliminary Response (“Prelim. Resp.”). Paper 10. With our authorization, Petitioner filed a Reply (Paper 12, “Reply”), and Patent Owner filed a Sur-Reply (Paper 13, “PO Sur-Reply”).

Under 35 U.S.C. § 324(a), a post-grant review may not be instituted “unless . . . the information presented in the petition . . . , if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” Upon considering the arguments and evidence, we determine that the information presented fails to demonstrate it is more likely than not that at least one of the challenged claims of the ’742 patent is unpatentable for ineligibility, lack of written description, or non-enablement. We also exercise our discretion to deny institution of post-grant review under 35 U.S.C. § 325(d).

### *A. Real Parties in Interest*

Petitioner and Patent Owner identify themselves as the only real parties-in-interest involved in this case. Pet. 98, Paper 4, 1.

### *B. Related Matters*

Petitioner and Patent Owner identify U.S. Application No. 17/477,886 as a continuation application that claims priority to U.S. Application No. 15/758,405, the application which issued as the ’742 patent. Pet. 99; Paper 4, 1.

*C. The '742 Patent*

The '742 patent, titled “Methods of Treating Neurological Disorders in a Particular Population” discloses “methods for treating, ameliorating, and/or preventing Alzheimer’s Disease in a specific patient population using tramiprosate, valyl-3-amino-1-propanesulfonic acid, or a pharmaceutically acceptable salt thereof based upon a combination of APOE4 status and disease severity.” Ex. 1001, codes (54), (57). The '742 patent discloses that tramiprosate and its valine prodrug from, ALZ-801, have stronger therapeutic effects on specific subsets of Alzheimer Disease (“AD”) patients. *Id.* at 1:55–59. The Specification discloses that ALZ-801 (valyl-3-amino-1-propane-sulfonic acid, “Val-APS”)<sup>1</sup> is an orally bioavailable, small-molecule prodrug of tramiprosate with improved pharmacokinetics and oral tolerability over tramiprosate. *Id.* at 1:64–67.

The '742 patent explains that Alzheimer’s Disease is a degenerative disease of the brain primarily associated with aging. Ex. 1001, 1:26–27. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. *Id.* at 1:33–34. The '742 patent discloses that the severity of AD can be measured through different assessment methods including the Mini-mental State Examination (“MMSE”). *Id.* at 2:12–14. According to the patent, a baseline MMSE score of 20–26 is considered to be mild AD; while a baseline MMSE score of 16–19 is considered to be moderate AD. *Id.* at 2:16–19. The '742 patent

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<sup>1</sup> We refer to these terms—ALZ-801, valyl-3-amino-1-propanesulfonic acid, and Val-APS—interchangeably throughout the decision. Petitioner’s declarant states that ALZ-801 is Val-APS. Ex. 1003 ¶ 41.

also subdivides mild AD into “less mild AD” (MMSE score of 20–21) and “more mild” AD (MMSE score of 22–26). *Id.* at 2:22–25.

The ’742 patent also explains that the methods of the invention are considered to be effective “if the decline of cognitive abilities is slowed as compared to a standard-of-care control treatment.” Ex. 1001, 4:61–64. According to the patent, the treatment efficacy can be measured by metrics known in the art such as the ADAS-Cog score or CDR-SB score,<sup>2</sup> where a higher score indicates lower cognitive ability. *Id.* at 4:66–5:2.

Examples 1 and 2 of the ’742 patent disclose data from Phase 3 clinical trials of tramiprosate to treat AD. Ex. 1001, 16:30–21:20. Based on an analysis of this data, the ’742 patent discloses that:

Applicants have surprisingly discovered based on clinical data, that APOE4/4 homozygous patients suffering from mild AD or mild-moderate AD respond unexpectedly better to treatment with tramiprosate or a prodrug thereof (e.g., ALZ-801) than the other AD patients (e.g., APOE4/4 homozygous patients with more moderate AD). In particular, APOE4/4 homozygous patients with mild AD (baseline MMSE score of 20-26) and mild moderate AD baseline MMSE score of 18-19) tend to show a higher improvement on tramiprosate at 150 mg BID than those with MMSE<18 at baseline. Additionally, ApoE4/4 homozygous patients with baseline MMSE  $\geq 22$  showed the highest efficacy and a progressive increase in cognitive benefit compared to placebo over the 78 weeks of the study.

*Id.* at 2:34–47. Similarly, according to the patent, “analysis of the data from the tramiprosate Phase 3 clinical trial surprisingly showed that APOE4/4

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<sup>2</sup> CDR is a Clinical Dementia Rating Scoring Algorithm developed by Washington University that is “based on areas of cognitive and functional deficit that characterize dementing illnesses.” *See* <https://knightadrc.wustl.edu/professionals-clinicians/cdr-dementia-staging-instrument/cdr-scoring-algorithm/> (last visited Dec. 20, 2022) (Ex. 3001).

homozygotes actually responded better if they had a more mild form of the disease as shown . . . in Example 2.” *Id.* at 20:32–36, Example 2, Figs. 7A and 7B.

Example 3 of the ’742 patent describes a Phase I bridging study of tramiprosate prodrug ALZ-801 and pharmacokinetic analysis compared to tramiprosate. Ex. 1001, 21:25–22:17. The ’742 patent states that, “[t]he data indicate that between 260 and 270 mg (e.g., 265 mg) BID dosing of ALZ-801 achieves steady-state tramiprosate exposure that is equivalent to 150 mg BID of oral tramiprosate.” *Id.* at 22:21–24.

#### *D. Statutory Disclaimer*

After the filing of the Petition in this proceeding, Patent Owner filed a statutory disclaimer, disclaiming claims 9 and 11–15 of the ’742 patent, effective October 7, 2022. Prelim. Resp. 12; Ex. 2001, 1. “No post-grant review will be instituted based on disclaimed claims.” 37 C.F.R. § 42.207(e). We do not analyze the validity of claims 9 and 11–15 based on Petitioner’s challenges (e.g., Grounds 2 and 3) because these claims have been statutorily disclaimed.

#### *E. Illustrative Claims*

Petitioner challenges claims 1–19 of the ’742 patent. Pet. 3–4. After Patent Owner’s statutory disclaimer, claims 1–8, 10, and 16–19 remain. Prelim. Resp. 12; Ex. 2001, 1. Claims 1, 10, and 16 are independent, and claims 2–8 and 17–19 depend from the independent claims. Ex. 1001, 22:40–24:31. Claims 1 and 10 are illustrative of the claimed subject matter and are reproduced below.

1. A method of treating Alzheimer’s Disease in a subject, the method comprising administering to the subject a pharmaceutical

composition comprising valyl-3-amino-1-propanesulfonic acid, or a pharmaceutically acceptable salt thereof, in an amount effective to reduce cognitive decline, only if the subject is determined to (i) be APOE4/4 homozygous; and (ii) have a baseline Mini-mental State Examination (MMSE) score of  $\geq 22$ , wherein the MMSE was performed within sixty days prior to the first administration of the composition.

*Id.* at 22:40–49.

10. A method of selecting and treating a patient suffering from Alzheimer's disease comprising the steps of:

(a) selecting the patient if the patient is both APOE4/4 homozygous and has a baseline Mini-mental State Examination (MMSE) score of  $\geq 22$ , wherein the MMSE was performed within sixty days prior to the first administration of the composition; and

(b) administering to the selected patient a pharmaceutical composition comprising valyl-3-amino-1-propanesulfonic acid or a pharmaceutically acceptable salt thereof, in an amount effective to reduce cognitive decline.

*Id.* at 23:12–23. Independent Claim 16 recites the same method as claim 1 with the administration of a specific dosage range of Val-APS to treat AD.

*Id.* at 24:14–24:22. Claims 2–8 and 17–19 are similar to the independent claims and recite additional limitations pertaining to the administration of Val-APS and the patients to be treated. *Id.* at 22:50–23:2; 24:14–31.

#### *F. Prior Art and Asserted Grounds*

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

| Ground | Claim(s)<br>Challenged | 35 U.S.C. § | Reference(s)/Basis |
|--------|------------------------|-------------|--------------------|
| 1      | 1–19                   | 101         | Eligibility        |

| Ground         | Claim(s)<br>Challenged | 35 U.S.C. §      | Reference(s)/Basis                                    |
|----------------|------------------------|------------------|-------------------------------------------------------|
| 2 <sup>3</sup> | 11–12, 15              | 103 <sup>4</sup> | Laurin '714, <sup>5</sup><br>Caltagirone <sup>6</sup> |
| 3 <sup>7</sup> | 11–12, 15              | 103              | Aisen (2007), <sup>8</sup><br>Caltagirone             |
| 4              | 1–3, 6–10              | 103              | Laurin '714, Caltagirone,<br>Froestl <sup>9</sup>     |
| 5              | 1–10, 13–14,<br>16–19  | 103              | Laurin '714, Caltagirone,<br>Kong <sup>10</sup>       |

<sup>3</sup> This ground is moot due to Patent Owner's statutory disclaimer of claims 11–12 and 15.

<sup>4</sup> The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the '742 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. § 103.

<sup>5</sup> U.S. Patent Pub. No. US 2006/0251714 A1, published Nov. 9, 2006 (Ex. 1061, "Laurin '714").

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

<sup>7</sup> This ground is moot due to Patent Owner's statutory disclaimer of claims 11–12 and 15.

<sup>8</sup> Aisen et al., *Alzhemed: A Potential Treatment for Alzheimer's Disease*, CURRENT ALZHEIMER RESEARCH, 4:473–478 (2007) (Ex. 1062, "Aisen 2007").

<sup>9</sup> Froestl et al., *Cognitive Enhancers (Nootropics). Part 3: Drugs Interacting with Targets other than Receptors or Enzymes. Disease Modifying Drugs. Update 2014*. JOURNAL OF ALZHEIMER'S DISEASE, 42:1079–1149 (2014) (Ex. 1064, "Froestl").

<sup>10</sup> U.S. Patent Pub. No. US 2014/0220122 A1, published Aug. 7, 2014 (Ex. 1069, "Kong").

| Ground | Claim(s)<br>Challenged | 35 U.S.C. § | Reference(s)/Basis                            |
|--------|------------------------|-------------|-----------------------------------------------|
| 6      | 1–3, 6–12, 15          | 103         | Laurin ’714, 2015 Press Release <sup>11</sup> |
| 7      | 1–19                   | 112(a)      | Written Description                           |
| 8      | 1–3, 6–13, 15          | 112(a)      | Enablement                                    |

Pet. 3–4.

In support of the contentions in its Petition, Petitioner relies on the supporting Declaration of Dr. Robert Ruffolo, Jr., dated June 30, 2022.

Ex. 1003.

## II. ELIGIBILITY FOR POST-GRANT REVIEW

The AIA’s post-grant review provisions apply to patents that “contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date . . . that is on or after [March 16, 2013].” Leahy-Smith America Invents Act (AIA) §§ 3(n)(1), 6(f)(2)(A) (2011). In addition, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be).” 35 U.S.C. § 321(c) (2012); *see* 37 C.F.R. § 42.202(a) (2019).

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<sup>11</sup> *Alzheon Announces Phase 1 Results of ALZ-801, a First-in-Class Inhibitor of Amyloid Formation and Neurotoxicity for Alzheimer’s Disease*, (Mar. 20, 2015), available at <https://www.businesswire.com/news/home/20150320005046/en/Alzheon-Announces-Phase-1-Results-of-ALZ-801-a-First-in-Class-Inhibitor-of-Amyloid-Formation-and-Neurotoxicity-for-Alzheimer%E2%80%99s-Disease> (Ex. 1065, “2015 Press Release”).

Here, the '742 patent is eligible for post-grant review because the Petition was filed within nine months of the '742 patent's issue date and the earliest possible priority date of the '742 patent is after March 16, 2013 (the effective date for the first inventor to file provisions of the Leahy-Smith America Invents Act). Ex. 1001, code (45) (showing an issue date of December 7, 2021); *id.* at 1:5–15 (claiming priority to a PCT application and four provisional applications, the earliest of which was filed on September 10, 2015); *id.* at codes (22), (60); Paper 3 (according the Petition a filing date of July 1, 2022).

### III. 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. 14–15 (citing Ex. 1003 ¶ 62) (internal citation omitted). Patent Owner does not contest the characterization offered by Petitioner. Prelim. Resp. 12–13.

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 ’742 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*

The parties do not propose any claim terms that need construction and we determine that no terms of the ’742 patent require express construction for purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *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.”)).

### *C. Asserted Patent Ineligibility of Claims 1–8, 10, and 16–19<sup>12</sup>*

Petitioner contends that claims 1–8, 10, and 16–19 of the ’742 patent are patent ineligible. Pet. 20–32. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 13–22.

#### *1. Legal Standard*

An invention is patent-eligible if it claims a “new and useful process, machine, manufacture, or composition of matter.” 35 U.S.C. § 101.

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<sup>12</sup> These are the remaining challenged claims after Patent Owner’s statutory disclaimer of claims 9 and 11–15. Ex. 2001.

However, the U.S. Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: “[l]aws of nature, natural phenomena, and abstract ideas” are not patentable. *E.g., Alice Corp. v. CLS Bank Int’l*, 573 U.S. 208, 216 (2014).

To determine whether a claim falls within a judicially recognized exception to patent eligibility under 35 U.S.C. § 101, we apply the two-step framework set forth in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), and reaffirmed in *Alice Corporation Proprietary LTD. v. CLS Bank International*, 573 U.S. 208 (2014). For the first *Alice* step, we determine whether the claims at issue are directed to a patent-ineligible concept such as an abstract idea, law of nature, or natural phenomenon. *Alice*, 573 U.S. 208 (citing *Mayo*, 566 U.S. at 78–79). If so, we advance to the second *Alice* step where “we consider the elements of each claim both individually and ‘as an ordered combination’ to determine whether the additional elements ‘transform the nature of the claim’ into a patent-eligible application” of the otherwise patent-ineligible concept. *Id.* (quoting *Mayo*, 566 U.S. 78–79).

We also follow the USPTO’s additional guidance. *See 2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50 (Jan. 7, 2019) (“Revised Guidance”). The Revised Guidance establishes a “two-prong inquiry” for determining whether a claim is directed to a judicial exception. *Id.* at 54. In prong one, we determine whether the claim *recites* a judicial exception, such as a law of nature, natural phenomenon, or abstract idea. *Id.* If so, we look to whether the claim recites additional elements that *integrate* the judicial exception *into a practical application*. *Id.* at 50. Thus, a claim is *directed to* a judicial exception only if the claim recites a judicial

exception *and* does not integrate that exception into a practical application. *Id.* The Revised Guidance instructs that an additional limitation that, *inter alia*, “applies or uses a judicial exception to effect a particular treatment or prophylaxis for a disease or medical condition” may integrate the judicial exception into a practical application and therefore not be unpatentable as directed to ineligible subject matter. *Id.* at 55.

If we determine that the judicial exception is not integrated into a practical application, we proceed to determine whether the claim adds a specific limitation beyond the judicial exception that is not well-understood, routine, and conventional activity in the field, or, alternatively, whether the claim simply appends well-understood, routine, and conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception. Revised Guidance, 84 Fed. Reg at 56.

## 2. *Petitioner’s Position*

Petitioner contends that the challenged claims are patent ineligible because they are directed to a natural law and an abstract idea. Pet. 20.

First, Petitioner asserts that the claims are directed to a natural law because the crux of the claimed invention is a “relationship between a patient’s genotype and state of disease progression, and the patient’s therapeutic response to a drug.” Pet. 20–21. According to Petitioner, an AD patient’s body will respond to tramiprosate or Val-APS in a certain way if the patient is APOE4/4 homozygous and experiencing mild AD and this “response is a biological result of the patient’s genetics and disease progression,” which is a natural law, rather than a product of any human action. *Id.* at 21 (citing Ex. 1003 § VIII.A.1, ¶ 322). Petitioner contends that the Federal Circuit found similar claims patent-ineligible in *INO*

*Therapeutics LLC v. Praxair Distribution, Inc.*, 782 F. App'x 1001, 1005 (Fed. Cir. 2019). *Id.* Petitioner further contends that the challenged claims involve nothing more than identifying a natural law and telling physicians to apply it in deciding who to treat, as in *INO*. *Id.*

Petitioner also asserts that the claims are not directed to any innovative laboratory technique or human-devised result but, rather, they “merely instruct administration of tramiprosate (or Val-APS) to the claimed patient subset—whose response to tramiprosate is a product of nature—and withholding treatment from patients not within the claimed subset whose response (or lack thereof) is also a product of nature.” Pet. 22. According to Petitioner, Patent Owner has relied on the claims’ exclusionary aspect as the sole invention. *Id.* at 23. Petitioner contends, “[l]ike the invalid claims in *INO*, the Challenged Claims ‘do[] no more than add an instruction to withhold’ treatment from excluded patients without reciting affirmative treatment for the excluded group, and therefore they merely recite a ‘method in which, for the []excluded patients, the body’s natural processes are simply allowed to take place.’” *Id.* (citing *INO*, 782 F. App'x at 1005) (second two alterations in original).

Petitioner further argues that the claims are directed to an abstract mental step applied to the natural law discussed above. Pet. 25. Petitioner argues that the “claims represent a physician’s decision to administer the drug to patients for whom the drug is expected to be effective; if not, the drug is not administered” and that “[t]his decision is a mental process routinely performed by physicians who evaluate patients and select treatment options.” *Id.* According to Petitioner, “[t]he entire selection

process may be performed in the human mind, without use of a particular machine or invention.” *Id.* (citing Ex. 1003 ¶ 335).

Petitioner also contends that the recited techniques were routine and conventional and that “[s]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable.” Pet. 25–26 (citing *Mayo*, 566 U.S. at 82). For example, Petitioner asserts that the Specification only teaches well-known methods for determining that a patient is both APOE4/4 homozygous and has an MMSE score of  $\geq 22$ . *Id.* at 26 (citing Ex. 1003 ¶ 338). Petitioner further contends that the ’742 patent does not provide specific instructions regarding how to make or use tramiprosate or Val-APS and relies on what is already known and established regarding these drugs. *Id.* at 27–28 (citing Ex. 1001, 13:58–14:4; Ex. 1003 ¶¶ 348–349). Similarly, Petitioner alleges that “[t]he ’742 patent treats dosages of tramiprosate and Val-APS ‘in an amount effective to reduce cognitive decline’ . . . as routine, conventional, and well-known.” *Id.* at 28 (citing Ex. 1003 ¶ 351).

### 3. Patent Owner’s Position

Patent Owner argues that the challenged claims are not directed to a law of nature or abstract mental steps but rather “recite new methods of treatments comprising administering a specific improved medication—ALZ-801—to a newly identified and specified patient population at specific doses to treat Alzheimer’s Disease.” Prelim. Resp. 13. According to Patent Owner, the Federal Circuit has consistently held that such method claims “‘directed to a *specific method* of treatment for *specific patients* using a *specific compound* at specific doses to achieve a *specific outcome*’ are

*patent eligible.*” *Id.* at 14 (citing *Vanda Pharm. Inc. v. West-Ward Pharm. Int’l Ltd.*, 887 F.3d 1122, 1133–1136 (Fed. Cir. 2018); *Boehringer Ingelheim Pharms. Inc. v. Mylan Pharms. Inc.*, 803 F. App’x 397, 400 (Fed. Cir. 2020) (citing *Vanda* and holding claims reciting administering a DPP-IV inhibitor to a specific patient subgroup with metabolic diseases are patent eligible); *Natural Alternatives Int’l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1343–44 (Fed. Cir. 2019) (citing *Vanda* and holding claims reciting methods of providing “an amount of beta-alanine to blood or blood plasma effective to increase beta-alanyl histidine dipeptide synthesis” are patent eligible (emphasis omitted)).

Patent Owner contends that, “[i]nstead of simply ‘indicating’ a need to adjust drug doses, the challenged claims here recite ‘[a]dministering certain quantities of [a specific drug] to a human subject alters that subject’s natural state.’” Prelim. Resp. 15 (citing *Vanda*, 887 F.3d at 1135; *Natural Alternatives*, 918 F.3d at 1343–44) (second two alterations in original). Patent Owner concludes that Petitioner fails to establish under *Mayo* step one that the challenged claims are directed to laws of nature. *Id.* at 20.

#### 4. Analysis

We agree with Patent Owner that the challenged claims of the ’742 patent are not directed to patent-ineligible subject matter. We also agree that the challenged claims are more similar to those in *Vanda* than those in *Mayo*. The claims in *Vanda* required a treating doctor to administer a drug to a patient in different amounts depending on the result of a genotyping assay. *Vanda*, 887 F.3d at 1135. In contrast, the claims in *Mayo* did not go beyond recognizing a need to increase or decrease a dose. *Id.* (citing *Mayo*,

566 U.S. at 75). Thus, the claim in *Mayo* was not a treatment claim. *Id.* (citing *Mayo*, 566 U.S. at 76).

Similar to *Vanda*, the challenged claims are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome. *Vanda*, 887 F.3d at 1136. Thus, as in *Vanda*, the instant claims recite “treatment steps,” in contrast to *Mayo*, where “the metabolite level in blood simply ‘indicate[d]’ a need to increase or decrease dosage.” *Id.* at 1135. Therefore, even though the claims may involve the natural phenomenon of a certain patient population responding better to treatment with ALZ-801, the claims are not directed to patent-ineligible subject matter because they require the treating doctor to administer ALZ-801 in an effective amount to this specific group of AD patients in order to reduce cognitive decline. Accordingly, we find that the claims integrate the recited judicial exception into a practical application. *See Revised Guidance*, 84 Fed. Reg. at 54.

We also find the challenged claims to be distinguishable from those in *INO*, cited by Petitioner. In *INO*, the focus of the claims was the instruction *not to treat* certain patients who had a screening-identified increased risk of side effects, while administering iNO (inhaled nitric oxide) gas to other patients as was done before. *INO*, 782 F. App’x 1001, 1002–1004, 1006–1007. In contrast, the current claims recite a method for selecting a certain sub-population of AD patients to affirmatively treat with a specific prodrug, ALZ-801. The ’742 patent discloses that this particular subgroup of AD patients (APOE4/4 homozygotes with a MMSE score of  $\geq 22$ ) surprisingly showed the highest efficacy and progressive increase in cognitive benefit with the administration of tramiprosate. Ex. 1001, 2:44–49, 21:6–13.

We also are not persuaded by Petitioner’s arguments regarding the claims’ alleged recitation of an abstract mental step. We agree with Patent Owner that Petitioner fails to specifically address any claim or limitation that recites such an abstract mental step. Prelim. Resp. 19. Rather, Petitioner’s argument appears to focus on “determining a subject’s suitability for treatment” (*see* Pet. 25), which is language from disclaimed claim 9. The remaining challenged claims recite administering a particular drug to a certain group of patients, which, as discussed above, integrates any judicial exception into a practical application.

Because we find that the claims are not directed to patent-ineligible subject matter as in *Vanda*, we need not address Petitioner’s argument that “[s]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable.” Pet. 26. This analysis only applies when the claim recites a judicial exception that does not integrate the exception into a practical application. Revised Guidance, 84 Fed. Reg. at 56; *see also Vanda*, 887 F.3d at 1134 (“If the claims are not directed to a patent ineligible concept at step one, we need not address step two of the inquiry”).

Therefore, for the above reasons, we find that Petitioner has not shown that it is more likely than not that the challenged claims are directed to ineligible subject matter.

*D. Asserted Lack of Written Description of Claims 1–8, 10, and 16–19*<sup>13</sup>

Petitioner contends that claims 1–8, 10, and 16–19 of the ’742 patent lack written description support. Pet. 75–86. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 23–32.

*1. Legal Standard*

To satisfy the written description requirement under 35 U.S.C. § 112(a), the specification must “reasonably convey[] to those skilled in the art that the inventor had possession” of the claimed invention as of the filing date based on an “objective inquiry into the four corners of the specification.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351–52 (Fed. Cir. 2010) (en banc). An adequate description does not require any particular form of disclosure or that the specification recite the claimed invention *in haec verba*, but must do more than render the claimed invention obvious. *Id.* at 1352.

The written description requirement is satisfied when the specification “set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.” *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 928 (Fed. Cir. 2004). The specification does not have to provide exact or verbatim textual support for the claimed subject matter at issue. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). The Federal Circuit has clarified that

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<sup>13</sup> These are the remaining challenged claims after Patent Owner’s statutory disclaimer of claims 9 and 11–15. Ex. 2001.

[a]lthough [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed . . . . The test for sufficiency of support . . . is whether the disclosure of the application relied upon “reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.”

*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citation omitted). Moreover, “the written description requirement does not demand either examples or an actual reduction to practice.” *Ariad Pharms.*, 589 F.3d at 1352. “[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). Furthermore, “[a] specification may . . . contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses.” *Id.*

Finally, the written description inquiry is a question of fact, is context specific, and must be determined on a case-by-case basis. *Ariad Pharms.*, 589 F.3d at 1351 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575; *Capon v. Eshhar*, 418 F.3d 1349, 1357–1358 (Fed. Cir. 2005)); *see also Vas-Cath*, 935 F.2d at 1562 (“Precisely how close the [original] description must come to comply with [the description requirement of] § 112 must be [determined on a] case-by-case basis.”) (quoting *In re Smith*, 258 F.2d 1389, 1395 (CCPA 1972)). “[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Ariad Pharms.* at 1351 (citing *Capon*, 418 F.3d at 1357–1358). Factors used to evaluate the sufficiency of a disclosure include: 1)

“the existing knowledge in the particular field”; 2) “the extent and content of the prior art”; 3) “the maturity of the science or technology”; and 4) “the predictability of the aspect at issue” (the “*Ariad* factors”). *Id.* (citing *Capon*, 418 F.3d at 1359).

## *2. Petitioner’s Position*

Petitioner asserts that the challenged claims are invalid for failing to satisfy the written description requirement for two reasons. Pet. 75–87. First, Petitioner asserts that the Specification does not adequately describe treating only the claimed subpopulation and excluding all others. *Id.* at 75–81. Second, Petitioner contends that the Specification does not provide detail beyond what was known in the art. *Id.* at 81–87. These two arguments are detailed further below.

### *a. Petitioner’s Argument that the Specification Does Not Adequately Describe Treating Only the Claimed Patient Subpopulation and Excluding All Others*

Petitioner contends that “there is no way a POSA would conclude from the Specification that the inventors possessed a method that requires excluding from treatment heterozygotes with moderate AD.” Pet. 75. According to Petitioner, “the specification consistently and unwaveringly teaches that APOE4 heterozygotes with moderate AD benefit from treatment and should be administered tramiprosate or Val-APS.” *Id.* (citing Ex. 1001, 1:58–63, 2:36–4:40; Ex. 1003 ¶¶ 694–696). Petitioner further contends that the Specification does not disclose an embodiment in which only homozygotes with mild AD are treated and all others excluded. *Id.* at 76 (citing Ex. 1003 ¶ 699).

Petitioner explains that the “only if” limitation, limiting the claims to the treatment of APOE4/4 homozygotes with a MMSE score of  $\geq 22$ , was added during prosecution to overcome prior art rejections. Pet. 77 (citing Ex. 1002, 453). According to Petitioner, the Examiner should not have allowed this amendment because the application contains no support for it. *Id.* (citing Ex. 1003 ¶¶ 701–702). Further, according to Petitioner, because the claims include an exclusionary element, there “must be something in the specification that conveys to a skilled artisan that the inventor intended the exclusion, such as a discussion of disadvantages or alternatives.” *Id.* at 78–79 (citing *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1017–18 (Fed. Cir. 2022)). Petitioner contends that the Specification of the ’742 patent contains no such discussion and, in fact, “repeatedly teaches that patients with ‘*moderate AD who are APOE4 positive*’ are the preferred group for treatment [] and that ‘patients with moderate AD are found to be more responsive to tramiprosate than the patients with mild AD.’” *Id.* at 79 (citing Ex. 1001, 9:63–10:8, 10:1–2, 10:29–11:24; 16:30–20:55; Ex. 1003). Petitioner further contends that the only group that is affirmatively excluded from treatment are subjects with mild AD and those who tested APOE4 negative. *Id.* (citing Ex. 1001, 10:40–50; Ex. 1003 ¶ 703).

Petitioner further contends that the ’742 Specification does not include any evidence that there is a deleterious effect of using tramiprosate to treat subjects that are APOE4 heterozygotes with moderate AD. Pet. 80. Petitioner acknowledges Example 2 from the Specification which shows that the APOE4/4 homozygous population with mild AD had a better response to tramiprosate compared to homozygous patients with moderate AD, but argue that Example 2 does not suggest treating only homozygous mild

patients to the exclusion of moderate homozygotes and moderate heterozygotes. *Id.* (citing Ex. 1001, 20:58–21:20; Ex. 1003 ¶ 706). Petitioner further contends that Example 2 suggests also treating other patients in stating that, “the trend suggests that APOE4+ homozygous patients with mild-moderate AD (baseline MMSE=18-19) may also show a higher improvement than APOE4+ homozygous patients with more moderate AD (baseline MMSE=16-17).” *Id.* (citing Ex. 1001, 21:14–20; Ex. 1003 ¶ 706).

*b. Petitioner’s Argument that the Specification Does Not Provide Detail Beyond What Was Known in the Art*

Petitioner also argues that, if the Board finds the challenged claims non-obvious or not routine and conventional with respect to patent ineligibility, then the ’742 patent Specification does not demonstrate possession of the claimed invention. Pet. 81. Specifically, Petitioner asserts that the “patent describes the claimed techniques almost entirely with reference to what was already known or understood in the art” so if a POSA would require more than routine and conventional techniques to perform the claimed methods, then the Specification does not disclose those techniques in sufficient detail to demonstrate to a POSA that the named inventors had possession of them. *Id.* at 81.

First, Petitioner contends that the ’742 patent discloses administering tramisprostate or Val-APS at only a high level of generality and does not demonstrate possession of a special method beyond what was known in the art. Pet. 81–82 (citing Ex. 1001, 13:58–14:4; Ex. 1003 ¶ 710). Petitioner also contends that the ’742 patent discusses only ranges of possible dosages at which tramisprostate or Val-APS could be administered and does not

suggest possession of where the metes and bounds lie regarding dosages “effective to reduce cognitive decline,” as claimed. *Id.* at 82 (citing Ex. 1003 ¶¶ 711–713). Petitioner also argues that the Specification does not show that administration of the recited doses of Val-APS in claims 4–5 and 16–19 reduce cognitive decline or treat AD. *Id.* at 83–84. Petitioner further alleges that the Specification does not disclose possession of using a 150 mg tramisprosate dose, as recited in claim 3, beyond what was already known and conventionally done in the prior art. *Id.* at 84. Petitioner also contends that the Specification does not show possession of the full scope of compounds that can deliver 150 mg of tramiprosate/dose as broadly claimed. *Id.*

With regard to the claimed patient population to be treated, Petitioner contends that the ’742 patent Specification discloses identifying APOE4/4 homozygotes at a high level, using known and well-established methods in the art but does not show possession of any new or nonconventional techniques for such identification. Pet. 85 (citing Ex. 1001, 9:55–58; Ex. 1003 ¶ 720). Petitioner makes similar arguments regarding the claim limitations of determining subjects to have “a baseline [MMSE] score of  $\geq 22$ ,” dosage regimens and formulations of claims 5, 6, 18, and 19, and treating subjects “85 years old or younger.” *Id.* at 85–87.

### *3. Patent Owner’s Position*

#### *a. Petitioner’s Argument that the Specification Does Not Adequately Describe Treating Only the Claimed Patient Subpopulation and Excluding All Others*

Patent Owner contends that the claimed methods of administering ALZ-801 to APOE4/4 homozygous patients that have a baseline MMSE score of  $\geq 22$  are fully described in the Specification. Prelim. Resp. 23.

Patent Owner also contends that excluding patients that are non-APOE4/4 homozygous or have a baseline MMSE score of <22 is also fully described. *Id.* Patent Owner cites to portions of the '742 patent Specification that support treatment of the claimed subgroup of patients. *Id.* at 23–25 (citing Ex. 1001, 1:54–63, 2:50–3:38, 4:36–40, 16:30–22:37, 21:11–12, Figure 7; Ex. 1002, 1424–25, 1427).

*b. Petitioner's Argument that the Specification Does Not Provide Detail Beyond What Was Known in the Art*

Patent Owner contends that every limitation challenged by Petitioner is described and has literal support in the '742 patent Specification. Prelim. Resp. 29–32 (providing citations from the '742 patent Specification to show written description support for the limitations challenged by Petitioner).

*4. Analysis*

We agree with Patent Owner that Petitioner has not satisfied its burden to show that the challenged claims lack written description support. We address Petitioner's arguments below.

*a. Petitioner's Argument that the Specification Does Not Adequately Describe Treating Only the Claimed Patient Subpopulation and Excluding All Others*

We find that the claimed methods of administering ALZ-801 to patients that are APOE4/4 homozygous and have a baseline MMSE score of  $\geq 22$  are sufficiently supported by the '742 patent Specification. The '742 patent Specification discloses methods of treating AD in patients that are APOE4 heterozygous with “moderate AD” or in patients that are APOE4/4 homozygous with “mild or mild-moderate AD.” Ex. 1001, 1:54–63, 2:50–3:38; Ex. 1002, 1424–1425, 1427. The '742 patent Specification supports treating the claimed subgroup of AD patients in stating:

In even more specific aspects of these embodiments, the subject is treated or determined to be suitable for treatment if they are APOE4/4 homozygous and have a baseline MMSE score of 22–26.

*Id.* at 4:36–40. The '742 patent Specification also describes analysis showing APOE4/4 homozygous subjects with more mild AD demonstrated better cognitive response to tramiprosate and concluded that:

APOE4/4 homozygous patients with baseline MMSE  $\geq 22$  showed the highest efficacy and a progressive increase in cognitive benefit compared to placebo over the 78 weeks of the study. The same is expected for the equivalent dose (265 mg NID) of ALZ-801—a tramiprosate prodrug.

*Id.* at 2:44–49; *see also id.* at 21:11–12, Figure 7. Therefore, we find that the '742 patent Specification specifically calls out and supports treating AD patients who are APOE4/4 homozygous and have a MMSE baseline score  $\geq 22$ .

We agree with Patent Owner that the Specification does not need to explicitly call out not treating different patient populations. *See Prelim. Resp.* 25–26 (citing *Inphi Corp. v. Netlist Inc.*, 805 F.3d 1350, 1355–56 (Fed. Cir. 2015) (holding that “properly describing alternative features” *even* “without articulating advantages or disadvantages of each feature” is sufficient written disclosure for a “reason to exclude” (citing *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1350–51 (Fed. Cir. 2012)); MPEP § 2173.05(i) (“If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.”); *Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1348 (Fed. Cir. 2016) (the same). We agree with Patent Owner that this case is different than *Novartis* because, in *Novartis*, the court found that the written description was insufficient to

support the claimed no “loading dose” negative limitation due to the specification being completely silent on the presence or absence of the excluded loading dose. *Novartis*, 38 F.4th at 1018. In contrast, the ’742 patent describes different alternatives of AD patient groups that may be treated and provides written description support for including or excluding each.

Also, as discussed above, the ’742 patent Specification does call out treating the claimed subgroup of patients as being preferred because this group “show[ed] the **highest efficacy** and a sustained cognitive benefit over the 78 weeks of the study.” Ex. 1001, 21:6–13 (emphasis added). This disclosure provides a “blaze mark” directed to the claimed treatment population. *See BASF Plant Sci., LP v. Commw. Sci. and Indus. Research Organisation*, 28 F.4th 1247, 1265 (Fed. Cir. 2022) (finding written description support for claim to canola oil based on its identification in the specification as a preferred embodiment).

Thus, we find that the ’742 patent Specification “reasonably convey[s] to those skilled in the art that the inventor had possession” of the claimed method of treating the selected patient population. *Ariad Pharms.*, 598 F.3d at 1351–52.

*b. Petitioner’s Argument that the Specification Does Not Provide Detail Beyond What Was Known in the Art*

We also find that Petitioner has not persuasively shown that the ’742 patent lacks support for the challenged limitations. Petitioner alleges that the ’742 patent Specification describes the claimed techniques almost entirely with reference to what was already known or understood in the art

and does not demonstrate that the inventors had possession of something more than these routine and conventional techniques.

As an initial matter, we disagree with Petitioner's assertion that the '742 patent must disclose unconventional and non-routine techniques for all of the challenged limitations in order to provide written description support. The written description requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *University of Rochester*, 358 F.3d 916, 928. Also, in evaluating the sufficiency of a disclosure, we look at factors including "the existing knowledge in the particular field"; "the extent and content of the prior art"; "the maturity of the science or technology"; and "the predictability of the aspect at issue." *Ariad Pharms.* at 1351 (citing *Capon*, 418 F.3d at 1359). With this in mind, we review the challenged limitations below.

(i) "*Administering*"

We find this term to have sufficient written description support in the '742 patent Specification. For example, the Specification discusses administration options for ALZ-801 as well as different methods of administration. Ex. 1001, 13:58–66, 14:5–12. Petitioner argues that the '742 patent Specification does not demonstrate possession of a special method of administration beyond what was known in the art (Pet. 81); however, the Specification need not disclose a special method of administration in order to provide written description for the claim limitation.

*(ii) Administering Val-APS “in an amount effective to reduce cognitive decline”*

We find this term to have sufficient written description support in the ’742 patent Specification. For example, the Specification describes ways to determine cognitive decline reduction and also describes general and specific ranges of Val-APS doses. Ex. 1001, 4:61–66, 14:29–51. Examples 1–3 of the Specification disclose tramiprosate doses used in a clinical study and bridging studies achieving equivalent ALZ-801 doses. *Id.* at 16:30–22:37.

*(iii) Administering Val-APS at 260–270 mg/Dose or 265 mg/Dose; Administering a composition comprising ALZ-801 that “delivers about 150 mg tramiprosate/dose”*

We find these terms to have sufficient written description support in the ’742 patent Specification. For example, the Specification discloses using ALZ-801 doses of 260–270 mg or 265 mg. Ex. 1001, 14:46–48, 14:52–59. Example 3 of the ’742 patent Specification also describes studies showing that “between 260 and 270 mg (e.g., 265 mg) BID dosing of ALZ-801 achieves steady-state tramiprosate exposure that is equivalent to 150 mg BID of oral tramiprosate,”<sup>14</sup> an amount which was showed to have efficacy in APOE4/4 homozygous patients with mild AD. *Id.* at 21:59, 22:22–24.

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<sup>14</sup> Petitioner also argues that the ’742 patent Specification does not show possession of the full scope of compounds that can deliver 150 mg tramiprosate but this argument appears to be directed to disclaimed claims 11–15, which do not recite the administration of Val-APS (as recited in independent claims 1, 10, and 16). Pet. 84–85; Ex. 1001, 22:40–49, 23:12–32, 24:13–22. Because claims 11–15 have been disclaimed, we need not address this argument.

*(iv) Determining subjects to be “APOE4/4 homozygous; Determining subjects to have a “baseline [MMSE] score of  $\geq 22$ ”*

We find these terms to have sufficient written description support in the '742 patent Specification. For example, the Specification discloses methods of identifying APOE4-positive patients such as using sequencing technology. Ex. 1001, 9:55–60. The '742 patent Specification also discloses using MMSE as a technique to determine the severity of AD in a patient. *Id.* at 8:37–44, 9:16–18, 9:60–62. Petitioner argues that the techniques disclosed in the Specification are standard techniques already known in the art; however, we do not find that this argument supports a finding of a lack of written description.

*(v) Dosage regimens and formulations*

We find these terms to have sufficient written description support in the '742 patent Specification. For example, the Specification describes an ALZ-801 composition comprising between 260 mg and 270 mg (e.g., 265 mg) of ALZ-801 “wherein the composition is formulated as an instant release, oral tablet, or capsule.” Ex. 1001, 5:22–27. The Specification also describes administering 260 mg–270 mg (e.g., 275 mg) of ALZ-801 in “instant release, oral” formulation “twice a day”), and Example 3 describes administering “an instant release oral formulation” of ALZ-801. *Id.* at 5:28–35; 22:29–37.

*(vi) Treating subjects “85 years old or younger”*

We find this term to have sufficient written description support in the '742 patent Specification. For example, the Specification discloses treating patients that are 85 years old or less, e.g., 65–85 years old. Ex. 1001, 5:18–19.

We, therefore, determine that Petitioner has not presented sufficient persuasive evidence that the '742 patent Specification fails to provide adequate disclosure to convey to a person of ordinary skill in the art that the inventors were in possession of the claimed invention. Accordingly, Petitioner has not established that it is more likely than not that the '742 patent Specification lacks written description support for the claims.

*E. Asserted Lack of Enablement of Claims 1–3, 6–8, and 10<sup>15</sup>*

Petitioner contends that claims 1–3, 6–8, and 10 of the '742 patent are not enabled. Pet. 87–92. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 33–36.

*1. Legal Standard*

Under 35 U.S.C. § 112(a), enablement is separate and distinct from the written description requirement. *Ariad*, 598 F.3d at 1344. “The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). “[A] patent specification complies with the statute even if a ‘reasonable’ amount of routine experimentation is required in order to practice a claimed invention . . . .” *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. *In*

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<sup>15</sup> These are the remaining challenged claims after Patent Owner's statutory disclaimer of claims 9 and 11–15. Ex. 2001.

*re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors, referred to as the *Wands* factors, include:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*Id.*

## 2. *Petitioner's Position*

Petitioner asserts that “if the knowledge in the art was not routine and conventional or does not render the claims obvious, then the disclosure is insufficient to teach a POSA to practice the breadth of the claimed invention without undue experimentation.” Pet. 87. Specifically, Petitioner contends that the nature of the invention in the ’742 patent is very broad and the full scope is not enabled because the claims “are drawn to a method of treating AD in the claimed patient subset by administering ***any dose in a broad range of doses*** of Val-APS that meet the limitation of reducing cognitive decline.” *Id.* (citing Ex. 1003 ¶¶ 727–728). According to Petitioner, the Specification does not identify any lower or upper limit on the range of dosages that might achieve a reduction in cognitive decline, nor does it disclose that 150 mg of tramiprosate is the only dosage that could achieve this limitation. *Id.* (citing Ex. 1003 ¶¶ 728–730). Petitioner also contends that the ’724 patent Specification provides that “the dosage range for oral administration of tramiprosate [or] ALZ-801 ... is generally ***about 0.001 mg to about 2000 mg*** of a compound per kg body mass,’ which “spans a ***2 million-fold variation*** in magnitude, and the specification does not disclose

which doses within this range can reduce cognitive decline in the claimed patient subset.” *Id.* at 88–89 (citing Ex. 1001, 14:29–32; Ex. 1003 ¶ 730) (alterations in original).

Petitioner also contends that “the level of ordinary skill in [the] relevant field is high as a POSA needs specialized knowledge of AD.” Pet. 89 (citing Ex. 1003 ¶¶ 733–734). However, Petitioner asserts that the ’742 patent Specification discloses only one example, Example 2, in which a single dose of 150 mg tramiprosate is used to treat the claimed patient subset and there is no disclosure that any other dosage of tramiprosate treats AD or reduces cognitive decline in the claimed patient subset. *Id.* (citing Ex. 1001, 20:57–21:20; Ex. 1003 ¶ 736). According to Petitioner, “[t]he patent’s sole working example of Val-APS discloses only its safety, tolerability, and pharmacokinetic properties, without any data regarding therapeutic efficacy.” *Id.* (citing Ex. 1001, Example 3; Ex. 1003 ¶ 737).

Petitioner further contends that the ’742 patent provides no direction or guidance as to which tramiprosate or Val-APS doses will treat AD or reduce cognitive decline in the claimed patient subset. Pet. 90 (citing Ex. 1003 ¶ 738). According to Petitioner, disclosure of a single 150 mg dose is insufficient to guide a POSA regarding the sub-range within a 2 million-fold range that may or may not achieve a reduction in cognitive decline. *Id.* (citing Ex. 1003 ¶ 739).

Petitioner also argues that AD is characterized by high-patient variability and different patient populations respond differently to treatment with AD therapeutics. Pet. 90 (citing Ex. 1003 ¶¶ 740–741). According to Petitioner, by 2015, virtually all clinical trials for AD therapeutics had failed and a POSA would understand that clinical testing was necessary to

demonstrate efficacy of any AD therapy in any AD patient subset. *Id.* at 90–91 (citing Ex. 1003 ¶ 741). Lastly, Petitioner contends that it would have required an extensive amount of experimentation to create and test the full range of doses recited in claims 1, 2, and 6–10 as well as the full range of compounds recited in claim 3. *Id.* at 91 (citing Ex. 1003 ¶ 743). According to Petitioner, a “POSA would need to screen numerous compounds and/or dosages, *e.g.*, to identify promising therapeutic candidates, which would require further clinical testing to determine utility for treatment as claimed.” *Id.* (citing Ex. 1003 ¶¶ 745, 747). Petitioner further contends that, “following such screening and clinical testing activities, undue experimentation would be needed to determine which AD patients can be treated with compounds and/or dosages that exhibit the claimed functional property.” *Id.* at 92 (citing Ex. 1003 ¶ 749).

### 3. *Patent Owner’s Position*

Patent Owner contends that “the claims are directed to ***specified patients*** treated with a ***specified drug***, in an amount effective or with specific doses, supported by detailed disclosures and working examples providing *in vivo* results.” Prelim. Resp. 33. According to Patent Owner, Petitioner has failed to show that a POSA would require undue experimentation to practice the claimed invention in view of the Specification’s teachings, guidance, and working examples. *Id.* at 34. Patent Owner also provides an analysis of the *Wands* factors to support its argument that Petitioner has failed to show that the claims are not enabled. *Id.* at 34–36.

#### 4. *Analysis*

First, we disagree with Petitioner’s assertion that “if the knowledge in the art was not routine and conventional or does not render the claims obvious, then the disclosure is insufficient to teach a POSA to practice the breadth of the claimed invention without undue experimentation.” Pet. 87. Claims can be non-obvious and also be enabled. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (rejecting argument “if the asserted claims are non-obvious, they cannot possibly be enabled” because one of ordinary skill “after reading the specification, would be able to make and use the claimed invention without undue experimentation, based on the ordinary skill in the art”). We analyze the *Wands* factors for enablement below.

##### *a. Nature of the Invention, Predictability of the Art, Breadth of the Claims, and Relative Skill in the Art*

The field of the invention relates to methods of treating Alzheimer’s Disease (“AD”) in a specific patient population using tramiprosate, Val-APS, or a pharmaceutically acceptable salt thereof, based upon a combination of APOE4 status and disease severity. Ex. 1001, code (57). The ’724 patent claims the administration of a specific prodrug, Val-APS (ALZ-801), in an amount affective to reduce cognitive decline or in specified quantified doses, to a specified AD patient population, i.e., APOE4/4 homozygous patients with a MMSE score of  $\geq 22$  measured within 60 days before administration. Ex. 1001, claims 1–8, 10, 16–19. While it may be true, as asserted by Petitioner, that AD is characterized by high inter-patient variability with different responses to treatment, the claimed invention is directed to a specific subset of AD patients.

As discussed above, and as acknowledged by Petitioner, the level of ordinary skill in the art is high, requiring “at least an M.D. or Ph.D. degree in a biomedical science or equivalent field” along with “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. 14–15, 89 (citing Ex. 1003 ¶¶ 62, 733–735).

We find that the relative skill in the art is high and the claims are relatively narrow, which weighs in favor of enablement.

*b. Direction or Guidance and Working Examples*

The '742 patent discloses components for pharmaceutical compositions as well as potential dose ranges for oral immediate release ALZ-801 formulations. Ex. 1001, 6:41–7:63, 14:52–59. Examples 1 and 2 of the '742 patent analyze the results of clinical trials of tramiprosate to treat AD in different patient populations. *Id.* at 16:26–21:20. The '742 patent discloses that “APOE4/4 homozygous patients with baseline MMSE  $\geq$  22 showed the highest efficacy and a progressive increase in cognitive benefit” when treated with tramiprosate at 150 mg BID. *Id.* at 2:44–46; 21:6–12; Figs. 7A and 7B. According to the '742 patent, “[t]he same is expected for the equivalent dose (265 mg BID) of ALZ-801.” *Id.* at 2:47–49. Example 3 of the Specification provides an ascending Phase 1 bridging study for an oral immediate release ALZ-801 formulation, providing in vivo “data indicat[ing] that between 260 and 270 mg (e.g., 265 mg) BID of ALZ-801 achieves a steady-state tramiprosate exposure that is equivalent to 150 mg BID of oral tramiprosate”). *Id.* at 22:21–37.

*c. Quantity of Experimentation*

We are not persuaded by Petitioner's arguments that the claimed invention would require undue experimentation. As an initial matter, Petitioner contends that a "POSA would need to screen numerous compounds and/or dosages, e.g., to identify promising therapeutic candidates" in order to "determine which AD patients can be treated with compounds and/or dosages that exhibit the claimed functional property." Pet. 91–92 (citing Ex. 1003 ¶¶ 745, 747, 749). However, as discussed above, the claims are directed to the administration of a specific prodrug, ALZ-801, in an amount affective to reduce cognitive decline or in specified quantified doses, to a specified AD patient population, i.e., APOE4/4 homozygous patients with a MMSE score of  $\geq 22$  measured within 60 days before administration. Ex. 1001, claims 1–8, 10, 16–19.

Also, although Petitioner alleges that it would have required an extensive amount of experimentation to test the full range of compounds in claim 3, claim 3 depends from claim 1, which specifies that the compound is Val-APS, or a pharmaceutically acceptable salt thereof.<sup>16</sup> Next, the claims recite the specific AD patient subgroup to be treated — those that are APOE4/4 homozygous with a MMSE score of  $\geq 22$  measured within 60 days before administration. Further, the '742 patent Specification discloses that this patient population showed the highest efficacy and sustained cognitive benefit with 150 mg BID of tramiprosate. Ex. 1001, 21:6–12. The Specification also provides bridging studies showing that between 260 and

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<sup>16</sup> Petitioner also makes this argument for claims 11–13 and 15, which do not recite a particular pharmaceutical composition to be administered; however, these claims have been disclaimed.

270 mg (e.g., 265 mg) BID of ALZ-801 achieves steady-state tramiprosate exposure that is equivalent to 150 mg BID of oral tramiprosate. *Id.* at 22:22–25.

Given the disclosure in the '742 patent and the high level of skill in the art, we do not find that undue experimentation would be required to determine effective doses of ALZ-801 for treatment of AD. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338–39 (Fed. Cir. 2013) (“the fact that a clinician’s involvement may be necessary to determine effective amounts of [a drug] does not itself constitute undue experimentation.”); *see also Ortho-McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1365, 1366 (Fed. Cir. 2008) (holding that “even if clinical trials informed the [effective amount],” the record did not show that extensive or “undue” tests would be required to practice the invention).

*d. Conclusion on Enablement*

Overall, in view of the relatively narrow scope of the claims, sufficient guidance provided in the Specification, and high level of skill in the art, Petitioner has not shown that it would take undue experimentation to practice the full scope of the claims. Therefore, for the above reasons, we find that Petitioner has not shown that it is more likely than not that the challenged claims lack enablement.

IV. 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. 48. Petitioner argues that the combination of references is materially different from and not cumulative to the art evaluated during prosecution, and that the Examiner erred in allowing the claims. Pet. 93–98.

*B. Legal Framework*

Pursuant to 35 U.S.C. § 325(d), in determining whether to institute a proceeding, “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. Pertinent Prosecution History*

The ’742 patent issued on December 7, 2021, from Application No. 15/758,405 (“the ’405 application”), and was filed as a national stage entry on March 8, 2018 of International Application No. PCT/US2016/051091, filed September 9, 2016. Ex. 1001, codes (21), (22), (45).

The application sought patenting of methods of treating patients who were APOE4 positive (heterozygotes or homozygotes) and had moderate, mild, or mild-moderate AD. Ex. 1002, 1420–22. Early in prosecution, Applicant amended the claims to restrict the target patient population to APOE4/4 homozygotes with a baseline MMSE score  $\geq 22$ . *Id.* at 1297–99.

The Examiner rejected the pending claims under 35 U.S.C. § 103 over Kong in view of John.<sup>17</sup> Ex. 1002, 1251. The Examiner cited Kong’s teachings of the APOE4 mutation as a risk factor for AD and administration of Val-APS to treat AD in various dosages, formulations, and intervals to slow or lessen the rate of cognitive decline. *Id.* at 1252. The Examiner cited John’s teachings of evaluation of persons with AD using the MMSE’s definition of “mild” cognitive impairment as a MMSE score of 21–24 points, and the administration of tramiprosate to treating AD. *Id.* The Examiner found that the ordinary artisan would have found it obvious “to treat AD by administering valyl-3-amino-1-propanesulfonic acid wherein the subject is homozygous and has a baseline [MMSE] score of  $>22$ , wherein the MMSE was performed within sixty days prior to the first administration of the composition, as suggested by John” and that motivation would be found in Kong’s use of Val-APS and a desire to treat patients at moderate risk. *Id.* at 1252–53. The Examiner further found the 60-day treatment window to be an obvious matter of optimization where the dosage ranges overlapped, and that the ordinary artisan would have had a reasonable expectation of success “absent evidence of criticality of the particular steps.” *Id.* at 1253–54.

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<sup>17</sup> U.S. Patent Pub. US 2012/0071468 A1, published March 22, 2012 (Ex. 1070, “John”).

Applicant amended the claims to recite that the subject having AD would be treated “*only if the subject is determined to (i) be APOE4/4 homozygous; and (ii) have a baseline Mini-mental State Examination (MMSE) score of  $\geq 22$ , wherein the MMSE was performed within sixty days prior to the first administration of the composition.*” Ex. 1002, 453 (emphasis added). Applicant argued the amendment created a “patient stratification method” to identify patients that would and would not be treated, and argued the cited references did not teach stratification. *Id.* at 456.

The Examiner did not find that the amendment advanced patentability and maintained the rejections. Ex. 1002, 420–21.

After an interview with the Examiner, Applicant argued that claim stratification caused the claims to “necessarily **exclude** from treatment any AD patient at moderate risk that does not have both a MMSE score of  $\geq 22$  and is APOE4/4 homozygous” to distinguish over art that included the recited patients within the treatment population. Ex. 1002, 403. Applicant argued “the recited MMSE score range is critical to the success of the claimed invention and the criticality of the claimed range would not have been expected by the person of ordinary skill in the art.” *Id.* Applicant argued that criticality was demonstrated by the study results reflected in Figure 7, reproduced below. *Id.* at 406–08.

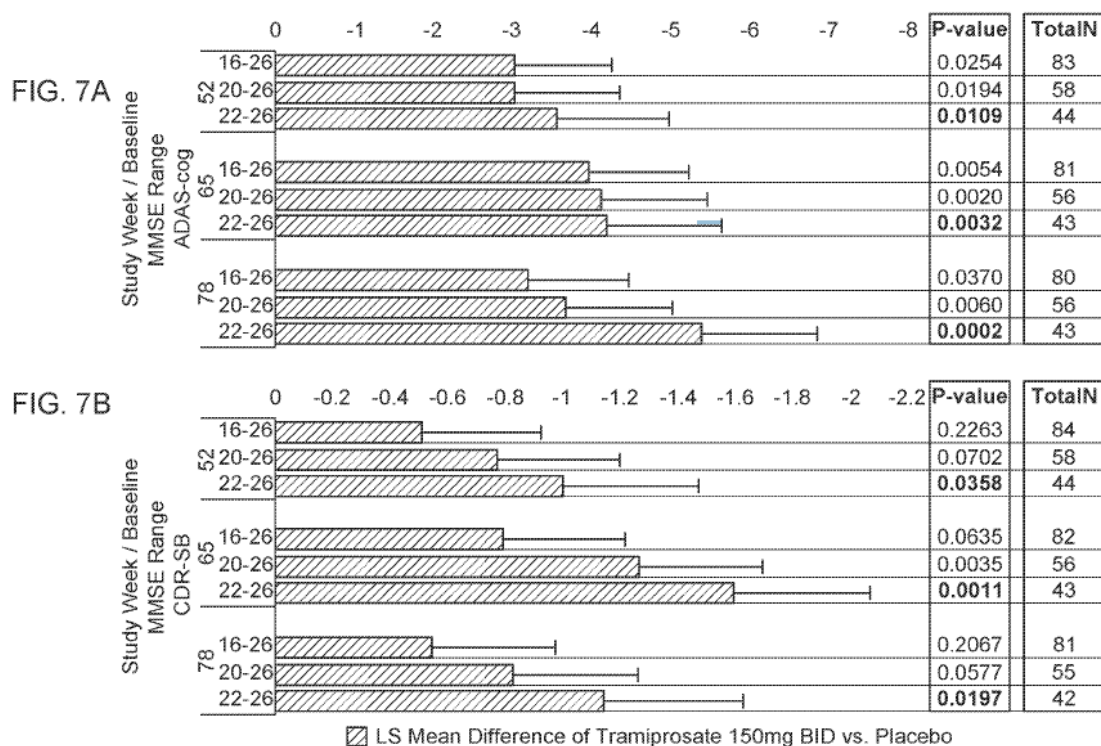


Figure 7 panel A:

demonstrates the effect of tramiprosate 150 mg BID on ADAS-Cog scores in APOE4/4 homozygous patients over 52, 65 and 78 weeks, broken down by various ranges of disease severity (as measured by baseline MMSE scores) as compared to a placebo control. FIG. 7, panel B, demonstrates the effect of 150 mg BID tramiprosate on CDR-SB scores in APOE4/4 homozygous patients over 52, 65 and 78 weeks, broken down by various ranges of disease severity (as measured by baseline MMSE scores) as compared to a placebo control.

Ex. 1001, 5:61–6:3. Applicant stated that Figure 7 divides subjects into three categories by their MMSE score: 16–26, 20–26, and 22–26. Ex. 1002, 406. From this division, Applicant argued, the data show “the clinical benefit of tramiprosate on ADAS and CDR compared to placebo increases when the population of APOE4/4 homozygous subjects is refined to subjects with MMSE ranges that are in the milder (MMSE ≥ 22) subgroups of AD patients.” *Id.* at 407. Applicant argued the MMSE 22–26 subgroup was the

“only subgroup wherein: (1) the difference in decline was statistically significant ( $P < 0.05$ ) at each time point in each test; and (2) the difference in decline was statistically significant after 78 weeks in the CDR test ( $P = 0.0197$  for MMSE 22-26 versus  $0.2067$  for MMSE 16-26 and  $.0577$  for MMSE 20-26).” *Id.* Applicant argued that the “unexpected criticality of the MMSE ranges supports the nonobviousness of the claimed invention.” *Id.*

The Examiner issued an Advisory Action noting the amended claims could not be examined without an additional search. Ex. 1002, 394.

Applicant filed a Request for Continued Examination, asserting the same arguments, and the Examiner issued the same rejections. *Id.* at 127–134.

Applicant then amended the claims to recite that the Val-APS is administered to the subject “in an amount effective to reduce cognitive decline” or in certain dependent claims, “about 150 mg of tramiprosate/dose.” Ex. 1002, 100. In support of its amendment, Applicant again argued the criticality of the milder ( $\text{MMSE} \geq 22$ ) subgroups of AD. *Id.* at 104–105. Applicant submitted a post-filing publication by Abushakra<sup>18</sup> in support of its argument that the  $\text{MMSE} \geq 22$  subgroup of AD demonstrated unexpected results and is therefore critical. *Id.* at 105. Applicant argued that Abushakra analyzed the same data that was provided in Figure 7 of the ’742 patent. Applicant noted that

[i]n the subgroup with a baseline MMSE score of 22 and above (blue curve in Panels D, E, F), **cognitive scores improve and remain above baseline for 78 weeks** at the 150 mg dose. However, this improvement is absent from the overall study

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<sup>18</sup> S. Abushakra et al., *Clinical Effects of Tramiprosate in APOE4/4 Homozygous Patients with Mild Alzheimer’s Disease Suggest Disease Modification Potential*, 4(3): J. PREV. ALZHEIMER’S DIS., 149–156 (2017) (Ex. 1019, “Abushakra”).

group, which underscores the criticality of the baseline MMSE score of  $\geq 22$ .

*Id.*

The Examiner subsequently allowed all but a single claim, which Applicant canceled. Ex. 1002, 74, 66. The Examiner's description of allowable subject matter stated "claim 1 recites a method of treating Alzheimer's Disease by administering [Val-APS] wherein subjects are APOE4/4 homozygous and have a baseline MMSE score of  $\geq 22$ , which are not obvious or anticipatory over the prior art." *Id.* at 77. The Examiner identified Kong as the closest prior art, and concluded that Kong did not describe treating AD where the patient is "determined to be APOE4/4 homozygous and have a baseline Mini-mental State Examination (MMSE) score of  $\geq 22$ . Thus, there would be no reason one skilled in the art at the time the invention was made would treat Alzheimer's Disease by administering valyl-3-amino-1-propanesulfonic acid based on the prior art references." *Id.* at 53–54.

Subsequently, Patent Owner withdrew the claims from issuance and submitted an additional IDS with a single reference, Hey.<sup>19</sup> Ex. 1002, 8–15. The Examiner considered Hey, and allowed the claims a second time. *Id.* at 3–7.

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<sup>19</sup> HEY, J. et al. *Analyses of Tramiprosate Phase 3 Trials Show Improvement in Cognition and Function In APOE4 Positive Alzheimer's Disease Subjects Reaching 4 Point Improvement From Placebo on ADAS-COG in Homozygous APOE4 Subjects, and Support Development Of ALZ-801, A Novel Prodrug of Tramiprosate with Optimized Drug Properties*, NEUROGEDER. DIS. 2015; 15(1):352—1969, pg. 798.

*D. Analysis*

*1. The Parties' Contentions*

Petitioner argues that *Becton, Dickinson* Factors (d) and (a) support institution because “there is virtually no overlap between the arguments advanced during ’742 patent prosecution and the manner in which Petitioner relies on the cited prior art.” Pet. 93–95. Petitioner argues that Grounds 4–6 rely on references that were not “substantively considered by the Examiner during prosecution.” *Id.* at 93. Petitioner argues that the only common reference here is Kong, which Petitioner asserted for the identical teachings the Examiner asserted during prosecution, which Patent Owner did not dispute. *Id.* at 93–94. Petitioner argues that the Examiner did not consider the asserted combination of references asserted in the Petition (or similar), did not point to “any prior art teaching that tramiprosate would be more effective in APOE4 carriers (e.g., as in Caltagirone), or mild AD patients (e.g., as in Laurin or Aisen (2007)),” and did not raise arguments under Sections 101 or 112 as are asserted here. *Id.* at 94. Petitioner further argues that *Becton, Dickinson* Factor (a) supports institution because the references cited in the Petition provide new teachings such as Laurin’s teachings that patients can respond to tramiprosate differently based on the presence of APOE4 or mild disease, and that the submitted expert declaration provides additional evidence not available to the Examiner. *Id.* at 95.

Petitioner argues *Becton, Dickinson* Factor (b) supports institution because the asserted art is not cumulative of the examined art, specifically because the cited references do not “teach that tramiprosate or Val-APS would be more effective in mild AD patients or APOE4 carriers.” Pet. 96. Petitioner argues Factor (c) also weighs against exercise of § 325(d)

discretion because the Examiner did not substantively evaluate any of Petitioner’s asserted references aside from Kong, which was the only reference from the Petition that formed the basis of a rejection during prosecution. *Id.*

Petitioner further argues *Becton, Dickinson* Factors (e) and (f) support institution because the Examiner erred by failing to appreciate the significance of cited art teaching that tramiprosate was effective in patients with mild AD and in concluding that the “efficacy disclosed in Abushakra (2017) was ‘surprising’ and ‘unexpected’” because the teachings of the art cited by Petitioner would have explained those findings as predictable. *Id.* at 97.

Patent Owner provides a table, reproduced below, of the five references asserted by Petitioner in Grounds 4–6.

| Reference              | PGR Grounds (Claims)            | Status Before the Office                                          |
|------------------------|---------------------------------|-------------------------------------------------------------------|
| Caltagirone (EX1007)   | 4, 5<br>(claims 1-8, 10, 16-19) | Considered                                                        |
| Laurin ’714 (EX1061)   | 4-6<br>(claims 1-8, 10, 16-19)  | Substantially the same as Laurin ’056 (EX1075)                    |
| Froestl (EX1064)       | 4<br>(claims 1-3, 6-8, 10)      | Substantially the same as Kong (EX1069)                           |
| Kong (EX1069)          | 5<br>(claims 1-8, 10, 16–19)    | Considered and a focus of examination                             |
| Press Release (EX1065) | 6<br>(claims 1–3, 6–8, 10)      | Substantially the same as Hey (EX2002, 10). <i>See</i> EX1002, 7. |

Prelim. Resp. 49. The table above lists the five references asserted by Petitioner, the respective grounds in which they are asserted and the claims at issue in each ground, and Patent Owner’s view as to the extent to which

the Examiner addressed each reference or a substantially similar reference during prosecution. *Id.* Patent Owner asserts that each asserted reference was either considered by the Office during examination, or is substantially similar to a reference that was considered by the Examiner. *Id.* at 49–61. Patent Owner also argues that Petitioner has not demonstrated the Examiner erred in any material manner. *Id.* at 63–73.

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

As discussed above in Sections III.C., III.D., and III.E., we do not find that Petitioner has established that it is more likely than not that the claims recite patent-ineligible subject matter under § 101, that the claims are inadequately described (§ 112(a)), or that an ordinary artisan would have been unable to practice the claimed subject matter in light of the teachings of the '742 patent Specification (§ 112(a)). Accordingly, we confine our analysis of the parties' arguments regarding whether we should exercise our discretion to deny institution under Section 325(d) to evaluation of Petitioner's Grounds 4–6 under the *Becton, Dickinson* factors.

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 Kong formed the basis of rejections during examination. Pet. 93–94; Prelim. Resp. 49.

Petitioner alleges that Caltagirone was cited during examination, but it was not a focus of examination. Pet. 95; Ex. 1001, 2 (listing “other publications”). In light of the guidance in *Advanced Bionics* that references considered in an IDS are considered presented to the Office, it is clear that

Caltagirone was previously presented to the Office. *See Advanced Bionics*, Paper 6, at 7 (holding previously presented art includes “art made of record by the Examiner,<sup>20</sup> 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.”).

Petitioner relies on Caltagirone’s disclosures that, when 150 mg tramiprosate was administered twice daily to mild-to-moderate AD patients, “tramiprosate showed improved efficacy in APOE4 carriers.” Pet. 35 (citing Ex. 1003 §§ VII.D, IX.B.). As discussed further below, these disclosures are cumulative to those of Laurin ’056,<sup>21</sup> which was also considered by the Examiner, with regard to improved cognitive treatment of mild-to-moderate AD patients. Ex. 1002, 129, 1246.

In addition, during examination, the Examiner addressed all of the teachings that Petitioner alleges Caltagirone discloses from other asserted references. *Compare* Ex. 1002, 421 (Examiner’s rejection for obviousness of claims directed to treating AD patients by administering Val-APS to APOE4/4 homozygous patients with a baseline MMSE score of greater than 22 based on assessment within 60 days of the first administration in light of Kong’s teachings of administering Val-APS to APOE4 patients, and Schmechel’s teachings of treatment of patients homozygous for APOE4); *with* Pet. 16–17 (Caltagirone teaches that, when administered 150 mg BID,

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<sup>20</sup> Allegations that an Examiner failed to appreciate teachings in a reference is an issue of Examiner error, which relates to the second part of the *Advanced Bionics* framework. We address Petitioner’s allegations in that regard in part two.

<sup>21</sup> U.S. Pat. Pub. US 2009/0182056 A1, published July 16, 2009 (Ex. 1075, “Laurin ’056”).

tramiprosate “showed a significant overall treatment effect” in “an APOE4+ sub-group,” including APOE4 homozygotes; “therapeutic interventions applied earlier in the course of AD more likely might achieve the goal of disease modification;” and that “AD would be optimally treated before significant cognitive impairment, during its pre-symptomatic or pre-clinical stages ...”) (emphases removed). Accordingly, Caltagirone was previously presented to the Office and we also find that Caltagirone’s disclosures are substantially similar to, or cumulative of, other references previously considered by the Examiner.

We address below the parties’ arguments regarding the disclosures of the newly asserted references and the parties’ allegations regarding the overlap in teachings from each with references considered by the Examiner.

*a. Laurin ’714 (Ex. 1061)*

Laurin ’714 is cited in Grounds 4–6. Pet. 48–74. Petitioner alleges that “Laurin [’714] teaches that, in mild-moderate AD patients receiving 150 mg BID tramiprosate, mild patients had the ‘best’ outcome.” *Id.* at 35 (statement in Ground 2, incorporated into Grounds 4–6).

Patent Owner argues that asserted reference Laurin ’714 is “materially the *same*, having identical or nearly identical relevant disclosures” to Laurin ’056 (Ex. 1075), a reference which was considered during prosecution and is by the same two inventors as Laurin ’714. Prelim. Resp. 50–51 (citing Ex. 1002, 450–451); Ex. 1061, code (76); Ex. 1075, code (76). Petitioner acknowledges that Laurin ’056 was considered by the Examiner (Pet. 95 fn. 6), but argues that Laurin ’056 does not disclose the same teachings. Pet. 95.

Patent Owner provides a table listing the various portions of Laurin '714 that Petitioner relies on in Grounds 4–6, and the corresponding teachings of Laurin '056. Prelim. Resp. 51–53. We agree with Patent Owner that these citations make clear that Laurin '056, which was considered by the Examiner, contains substantially similar, and in some cases, identical, teachings as the relied upon portions of Laurin '714. We address Petitioner's alleged differences below.

Petitioner alleges that the references the Examiner considered, including Laurin '056, “do not contain Laurin '714's teachings that patients can respond to tramiprosate differently based on the presence of APOE4 or mild disease (e.g., EX1061 [0113]). Additionally, unlike Laurin [’714], these references teach efficacy only in a ‘subset’ of mild AD patients.”

Pet. 95. Paragraph 113, which Petitioner cites for the disclosure is copied below:

The methods and compositions of the invention may, in one aspect, be useful for the treatment of particular Subgroups of Alzheimer's patients. Particular subgroups would include Alzheimer's patients having mild or mild to moderate disease, for example patients having an MMSE score of from 16-26. Other subgroups would include patients who have been recently diagnosed with Alzheimer's disease, for example within 5 years from diagnosis, preferably within less than 4, 3, 2, or 1 year. Other subgroups of Alzheimer's disease patients include patients who have or are lacking the ApoE-4 allele. Still further subgroups of patients may be identified using known methods and biomarkers of Alzheimer's disease state as described for example in published patent application US 2006/0014209 which is incorporated herein by reference.

Ex. 1061 ¶ 113.

Patent Owner asserts that a corresponding teaching from Laurin '056 is the disclosure that “[T]he present methods are especially useful for

individuals who do have a known risk of Alzheimer's disease." Prelim. Resp. 51 (citing Ex. 1075 ¶ 199). Both of these citations are general and conclusory, and thus we look deeper at what each reference teaches about the response of patients having APOE4 or mild disease to treatment with tramiprosate, as recited in the claims.

Both references cite the same study of fifty-eight "mild to moderate AD patients" with MMSE scores of 13–26. Ex. 1061 ¶ 475; Ex. 1075 ¶ 452. In this study, the patients were given 150 mg tramiprosate or a placebo twice a day for twenty months. Ex. 1061 ¶ 477; Ex. 1075 ¶ 452–53. Both references state: "Overall, approximately 70% of the mild AD patients show stabilized or improved cognitive function tests after 20 months." Ex. 1061 ¶ 477; Ex. 1075 ¶ 453. Laurin '714 reports that "Mild AD patients (n=13) responded best," while Laurin '056 states "A subset of mild AD patients (n = 10) responded best." Ex. 1061 ¶ 477; Ex. 1075 ¶ 453. The remainder of the disclosures cited by Petitioner in its grounds are identical between the two references. *See, e.g.*, Prelim. Resp. 51–53 (table comparing references).

Petitioner does not persuasively show that Laurin '714 contains disclosures not taught in Laurin '056. The fact that Laurin '056 refers to a "subset" of ten of the thirteen mild patients is an insubstantial difference because the teaching still conveys that mild AD patients falling within the claimed MMSE range respond the best to tramiprosate, which is the teaching Petitioner relies on for Laurin '714. *See, e.g.*, Pet. 41. We further agree with Patent Owner that Laurin '714's teachings regarding the cognitive improvement achieved by administering tramiprosate to APOE4+ patients are equally taught by Laurin '056, and that the Examiner previously addressed the argument that the ordinarily skilled artisan would have been

motivated to treat AD patients at both mild and moderate risk, with the treatment expected to be more effective for mild AD patients. *See, e.g.*, Ex. 1002, 129 (“Examiner respectfully disagrees [with the assertion of nonobviousness] since one of ordinary skill in the art would expect that any treatment for AD would have higher efficacy for patients with a milder level of the condition . . .”); 1246 (stating the skilled artisan would have been motivated to treat AD patients at moderate risk, which would include patients with an MMSE score of at least 22 as taught by John). We find the disclosure of Laurin ’714 substantially similar to Laurin ’056, and the arguments asserted by Petitioner regarding the disclosures of Laurin ’714 to be cumulative to those previously considered by the Examiner. In addition, we find that Ground 5, which asserts the combined teachings of Laurin ’714, Caltagirone, and Kong presents the same or substantially the same arguments previously considered by the Examiner during prosecution.

*b. Froestl (Ex. 1064)*

Froestl is cited in Ground 4. Pet. 48–74. Petitioner alleges that Froestl teaches that ALZ-801 “is a prodrug of tramiprosate” which “showed improved gastrointestinal tolerability and lower inter-individual variability of drug exposure compared to comparable doses of tramiprosate.” *Id.* at 48–49. Petitioner asserts that Froestl provides motivation to substitute ALZ-801 for tramiprosate. *Id.* at 49. Petitioner argues that Froestl was not cited or discussed during prosecution, but makes no specific argument regarding how this reference is non-cumulative or presents information not previously considered by the Examiner. *Id.* at 95.

Patent Owner argues that Froestl’s disclosures are “substantially the same as Kong’s disclosures considered and discussed by the Examiner.”

Prelim. Resp. 56. The Examiner cited Kong for teaching administration of a pro-drug of tramiprosate, Val-APS, also called ALZ-801, as a method of treating the progression of AD. Ex. 1002, 1245. The Examiner rejected claims over Kong in combination with John, finding that the ordinary artisan would have been motivated to use ALZ-801 to treat AD. *Id.* at 1245–46.

Petitioner has not sufficiently shown that Froestl’s disclosures provide any information not previously considered and used by the Examiner in rejecting the claims; thus, we find Froestl is cumulative art. In addition, we find that Ground 4, which asserts the combined teachings of Laurin ’714, Caltagirone, and Froestl, asserts the same or substantially the same arguments previously considered by the Examiner during prosecution.

*c. 2015 Press Release<sup>22</sup> (Ex. 1065)*

Press Release is cited in Ground 6. Pet. 62–74. Petitioner argues that Press Release discloses that “homozygous APOE4-positive Alzheimer’s disease patients who received twice-daily administration of 150 mg tramiprosate demonstrated a greater than 4-point improvement in ADAS-cog ... compared to the placebo group.” *Id.* at 63 (quoting Ex. 1065, 2) (emphasis removed). Petitioner argues that Press Release also discloses that ALZ-801 “‘demonstrated superior therapeutic attributes over ... tramiprosate,’ including ‘improved gastrointestinal tolerability.’” *Id.* Petitioner argues that Press Release would have informed the ordinary artisan of the advantages of using ALZ-801 for AD treatment and motivated the artisan to substitute ALZ-801 for tramiprosate to reduce toxicity. *Id.* at

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<sup>22</sup> For the purpose of deciding whether to exercise discretion to deny under Section 325(d), we consider the disclosures in 2015 Press Release without deciding the issue of whether it is a prior art printed publication.

63 (citing Ex. 1003 ¶¶ 605–612). Petitioner argues that Press Release was not cited or discussed during prosecution, but makes no specific argument regarding how this reference is non-cumulative or presents information not previously considered by the Examiner. *Id.* at 95.

Patent Owner argues that Press Release is substantially similar to Hey (Ex. 2002), a reference submitted “as the only reference in a new IDS” by Patent Owner after the claims were first allowed. Prelim. Resp. 59; Ex. 1002, 7–15, 52–55. Patent Owner argues that the Examiner considered Hey, and agreed to allow the claims a second time after considering Hey’s disclosures. Prelim. Resp. 59 (citing Ex. 1002, 3). Patent Owner provides a table listing the various portions of Press Release that Petitioner relies on in Ground 6, and the corresponding teachings of Hey. *Id.* at 59–61.

We agree with Patent Owner that these citations make clear that Hey, which was considered by the Examiner, contains substantially the same teachings as the relied-upon portions of Press Release. Specifically, both Press Release and Hey disclose a 4-point improvement in ADAS-Cog assessment scores of homozygous APOE4/4 patients after treatment with 150 mg tramiprosate twice daily for at least 18 months (72 weeks). Ex. 1065, 2; Ex. 2002, 10. Both references also disclose that ALZ-801 is a pro-drug of tramiprosate with improved gastrointestinal tolerability and pharmacokinetic properties. Ex. 1065, 2; Ex. 2002, 10. We further agree with Patent Owner that the key disclosures in Press Release, that homozygous APOE4/4 AD patients respond to tramiprosate and the prodrug ALZ-801 is beneficial with respect to tramiprosate, are the same disclosures the Examiner addressed with respect to the Examiner’s rejection of claims over Kong and Schmechel, discussed above. *See, e.g.*, Ex. 1002, 1245–46.

Accordingly, we find Press Release is cumulative art, and that Ground 6, which asserts the combined teachings of Laurin '714 and Press Release, asserts the same or substantially the same arguments previously considered by the Examiner during prosecution.

With regard to Petitioner's argument that the asserted art is not cumulative because the Examiner did not point to any prior art teaching that "tramiprosate or Val-APS would be more effective in mild AD patients or APOE4 carriers" (Pet. 96), as discussed above, the references considered by the Examiner showed that tramiprosate or Val-APS were effective to reduce cognitive decline, *e.g.*, Laurin '056 in mild AD patients (Ex. 1075, 44) and Hey in APOE4 carriers (Ex. 2002, 10). Finally, we find that Petitioner's declarant's testimony, while helpful, did not provide information characterizing the prior art in a manner sufficiently different to provide a basis for determining that the asserted art was not cumulative to that examined during prosecution. For this reason, we are not persuaded by Petitioner's argument (Pet. 95–96) that the declarant's testimony weighs against the exercise of discretion.

Having determined that the art is cumulative and the arguments are substantially the same, 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) overlooking Caltagirone's teaching that tramiprosate was more effective

in APOE4 carriers; 2) failing to recognize the significance of teachings in the cited art that tramiprosate was effective in at least some mild AD patients; and 3) finding the efficacy disclosed in Abushakra (2017) “surprising” and “unexpected.” Pet. 96–98.

With regard to the first allegation of error, we addressed this issue in part one of this analysis, above, where we concluded that the Examiner considered Caltagirone in an IDS, and used Laurin '056 and Schmechel's teachings to conclude that the ordinary artisan would have been motivated to treat AD in its early stages with a pro-drug of tramiprosate, including in APOE4/4 homozygous patients. *See* Ex. 1002, 421. In addition, after the claims were allowed, Patent Owner petitioned to withdraw the application from issuance in order to submit Hey for consideration by the Examiner. *Id.* at 8–15. Hey discloses a 4-point improvement in ADAS-Cog assessment scores of homozygous APOE4/4 patients after treatment with 150 mg tramiprosate twice daily for at least 18 months (72 weeks). Ex. 2002, 10. In light of these disclosures, which contain the same teachings Petitioner alleges the Examiner failed to appreciate in Caltagirone, we conclude Petitioner has insufficiently shown that the Examiner erred in this regard.

We likewise addressed the second allegation of error in part one of this analysis. We concluded that the Examiner both understood that tramiprosate was effective in at least some mild AD patients, and asserted as a rejection that the ordinary artisan would have found it obvious to treat mild AD patients with tramiprosate. Ex. 1002, 129, 1246. We therefore conclude that Petitioner has insufficiently shown that the Examiner erred in this regard.

We next address Petitioner’s allegation that the Examiner erred in finding the efficacy disclosed in Abushakra (2017) “surprising” and “unexpected.” Pet. 97. Petitioner argues:

The Examiner’s incorrect conclusion underscores that the Examiner was unaware of the teachings of Laurin, Aisen (2007), and others that tramiprosate was more efficacious in mild AD patients as well as APOE4 carriers, and, thus, that any enhanced efficacy in the claimed patient subset is merely in line what a POSA would predict from the prior art rather than surprising by comparison.

*Id.* Petitioner argues that, “[b]ecause the art taught enhanced tramiprosate efficacy in mild compared to moderate AD patients (EX1061, EX1062), a POSA would predict more efficacy in ‘more mild’ AD patients (MMSE  $\geq 22$ ) compared to mild” and, “because the art taught enhanced tramiprosate efficacy in APOE4 carriers compared to non-carriers, a POSA would predict more efficacy in APOE4 homozygotes compared to heterozygotes.” *Id.* at 71 (citing Ex. 1003 ¶¶ 672–673). According to Petitioner, the results Patent Owner presented as unexpected fail to meet the requirements of indicia of nonobviousness, and the Examiner did not require Patent Owner to demonstrate superior results over “tramiprosate’s enhanced efficacy in certain AD patient subpopulations.” *Id.* at 72.

Petitioner, through its declarant, opines that the data in Figure 7 of the ’742 patent, which Patent Owner used to support its claim of unexpected results, does not support a claim of significant difference between patient groups and suggests “only a weak potential trend towards very slightly higher efficacy in ‘more mild’ patients, with none of the difference within a timepoint likely being close to statistically significant.” Pet. 73 citing (Ex. 1003 ¶ 677). Petitioner also alleges that Abushakra teaches that “within

APOE4 homozygotes, tramiprosate ‘showed promising clinical benefits in the overall Mild to Moderate AD group,’” which is consistent with Caltagirone and Abushakra 2016. *Id.* at 73–74 (citing Ex. 1003 ¶¶ 678–679; Ex. 1019, 150; Ex. 1072).

Finally, Petitioner alleges that Patent Owner “highlighted Figure 1 [of Abushakra] to the Examiner to suggest that tramiprosate (150 mg) was more effective in homozygotes with mild AD,” and that had the Examiner considered the full data subset, “the Examiner would likely have come to a different conclusion” because “the statistical significance that PO emphasized largely disappears” when the entire data set is considered. Pet. 74 (citing Ex. 1003 ¶¶ 680–685).

Patent Owner responds by noting, as we do above, that the Examiner asserted in rejecting claims that the ordinary artisan would have expected treatment for AD to be more effective in patients with mild AD (e.g., Ex. 1002, 129), and that Patent Owner’s response highlighted the criticality of the claimed range because the improvement seen for those patients was “absent from the overall study group.” Prelim. Resp. 65–66 (citing Ex. 1002, 129, 104–06). Patent Owner alleges that Petitioner’s arguments do not establish Examiner error, but rather evidence a disagreement with the conclusions reached by the Examiner in allowing the claims. *Id.* at 66.

Patent Owner argues that Petitioner’s characterization of the data in Figure 7 raises the same questions that the Examiner did during examination, and does not “dispute the accuracy of this data or rebut Patent Owner’s explanations that the Examiner rightfully considered before allowing the claims.” Prelim. Resp. 67–68. Moreover, Patent Owner argues, Abushakra reports similar data in that the improvement shown in

mild AD patients is absent from the overall group. *Id.* at 68 (citing Ex. 1019, 153, Figure 1).

Patent Owner argues that Petitioner’s critique that improvement is shown in all groups fails to explain why, as Patent Owner argued to the Examiner that, in Figure 7 of the patent, “[a]t each time point in both the ADAS and CDR tests, the MMSE 22-26 subgroup showed ***a greater difference in decline versus a placebo than either the MMSE 20-26 or the MMSE 16-26 subgroups.***” Prelim. Resp. 69 (citing Ex. 1002, 105). Patent Owner notes that Petitioner’s contention that the claimed statistical significance shown in Abushakra Figure 1 “largely disappears” when the entire data set is considered, is attorney argument alone because the cited declarant testimony, which provides no “new data or independent statistical analysis,” does not contain this assertion despite the citation to declarant testimony. *Id.* at 70 (citing Ex. 1003 ¶ 685). Patent Owner further argues that Petitioner provides no basis to dispute Abushakra’s report of statistically significant increase in the mild AD patient group with respect to other patient subgroups. *Id.* (quoting Ex. 1019, 153).

Finally, Patent Owner argues that Petitioner has insufficiently shown that its asserted additional evidence warrants reconsideration or would assist in determining the Examiner’s material error, in particular because the declarant testimony is devoid of additional underlying data or further analysis. Prelim. Resp. 71–72.

Having reviewed the record and the arguments of the parties, we conclude that Petitioner does not establish that the Examiner materially erred in allowing the claims. The cited testimony by Dr. Ruffolo reflects an opinion based on broad characterizations of the teachings of the cited

references. *See, e.g.*, Ex. 1003 ¶ 666 (Aisen (2007) teaches that a study of tramiprosate therapy “suggested a stabilization of cognitive function especially in mild subjects” and Aisen (2008) reports that tramiprosate therapy is “consistent with a slowing of cognitive and clinical decline, particularly in mild subjects” (emphasis omitted)). These characterizations, in addition to those in the art that we have concluded above were reviewed by the Examiner, are all consistent with the Examiner’s assertion during examination that the ordinary artisan would have found it obvious to treat mild AD patients with tramiprosate. Ex. 1002, 129, 1246.

What Petitioner and its declarant do not explain or otherwise account for – with data and not opinion testimony – is the statistical significance shown in Figure 7 of the patent and Figure 1 of Abushakra, which is what ultimately appears to have persuaded the Examiner to allow the claims. Dr. Ruffolo’s testimony regarding additional studies with larger patient populations, while relevant, still fails to provide concrete evidence of error. *See, e.g.*, Ex. 1003 ¶ 685 (stating “[a] POSA would recognize that the reliability of the analyses based on such small numbers of homozygous patients with mild Alzheimer’s disease is highly questionable”). Without more, we find that Petitioner has not sufficiently shown the Examiner’s actions were error rather than an exercise of judgment on which reasonable minds can disagree. We conclude the evidence of record does not establish error by the Office and; therefore, we exercise our discretion to deny institution under 35 U.S.C. § 325(d).

## V. CONCLUSION

As discussed above, we find that Petitioner has not shown that it is more likely than not that the claims are unpatentable based on the arguments

in grounds 1, 7, and 8. Grounds 2 and 3 are moot due to Patent Owner's statutory disclaimer. With respect to grounds 4–6, discretionary denial under 35 U.S.C. § 325(d) is warranted.

#### VI. 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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Patent 11,191,742 B2

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