

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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GRÜNENTHAL GMBH,  
Petitioner,

v.

ANTECIP BIOVENTURES II LLC,  
Patent Owner.

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PGR2019-00027  
Patent 10,039,774 B2

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Before GRACE KARAFFA OBERMANN, CHRISTOPHER M. KAISER,  
and WESLEY B. DERRICK, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge*.

JUDGMENT  
Final Written Decision  
Determining All Claims Unpatentable  
*35 U.S.C. § 328(a)*

## INTRODUCTION

### *A. Background*

Grünenthal GmbH (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting a post-grant review of claims 1–29 of U.S. Patent No. 10,039,774 B2 (Ex. 1002, “the ’774 patent”). Antecip Bioventures II LLC (“Patent Owner”) did not file a Preliminary Response. We instituted review of all challenged claims on each of the grounds asserted in the Petition. Paper 6 (“Dec. Inst.”). Following institution, Patent Owner filed a Response (Paper 10, “PO Resp.”), Petitioner filed a Reply (Paper 12, “Reply”), and Patent Owner filed a Sur-Reply (Paper 15, “PO Sur-Reply”). Patent Owner also filed a motion to exclude certain evidence. Paper 20 (“Mot. Exclude”). Petitioner opposed this motion (Paper 21, “Opp. Mot.”), and Patent Owner filed a Reply (Paper 22, “Reply Mot.”). We held a hearing on April 24, 2020, the transcript of which has been entered into the record. Paper 23.

We have jurisdiction under 35 U.S.C. § 6, and we issue this Final Written Decision pursuant to 35 U.S.C. § 328(a). We conclude that Petitioner has established by a preponderance of the evidence that claims 1–29 of the ’774 patent are unpatentable.

### *B. Related Matters*

The parties do not direct us to any judicial matter that would be affected by the outcome of this proceeding. Pet. 4–5; Paper 3, 2. Petitioner, however, challenges patents related to the ’774 patent in additional administrative petitions for review. Pet. 4; Paper 3, 2. In particular, according to the parties, the Board has issued final written decisions in PGR2017-00008 and PGR2017-00022, and petitions are pending in PGR2018-00001, PGR2018-00062, PGR2019-00003, PGR2019-00026, and

PGR2019-00028. *Id.* After the parties identified related matters, the Board issued a final written decision in PGR2018-00001. *See* PGR2018-00001, Paper 48 (PTAB April 29, 2019).

*C. The Asserted Grounds of Unpatentability*

Petitioner contends that claims 1–29 of the ’774 patent are unpatentable based on the following grounds (Pet. 22–75):<sup>1</sup>

| 35 U.S.C. § | References/Basis                                                                                                      | Challenged Claims |
|-------------|-----------------------------------------------------------------------------------------------------------------------|-------------------|
| 103         | Varena 2011, <sup>2</sup> Gatti, <sup>3</sup><br>Muratore, <sup>4</sup> Harden, <sup>5</sup><br>Drummond <sup>6</sup> | 1–15              |

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<sup>1</sup> Petitioner also relies on a Declaration from Lawrence Poree, M.D., Ph.D. Ex. 1004.

<sup>2</sup> Massimo Varena, *The Clinical Framework of Algodystrophy (Complex Regional Pain Syndrome Type I), An Update*, 37 IT. J. ORTHOPEDICS & TRAUMATOLOGY 227, 227–34 (Oct. 2011) (Ex. 1006, “Varena 2011”) (English translation).

<sup>3</sup> Davide Gatti, Ombretta Viapiana, Luca Idolazzi, Elena Fracassi & Silvano Adami, *Neridronic Acid for the Treatment of Bone Metabolic Diseases*, 5 EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY 1305, 1305–11 (2009) (Ex. 1008, “Gatti”).

<sup>4</sup> M. Muratore, F. Calcagnile, L. Cosentino, M. Serra, C. Circhetta, & E. Quarta, *Neridronate in the Treatment of Reflex Sympathetic Hip Algodystrophy: Open Comparison with Clodronate*, PROGRESS IN RHEUMATOLOGY (Apr. 2004) (Ex. 1007, “Muratore”) (English translation).

<sup>5</sup> R. Norman Harden, Stephen Bruehl, Roberto S.G.M. Perez, Frank Birklein, Johan Marinus, Christian Maihofner, Timothy Lubenow, Asokumar Buvanendran, Sean Mackey, Joseph Graciosa, Mila Mogilevski, Christopher Ramsden, Melissa Chont, & Jean-Jacques Vatine, *Validation of Proposed Diagnostic Criteria (the “Budapest Criteria”) for Complex Regional Pain Syndrome*, 150 PAIN 268, 268–74 (Apr. 2010) (Ex. 1009, “Harden”).

<sup>6</sup> Peter D. Drummond, *Sensory Disturbances in Complex Regional Pain Syndrome: Clinical Observations, Autonomic Interactions, and Possible*

| 35 U.S.C. § | References/Basis                                  | Challenged Claims |
|-------------|---------------------------------------------------|-------------------|
| 103         | Varena 2011, Gatti, Muratore, Harden <sup>7</sup> | 16–29             |
| 112         | Written Description                               | 1–29              |

*D. The '774 Patent*

The '774 patent, titled “Neridronic Acid for Treating Complex Regional Pain Syndrome,” issued on August 7, 2018. Ex. 1002, at (45), (54). The '774 patent relates to “[o]steoclast inhibitors, such as neridronic acid, in an acid or a salt form” that “can be used to treat or alleviate pain or related conditions, such as complex regional pain syndrome” (“CRPS”). *Id.* at (57).

According to the '774 patent, “[b]isphosphonate compounds are potent inhibitors of osteoclast activity, and are used clinically to treat bone-related conditions such as osteoporosis and Paget’s disease of bone,” as well as “cancer-related conditions including multiple myeloma, and bone metastases from solid tumors,” but these compounds “generally have low oral bioavailability.” *Id.* at 1:38–43. “[O]ral dosage forms of bisphosphonate compounds . . . can be used to treat or alleviate pain or related conditions.” *Id.* at 1:51–54. Two of these conditions are “changes in skin blood flow” and “abnormal sudomotor activity” associated with CRPS,

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*Mechanisms*, 11 Pain Medicine 1257, 1257–66 (2010) (Ex. 1010, “Drummond”).

<sup>7</sup> This ground advances the same prior art references as the obviousness ground asserted against claims 1–16. We address this as a distinct ground to mirror the structure of the Petition.

which is a “debilitating pain syndrome[] . . . characterized by severe pain in a limb.” *Id.* at 13:23–32.

None of the figures or working examples in the specification of the ’774 patent relate to the use of neridronic acid. *Id.* at 3:21–4:13 (describing Figs. 1–16), 49:33–65:24 (Examples 1–10); *see id.* at Figs. 1–16 (all discussing the use of zoledronic acid). Nevertheless, the specification identifies neridronic acid as a bisphosphonate suitable for use in the invention and contains information pertaining to daily oral dosing of neridronic acid. *Id.* at 3:4–10, 31:40–45. The specification also refers to a “molecular complex comprising neridronic acid” that “is administered in an amount that results in” certain disclosed blood plasma concentration curves. *Id.* at 26:30–43. Moreover, the specification contains other general information pertaining to the dosing of neridronic acid. For example, the ’774 patent describes the administration of “[a]ny suitable amount of an osteoclast inhibitor, including a bisphosphonate,” from a list that includes “neridronic acid” and identifies broad dosing ranges (from about 0.005 mg to about 2000 mg). *Id.* at 33:25–57. The ’774 patent also describes the administration of “any amount of osteoclast inhibitor” that is “in a range bounded by, or between, any of these values.” *Id.* at 34:12–13. The specification compares oral forms of bisphosphonates to “parenteral modes of administration, such [as] intravenous or subcutaneous” modes. *Id.* at 26:57–61. The specification explains that “[c]ommonly used measures of pain intensity include the visual analog scale (VAS) and the numerical rating scale (NRS).” *Id.* at 10:9–11.

*E. Illustrative Claims*

Claims 1–29 of the '774 patent are challenged. Claims 1 and 16 are independent and illustrative; they recite:

1. A method of treating changes in skin blood flow associated with complex regional pain syndrome, comprising parenterally administering neridronic acid in a salt form or an acid form to a human being suffering from changes in skin blood flow associated with complex regional pain syndrome, wherein the human being has a pain intensity of at least 7 cm on the 10 cm visual analogue scale (VAS) or at least 7 on the 0–10 numerical rating scale (NRS).

Ex. 1002, 90:33–40.

16. A method of treating abnormal sudomotor activity associated with complex regional pain syndrome, comprising parenterally administering neridronic acid in a salt form or an acid form to a human being suffering from abnormal sudomotor activity associated with complex regional pain syndrome, wherein the human being has a pain intensity of at least 7 cm on the 10 cm visual analogue scale (VAS) or at least 7 on the 0–10 numerical rating scale (NRS).

*Id.* at 91:14–21.

## ANALYSIS

*A. Eligibility of the '774 Patent for Post-Grant Review*

Post-grant reviews are available only for patents “described in section 3(n)(1)” of the Leahy-Smith America Invents Act (“AIA”), Pub L. No. 112-29, 125 Stat. 284 (2011). AIA § 6(f)(2)(A). These patents are those that issue from applications “that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after” “the expiration of the 18-month period beginning on the date of the enactment of” the AIA.

*Id.* § 3(n)(1). Because the AIA was enacted on September 16, 2011, post-grant reviews are available only for patents that issue from applications that at one point contained at least one claim with an effective filing date on or after March 16, 2013, with “effective filing date” having the definition given to it by 35 U.S.C. § 100(i). The effective filing date of an application for a patent on an invention is “the filing date of the earliest application for which the . . . application is entitled, as to such invention, to a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c).” 35 U.S.C. § 100(i)(1)(B).

Petitioner argues that, although the ’774 patent claims priority to several applications filed before March 16, 2013, it nevertheless is eligible for post-grant review because it “contains . . . at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the” applications to which it claims priority. Pet. 19 (quoting *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 11 (PTAB Dec. 22, 2015)). Specifically, Petitioner argues that none of the applications to which the ’774 patent claims priority sufficiently describes claims 10–13 or 25–28. *Id.* at 20–22. Those claims recite limitations regarding the age of patients being treated or the duration of the patient’s suffering from complex regional pain syndrome. Ex. 1002, 90:65–91:8, 92:16–26. According to Petitioner, none of the priority applications describe these limitations. Pet. 20–22.

In our Decision on Institution, based on Petitioner’s representations, we preliminarily found that the ’774 patent was eligible for post-grant review. Dec. Inst. 8–9. We observed that “Patent Owner may dispute that

finding in a timely-filed response to the Petition.” *Id.* at 9. Patent Owner did not dispute our finding or otherwise argue that the ’774 patent was ineligible for post-grant review in its Response. PO Resp. 1–25.

Accordingly, we find that the ’774 patent is eligible for post-grant review.

*B. Claim Construction*

In a post-grant review, we construe claim terms in an unexpired patent “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent,” as the claims would be construed “in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.200(b) (2018). Only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). On the question of claim construction, the sole dispute is whether the preambles of the challenged claims should be treated as limiting the scope of those claims. Pet. 15–18; PO Resp. 2–4; Reply 1–2; PO Sur-Reply 1. We agree that no other limitation requires express discussion for our purposes here.

Claim 1 recites “[a] method of treating changes in skin blood flow associated with complex regional pain syndrome.” Ex. 1002, 90:33–40. Claim 16 similarly recites “[a] method of treating abnormal sudomotor activity associated with complex regional pain syndrome.” *Id.* at 91:14–21. Petitioner argues that these preambles should not be interpreted as limiting the scope of the challenged claims. Pet. 13–18; Reply 1–2. Patent Owner disagrees, arguing that the preambles should be construed as limiting. PO Resp. 2–4; PO Sur-Reply 1.

The result of Petitioner's unpatentability challenges would not change regardless of whether the preambles are limiting. Even if the preambles are limiting, their scope is so broad as to be hardly different from no limitation at all. The specification of the '774 patent defines "treating" as "includ[ing] any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals." Ex. 1002, 7:43–47. This definition exhibits "reasonable clarity, deliberateness, and precision" and is "'set out . . . within the patent disclosure' so as to give one of ordinary skill in the art notice of the change" in meaning. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (quoting *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387–88 (Fed. Cir. 1992)). Accordingly, we give effect to this definition of "treating."

Under the definition of "treating" in the specification of the '774 patent, "[a] method of treating" changes in skin blood flow (claim 1) or abnormal sudomotor activity (claim 16) "associated with complex regional pain syndrome" means a method of diagnosing, curing, mitigating, or preventing that condition associated with complex regional pain syndrome, or otherwise affecting the structure or any function of the body of someone suffering from the condition associated with complex regional pain syndrome. To the extent that this requires carrying out the method on a patient suffering from changes in skin blood flow (claim 1) or abnormal sudomotor activity (claim 16) associated with complex regional pain syndrome, this is already part of the method recited in the body of the claims, Ex. 1002, 90:33–40, 91:14–21, so the preambles provide no additional limitation. To the extent that the preambles require some

particular result to be brought about, that result could be the diagnosis, cure, mitigation, or prevention of the symptom in question, or it could be any effect at all on the structure or any function of the patient's body. Thus, even when construed as limiting, the preambles provide little, if any, further restriction on the scope of the challenged claims beyond that set forth in the body of the claims.

Moreover, as discussed below with respect to the asserted grounds of obviousness, Petitioner directs us to evidence that the prior art teaches or suggests the subject matter of the preambles, even when those preambles are construed as limiting in accordance with the meaning of "treating" provided in the specification.<sup>8</sup> Thus, whether or not we treat the preambles as limiting, the outcome does not change. Given this circumstance, we treat the preambles of the challenged claims as limiting and assign them a meaning consistent with the specification's definition of "treating."

*C. Asserted Obviousness of Claims 1–15 over Harden, Drummond, and One or More of Varennna 2011, Gatti, and Muratore*

Petitioner argues that the subject matter of claims 1–15 would have been obvious over the combination of Harden, Drummond, and one or more of Varennna 2011, Gatti, and Muratore. Pet. 22–50.

*1. Varennna 2011*

Varennna 2011 relates to "[t]he Clinical Framework of Algodystrophy," which is also referred to as "Complex Regional Pain Syndrome Type I" or "Algodystrophic Syndrome." Ex. 1006, 227, 228.

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<sup>8</sup> The asserted ground of unpatentability based on lack of written description support can be resolved without deciding whether the preambles of the challenged claims are limiting.

According to Varenna 2011, the “Budapest Criteria” are “used for the diagnosis of” CRPS:

1. Continuous pain disproportionate to the triggering event
2. Patient must report the presence of at least one symptom in three of the following four categories:
  - Sensory changes: hyperesthesia and/or allodynia
  - Vasomotor changes: asymmetry of warmth when touched and/or change and/or asymmetry of skin color
  - Sudomotor changes/edema: edema and/or perspiration anomalies and/or asymmetry
  - Motor/trophic changes: reduced range of motion and/or motor anomalies (hyposthenia, tremors, dystonia) and/or trophic changes (skin, nails, hair follicles)
3. At least one sign in two or more of the following categories must be objectivized:
  - Sensory changes: hyperalgesia and/or allodynia
  - Vasomotor changes: evidence of asymmetry in contact with heat and/or change and/or asymmetry of skin color
  - Sudomotor changes/edema: evidence of . . . edema and/or perspiration anomalies and/or asymmetry
  - Motor/trophic changes: evidence of: reduced range of motion and/or motor anomalies (hyposthenia, tremors, dystonia) and/or trophic changes (skin, nails, hair follicles)
4. Absence of alternative diagnostic interpretation

*Id.* at 228 (Table 1).

In addition, Varena 2011 teaches that “various studies . . . seem to demonstrate the efficacy of Bisphosphonates administered intravenously at high dosages” in treating CRPS. *Id.* at 233. Among these bisphosphonates, “the molecule that has most recently demonstrated efficacy is Neridronate which seems to possess an excellent efficacy profile when administered intravenously at a dosage of 100 mg per four infusions every fourth day.” *Id.*

## 2. *Gatti*

Gatti<sup>9</sup> reports that “[i]ntravenous high doses of bisphosphonates are increasingly used for the treatment of reflex sympathetic dystrophy syndrome or algodystrophy,” which is another term for CRPS. Ex. 1008, 1308; *supra* 10. According to Gatti, “the most effective dose is 100 mg diluted in 250 ml of saline solution given intravenously over 4 days,” and, “[w]ith this treatment regimen, the proportion of patients experiencing rapid (in 7 – 12 days) > 70% symptomatic improvements is close to 80%.” Ex. 1008, 1308. Because of these “preliminary observations,” Gatti reports that “the first formal registrative randomized double-blind clinical trial comparing 400 mg neridronic acid to placebo in patients with foot or forearm algodystrophy syndrome has been designed and is underway.” *Id.*

## 3. *Muratore*

Muratore reports the results of a comparison of neridronate and clodronate “in the treatment of reflex sympathetic hip algodystrophy.” Ex. 1007, 89. The purpose of the study was “[t]o evaluate the therapeutic

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<sup>9</sup> Gatti originally was written in Italian, but we refer to the English translation Petitioner submitted.

efficacy of Neridronate.” *Id.* One group of patients in the study “was administered neridronate 100 mg, intravenously diluted in 250 cc of saline solution every 4 days 4 times.” *Id.* Both neridronate and clodronate “demonstrated being efficacious in the treatment of Reflex Sympathetic Algodystrophy” (that is, CRPS (Pet. 31–32)), “but the speed of improvement of pain symptoms with recovery of functional/motor capability . . . was demonstrated to be statistically more significant in patients treated with Neridronate.” Ex. 1007, 89.

#### 4. *Harden*

Harden reports the results of a study that “sought to compare the relative diagnostic efficiency of [the Budapest Criteria and an alternative, older set of diagnostic criteria] in discriminating between CRPS and non-CRPS neuropathic pain patients.” Ex. 1009, 269. The Budapest Criteria are listed in Harden; they are similar, with minor differences in wording, to the Budapest Criteria reported in Varenna 2011. *Id.* at 274 (Appendix II). Harden teaches that significant numbers of CRPS patients self-reported or were observed to exhibit changes in skin blood flow (such as skin color asymmetry) and abnormal sudomotor activity (such as sweating asymmetry). *Id.* at 271 (Table 2). In particular, Harden teaches that:

- 69.4% of CRPS patients exhibited symptoms of temperature asymmetry on examination;
- 83.9% of CRPS patients exhibited symptoms of skin color asymmetry on examination;; and
- 43.8% of CRPS patients exhibited sweating asymmetry on examination.

*Id.*

5. *Drummond*

Drummond reports a review of “mechanisms that might contribute to sensory disturbances and sympathetically-maintained pain in complex regional pain syndrome (CRPS).” Ex. 1010, 1257. Drummond teaches that “CRPS is associated with a range of . . . autonomic abnormalities.” *Id.* According to Drummond, these “[a]utonomic disturbances . . . range from signs of sympathetic deficit (warmth and loss of vasoconstrictor reflexes) to sympathetic overactivity (sweating and coldness).” *Id.* at 1260. This effect can “spread beyond the CRPS-affected limb.” *Id.* “‘Vasomotor’ refers to changes in the diameter of blood vessels, namely the dilation or constriction of blood vessels.” Pet. 27 (citing Ex. 1004 ¶ 71). Drummond demonstrates “that the vasomotor signs and symptoms listed in the Budapest Criteria are related to changes in skin blood flow.” *Id.*; *see id.* at 28–29 (quoting Ex. 1010, 1260 and citing Ex. 1004 ¶¶ 70–73).

6. *Analysis*

Petitioner argues that claims 1–15 of the ’774 patent would have been obvious over the combined teachings of Harden, Drummond, and one or more of Varenna 2011, Gatti, and Muratore. Pet. 22–50.

Patent Owner argues, with respect to claims 1–15, that the evidence of record does not show that a person of ordinary skill in the art would have had a reasonable expectation of success in treating complex regional pain syndrome with neridronic acid. PO Resp. 17–24; PO Sur-Reply 4–13. Patent Owner also argues that none of the asserted references qualifies as a printed publication under 35 U.S.C. § 102. PO Resp. 4–17; PO Sur-Reply 14–21. Finally, with respect to claim 12, Patent Owner argues that none of

the asserted references teaches or suggests the duration of symptoms recited in the claim. PO Resp. 20–24; PO Sur-Reply 13–14.

a. Reasonable Expectation of Success

Patent Owner argues that Petitioner has not shown that a person of ordinary skill in the art would have had “a reasonable expectation of success in treating complex regional pain syndrome by administering neridronic acid.” PO Resp. 17. Specifically, Patent Owner argues that none of Petitioner’s asserted references provides data showing efficacy (namely, that administering neridronic acid improves the symptoms of CRPS). *Id.* at 17–18. Patent Owner also argues that the failure of Petitioner’s Phase III clinical trials of neridronic acid for treating CRPS demonstrates the lack of any reasonable expectation of success. *Id.* at 19–20. Despite these arguments, we are persuaded that Petitioner has shown by a preponderance of the evidence the reasonable expectation of success necessary to support the obviousness of claims 1–15.

As discussed below with respect to claim 1, Petitioner’s position is that a person of ordinary skill in the art “would have been motivated to administer neridronic acid to [patients suffering from CRPS] based on the disclosures of Varenna 2011, Gatti, and/or Muratore, which teach that neridronic acid is effective for treating CRPS and its symptoms.” Pet. 36. There is evidence in each of these references that supports a finding that a person of ordinary skill in the art reasonably would have expected neridronic acid to treat CRPS successfully. Varenna 2011 describes “Neridronate”<sup>10</sup> as having “recently demonstrated efficacy” and as “seem[ing] to possess an

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<sup>10</sup> “Neridronate” is the salt form of neridronic acid. Ex. 1004 ¶ 43.

excellent efficacy profile” in treating CRPS. Ex. 1006, 233. Muratore describes the treatment of CRPS using “Neridronate” as resulting in faster “improvement of pain symptoms with recovery of functional/motor capability, reduction of bone reabsorption markers,” and “statistically more significant” bone condition restoration, when compared with other drugs. Ex. 1007, 89. Gatti discloses that a Phase II clinical trial has shown that neridronic acid, used for treating CRPS, resulted in “close to 80%” of patients “experiencing rapid (in 7 – 12 days) > 70% symptomatic improvements.” Ex. 1008, 1308. Because each of these disclosures suggests successful treatment of CRPS and its symptoms with neridronic acid, we credit Dr. Poree’s testimony that a person of ordinary skill in the art “would have known that neridronate is effective to treat CRPS and its symptoms.” Ex. 1004 ¶ 38.

Against this evidence, Patent Owner first argues that none of Petitioner’s asserted references provides data showing that administering neridronic acid improves the symptoms of CRPS. PO Resp. 17–18. But “[o]bviusness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988). It is sufficient that Varenna 2011, Gatti, and Muratore would have informed the ordinarily skilled artisan that successful treatment of CRPS and its symptoms was likely; there is no requirement that Petitioner show that the prior art taught that success was certain.

Moreover, even if Petitioner’s references insufficiently demonstrate that administering neridronic acid improves the symptoms of CRPS, it would be immaterial to the question of whether Petitioner had shown a

reasonable expectation of success. To show the reasonable expectation of success necessary to prove obviousness, Petitioner need only show that a person of ordinary skill in the art would have had “a reasonable expectation of achieving what is claimed in the patent-at-issue.” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Here, the claims at issue recite “[a] method of treating changes in skin blood flow” or “treating abnormal sudomotor activity” that is “associated with complex regional pain syndrome.” Ex. 1002, 90:33–40, 91:14–21. It might be possible to interpret the phrases “treating changes in skin blood flow” or “treating abnormal sudomotor activity” to require some improvement in those specified symptoms of CRPS, but, as discussed above, that is not the definition the ’774 patent provides. Instead, as defined in the specification of the ’774 patent, “[a] method of treating” a symptom associated with CRPS means a method of diagnosing, curing, mitigating, or preventing a symptom associated with complex regional pain syndrome, or otherwise affecting the structure or any function of the body of someone suffering from that symptom. Ex. 1002, 7:43–47. The disclosures of Varenna 2011, Gatti, and Muratore certainly suggest that the administration of neridronic acid to CRPS patients produced some effect in the structure or function of the patients’ bodies, including structure and function affected by CRPS. Given the ’774 patent’s broad definition of “treating,” there is no requirement that the neridronic acid produces any particular effect, much less achieves any particular degree of efficacy in improving the symptoms of CRPS.

Patent Owner next argues that the failure of Petitioner’s Phase III clinical trials of neridronic acid for treating CRPS demonstrates the lack of

any reasonable expectation of success. PO Resp. 19–20. We are not persuaded by this argument. The record shows that, in 2019, Petitioner “decided to discontinue its two ongoing Phase III clinical trials of Neridronate . . . in patients with Complex Regional Pain Syndrome” because the “trials were unlikely to meet the primary endpoint.” Ex. 2001, 1–2. At best, this evidence demonstrates that, in 2019, neridronic acid was known to be unlikely to achieve some specific result (that is, the primary endpoint of the trials) when used to treat CRPS. As discussed above, however, Petitioner need not show that neridronic acid would have been understood to bring about any particular result; the challenged claims require the neridronic acid only to produce any effect at all on the structure or function of a CRPS patient’s body. Thus, the failure to achieve some specific result weighs little in the reasonable-expectation-of-success inquiry. In addition, even if we accept that the claims of the ’774 patent require some particular effect, the record contains no explanation of what was the primary endpoint of Petitioner’s Phase III clinical trials, much less any evidence that that endpoint was the same effect required by the challenged claims. For this reason too, the failure of the Phase III clinical trials to achieve some particular unspecified result is of little probative value in the reasonable-expectation-of-success inquiry. In the alternative, even if the failure of the clinical trials to achieve their endpoint is somehow relevant to the question of whether a person of ordinary skill in the art reasonably would have expected success, that failure speaks only to what would have been expected in 2019, years after the date of the invention of the ’774 patent. *Bristol-Myers Squibb Co. v. Teva Pharm., Inc.*, 752 F.3d 967, 976 (Fed. Cir. 2014) (“[T]he skilled artisan’s reasonable expectation of success is measured ‘as of

the date of the invention.” (quoting *Amgen Inc. v. Hoffman–La Roche*, 580 F.3d 1340, 1362 (Fed. Cir. 2009)).

Accordingly, based on the evidence of record, we find that a person of ordinary skill in the art at the time of the invention reasonably would have expected to achieve success in attaining the result claimed in the ’774 patent (namely, any effect at all on the structure or function of a CRPS patient’s body due to the administration of neridronic acid).

b. Printed-Publication Status

Patent Owner argues that none of Petitioner’s asserted references qualifies as a printed publication under 35 U.S.C. § 102. PO Resp. 4–16; PO Sur-Reply 14–21. “To qualify as a printed publication, a reference ‘must have been sufficiently accessible to the public interested in the art.’” *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (quoting *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989)). “A reference will be considered publicly accessible if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.” *Id.* (quoting *Kyocera Wireless Corp. v. Int’l Trade Comm’n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008)) (internal quotation marks omitted). Thus, there are two ways to show that a reference was sufficiently accessible: show it was disseminated or show it was “otherwise made available to the extent that” interested people of ordinary skill in the art could have located it after exercising reasonable diligence. *Id.* Here, according to Petitioner, the asserted references “are articles published in periodical journals by an

identified and reputable publisher.” Reply 3.<sup>11</sup> Petitioner argues that the references were “disseminated on the[ir] stated publication date[s].” *Id.* at 5. We agree.

Varennia 2011 includes on its face the notations “Original Article,” “Received on July 15, 2011,” and “Accepted on August 30, 2011.” Ex. 1006, 227. It also indicates that the article appeared in the October 2011 publication of “GIOT.” *Id.* The evidence of record shows that “GIOT” stands for “Giornale Italiano di Ortopedia e Traumatologia,” which means “Italian Journal of Orthopedics and Traumatology.” Ex. 1004 ¶ 40; Ex. 1038, 1. The October 2011 issue of GIOT was disseminated in two ways, with 150 copies being handed out “at the 96<sup>th</sup> National Convention of [the Italian Society of Orthopedics and Traumatology]” on September 26, 2011, and sixty-nine copies being mailed to people on a subscription list. Ex. 1046.

Gatti, on its face, indicates that it was published in 2009 in the journal “Expert Opinion on Drug Metabolism & Toxicology.” Ex. 1008, 1305. Evidence of record shows that the publisher of this journal received, prepared, and printed this article between May 2009 and September 2009 and that Gatti was made accessible to the public online by September 17,

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<sup>11</sup> Patent Owner argues that Petitioner was required to submit any evidence of the printed-publication status of its asserted references with the Petition rather than with the Reply. PO Resp. 6. That argument is unpersuasive in view of the decision in *Hulu, LLC v. Sound View Innovations, LLC*, which held that, “if the patent owner challenges a reference’s status as a printed publication, a petitioner may submit a supporting declaration with its reply to further support its argument that a reference qualifies as a printed publication.” IPR2018-01039, Paper 29 at 15 (PTAB Dec. 20, 2019) (precedential).

2009. Ex. 1044. In view of this corroborating objective proof, we credit Dr. Poree's testimony that this article "was published no later than September 2009." Ex. 1004 ¶ 46.

Muratore, on its face, indicates that it was published in 2004 in "Progressi in Reumatologia." Ex. 1007, 3–4. Evidence of record shows that the National Library of Medicine received Muratore in July 2004. *Id.* at 3; Ex. 1043 ¶ 7. Accordingly, we credit Dr. Poree's well-supported testimony that Muratore was disseminated no later than 2004. Ex. 1004 ¶ 50.

Harden includes the notations "Received 18 November 2009," "Received in revised form 19 March 2010," and "Accepted 20 April 2010." Ex. 1009, 268. A further notation on the face of Harden indicates that the article appeared in 2010 in "Pain," published by the "International Association for the Study of Pain." *Id.* In addition, an article published in 2012 cites Harden among its references, suggesting that Harden must have been disseminated no later than 2012. Ex. 1041, 541.

Drummond, on its face, indicates that it appeared in the journal "Pain Medicine," published by "Wiley Periodicals, Inc." in 2010. Ex. 1010, 1257. Other articles published in the same journal at around the same time appear in the prosecution history of the '774 patent. Ex. 1037, 192 (September 2004 publication by Robinson), 216 (September 2016 publication by Varena), 231 (August 2010 publication by Coderre). This strongly suggests that articles published in Pain Medicine, including Drummond, were disseminated publicly. Against this evidence supporting dissemination of Drummond, Patent Owner does not direct us to contrary evidence, so we find that the preponderance of the evidence supports a finding that Drummond qualifies as a printed publication.

Accordingly, evidence of record tends to establish that each of the references Petitioner asserts against claims 1–15 was disseminated publicly before the critical date, and that each, therefore, qualifies as a prior art printed publication. Patent Owner does not direct us to any contrary evidence; therefore, we determine that the preponderance of the evidence supports a finding that Petitioner’s references are printed publications.

On that point, we are not persuaded by Patent Owner’s argument that Petitioner fails to show that an interested person of ordinary skill in the art could have located the asserted references. PO Resp. 13–16. Nor do we find merit in Patent Owner’s further argument that some of the asserted references were not available to a person of ordinary skill in the art because they were written and published in Italian rather than English. PO Sur-Reply 3–4. These arguments ignore Petitioner’s evidence that each of the asserted references was disseminated publicly, which is sufficient on its own to prove printed-publication status, without additional proof that a person of ordinary skill in the art could have located the references. *See Blue Calypso*, 815 F.3d at 1348 (quoting *Kyocera*, 545 F.3d at 1350). Moreover, to the extent that the ability of a person of ordinary skill in the art to locate a reference is important to establishing the public dissemination of the references, we find that an ordinarily skilled artisan interested in the subject matter could have located the references asserted here through reasonable diligence. The evidence of record tends to establish that the asserted references were articles in circulation at the time of the invention; therefore, a person of ordinary skill in the art could have reviewed them.

In addition, Patent Owner argues that indicia on the face of a non-patent reference are never sufficient on their own to prove printed-

publication status. PO Sur-Reply 14–15. As noted above, the evidence of dissemination of Petitioner’s references comes from the face of the references,<sup>12</sup> from Dr. Poree’s testimony, and from additional evidence submitted along with Petitioner’s Reply. Accordingly, the question whether the printed-publication status of a reference may be established solely based on evidence taken from the face of the document itself is not before us.

Because the preponderance of the evidence of record shows that Petitioner’s references were disseminated publicly before the critical date, we find that the asserted references are printed publications.

c. Claim 1

Claim 1 recites,

A method of treating changes in skin blood flow associated with complex regional pain syndrome, comprising parenterally administering neridronic acid in a salt form or an acid form to a human being suffering from skin blood flow associated with complex regional pain syndrome, wherein the human being has a pain intensity of at least 7 cm on the 10 cm visual analogue scale (VAS) or at least 7 on the 0–10 numerical rating scale (NRS).

Ex. 1002, 90:33–40.

Although changes in skin blood flow are not expressly listed in the Budapest Criteria, those criteria include “‘vasomotor’ signs and symptoms,” such as “temperature asymmetry and/or skin color changes and/or asymmetry.” Ex. 1004 ¶ 71. Petitioner directs us to evidence, moreover,

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<sup>12</sup> Evidence on the face of a reference may be considered in deciding whether the reference is a printed publication. *Hulu*, IPR2018-01039, Paper 29 at 17–18 (precedential) (evidence taken from the face of a reference is to be “considered as part of the totality of the evidence”).

that “[v]asomotor’ refers to changes in the diameter of blood vessels, namely the dilation or constriction of blood vessels.” *Id.* (citing Ex. 1039, 2093). We are persuaded that a person of ordinary skill in the art “would have known that the vasomotor signs and symptoms listed in the Budapest Criteria are related to changes in blood flow.” *Id.* at ¶ 72; *see* Pet. 29 (citing Ex. 1004 ¶¶ 70–73); *see also id.* at 24–25 (for citations to additional persuasive information on point).

We also are persuaded that it would have been well known in the art “to paternally administer neridronic acid to CRPS patients having pain intensity of at least 7 cm on the VAS, as required by claim 1.” *Id.* at 34 (citing Ex. 1004 ¶¶ 79–80). To the extent that the claimed VAS limitation is deemed critical, we find that an ordinarily skilled artisan reasonably would have expected neridronate to treat successfully changes in skin blood flow associated with CRPS in patients presenting with the level of pain intensity required by claim 1. *Id.* at 34–35 (citing Ex. 1004 ¶¶ 90–93).

Petitioner argues that a person of ordinary skill in the art “would have been motivated to administer neridronic acid to [patients suffering from CRPS] based on the disclosures of Varenna 2011, Gatti, and/or Muratore, which teach that neridronic acid is effective for treating CRPS and its symptoms.” Pet. 36 (citing Ex. 1004 ¶¶ 81–84). Petitioner argues further that, having been so motivated, the person of ordinary skill in the art would have “look[ed] to other references like Varenna 2011, Harden, and Drummond, which describe the diagnostic criteria, signs, and symptoms of [CRPS].” *Id.* at 34 (citing Ex. 1004 ¶ 85). Because these references teach that neridronate is useful for treating CRPS and its symptoms, and changes in skin blood flow would have been recognized as such a symptom,

Petitioner argues that the person of ordinary skill in the art “would have had a reasonable expectation that neridronic acid or one of its salts could successfully be administered to a patient suffering from changes in skin blood flow associated with CRPS.” *Id.* at 36 (citing Ex. 1004 ¶¶ 81–84).

With the exception of arguments discussed above, pertaining to reasonable expectation of success and printed-publication status, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. Patent Owner, however, contends that the use of the phrase “and/or” in the asserted obviousness grounds results in an impermissibly vague challenge. PO Resp. 10–11 n.5; PO Sur-Reply 2. For support, Patent Owner directs us to the Board’s informative decision in *Adaptics Limited v. Perfect Company*, Case IPR2018-01596, Paper 20 at 1 (PTAB Mar. 6, 2019) (“*Adaptics*”)(informative). The facts of *Adaptics* are inapposite. There, the petitioner strung together ten prior art references by the phrase “and/or,” resulting in no less than “seventeen possible combinations” of prior art references, and leading to “voluminous and excessive” grounds nowhere explained adequately by the patent challenger. *Adaptics*, Paper 20 at 2, 6, 18–19, 21. Here, by contrast, only three prior art references are combined by the phrase “and/or,” and the same combination is at issue across both grounds at hand. Pet. 22, 51. Further, and most significantly, Petitioner cogently explains the relevant facts underlying both grounds and Patent Owner does not contest those facts. *Id.* at 22–71. Accordingly, we are unpersuaded by Patent Owner’s argument that the grounds presented here are comparable to those in *Adaptics*, or result in an impermissibly vague challenge. PO Resp. 10–11 n.5; PO Sur-Reply 2.

Based on the full trial record, we find that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claim 1 would have been obvious. Varena 2011 teaches that neridronate “seems to possess an excellent efficacy profile” in treating CRPS. Ex. 1006, 233. In the context of reporting the use of “[n]eridronic acid for the treatment of bone metabolic diseases,” Gatti teaches that “[i]ntravenous high doses of bisphosphonates are increasingly used for the treatment of [CRPS].”<sup>13</sup> Ex. 1008, 1305, 1308. Gatti also reports that a clinical trial of neridronic acid “is underway.” *Id.* Muratore teaches that neridronate was “efficacious in the treatment of [CRPS].” Ex. 1007, 89. Thus, on this record, each of these references sufficiently teaches the efficacy of neridronic acid or its salt in treating CRPS, suggesting that a person of ordinary skill in the art would have been motivated to use neridronic acid in treating CRPS.

With respect to the limitation of claim 1 requiring that the neridronic acid be “parenterally administer[ed],” each of Varena 2011, Gatti, and Muratore teaches intravenous administration of neridronic acid. Ex. 1006, 233; Ex. 1007, 89; Ex. 1008, 1308. Intravenous administration is a type of parenteral administration. Ex. 1004 ¶ 44.

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<sup>13</sup> Gatti uses the terms “reflex sympathetic dystrophy syndrome” and “algodystrophy.” Ex. 1008, 1308. On the present record, we interpret both of these terms as synonymous with “complex regional pain syndrome,” “CRPS,” “complex regional pain syndrome type I,” “CRPS I,” “reflex sympathetic algodystrophy,” “reflex sympathetic dystrophy,” and “causalgia.” Ex. 1006, 227 (equating “algodystrophy,” “complex regional pain syndrome type I,” and “CRPS I”); Ex. 1007, 89 (using the term “reflex sympathetic algodystrophy”); Ex. 1019, 713 (equating “complex regional pain syndrome,” “CRPS,” “reflex sympathetic dystrophy,” and “causalgia”).

Harden teaches that the Budapest Criteria are used as “clinical diagnostic criteria for CRPS” and that they include changes in skin blood flow, by reference to the symptoms of “temperature asymmetry” and “skin color asymmetry.” Ex. 1009, 274 (Appendix II). Further, Harden teaches that 69.4% of patients diagnosed with CRPS were observed on examination to exhibit temperature asymmetry, and 83.9% were observed on examination to exhibit skin color asymmetry. *Id.* at 271 (Table 2). Thus, Harden teaches that a majority of patient with CRPS suffer from changes in skin blood flow. Because Varenna 2011, Gatti, and Muratore teach that neridronic acid is effective in treating CRPS, the combination of any of those references with Harden<sup>14</sup> would have suggested to a person of ordinary skill in the art that neridronic acid would be effective in alleviating changes in skin blood flow associated with CRPS.

Thus, the combination of Harden and one or more of Varenna 2011, Gatti, and Muratore sufficiently teaches or suggests all the limitations of claim 1. Moreover, Petitioner has shown that a person of ordinary skill in the art would have had reason to combine the teachings of one or more of Varenna 2011, Gatti, and Muratore with those of Harden in order to

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<sup>14</sup> Petitioner further argues that Drummond teaches that CRPS patients may suffer from changes in skin blood flow. Pet. 56–57. As discussed below, Patent Owner moves to exclude the evidence of Drummond’s status as prior art. We need not resolve the issue of whether that evidence should be excluded, however, because, even without the teachings of Drummond, Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have understood that the defining symptoms of CRPS include changes in skin blood flow, including temperature asymmetry and skin color asymmetry. Accordingly, we do not consider the teachings of Drummond in evaluating this obviousness ground.

determine the symptoms of CRPS that could be improved by the treatment. Ex. 1004 ¶¶ 80–84. Accordingly, we conclude that Petitioner has shown by a preponderance of the evidence that the subject matter of claim 1 would have been obvious over the combination of Harden and one or more of Varena 2011, Gatti, and Muratore.

d. Claims 2 and 3

Claim 2 of the '774 patent depends from claim 1 and adds a limitation requiring that “a total of about 200 mg to about 500 mg of the neridronic acid [be] administered parenterally to the human being.” Ex. 1002, 90:41–43. Claim 3 depends from claim 1 and adds a limitation requiring that “a total of about 400 mg of the neridronic acid [be] administered parenterally to the human being.” *Id.* at 90:44–46. Petitioner argues that both Varena 2011 and Muratore teach these limitations. Pet. 39. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claims 2 and 3 would have been obvious.

Muratore teaches administering 100 mg of neridronate per infusion, with one infusion occurring every four days until four total infusions have been administered. Ex. 1007, 89. This is a total of 400 mg of neridronate, which both falls within the recited range of claim 2 and is the specific amount recited in claim 3. Based on this evidence, we determine that Petitioner has shown by a preponderance of the evidence that the

combination of Harden and at least one of Varena 2011, Gatti, and Muratore teaches or suggests the limitations of claims 2 and 3.

e. Claim 4

Claim 4 depends from claim 1 and adds a limitation requiring that “a total of about 100 mg to about 200 mg of the neridronic acid [be] administered parenterally to the human being within a period of about 1 month.” Ex. 1002, 90:47–50. Petitioner argues that Gatti teaches this limitation. Pet. 40. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 4 would have been obvious.

Gatti teaches that “the most effective dose is 100 mg diluted in 250 ml of saline solution given intravenously over 4 days.” Ex. 1008, 1308. This statement in Gatti may refer to “bisphosphonates” generally, rather than to neridronic acid specifically, because the paragraph in which this statement appears begins with a reference to “high doses of bisphosphonates.” *Id.* The following paragraph, however, states that, because of the efficacy of the specified dose, a clinical trial of neridronic acid “is underway.” *Id.* This suggests that the specific bisphosphonate for which “the most effective dose is 100 mg diluted in 250 ml of saline solution given intravenously over 4 days” is neridronic acid. *Id.* Moreover, the entirety of Gatti discusses “[n]eridronic acid for the treatment of bone metabolic diseases,” which also suggests that the particular bisphosphonate in question is neridronic acid. *Id.*

at 1305. Thus, Gatti teaches or suggests the administration of 100 mg of neridronic acid.<sup>15</sup> Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varena 2011, Gatti, and Muratore teaches or suggests the limitations of claim 4.

f. Claim 5

Claim 5 depends from claim 1 and adds a limitation requiring that “a total of about 250 mg of the neridronic acid [be] administered parenterally to the human being within a period of about 1 month.” Ex. 1002, 90:54–56. Petitioner argues that the claimed dose falls within the range of doses that the prior art describes as effective and that a person of ordinary skill in the art would have been motivated and able to arrive at the optimum dose of neridronic acid. Pet. 40–43. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 5 would have been obvious.

Gatti teaches that a dose of 100 mg of neridronic acid is effective in treating CRPS. Ex. 1008, 1308 (this dose reduces symptoms of CRPS by more than 70% in “close to 80%” of patients). Muratore teaches that a dose of 400 mg of neridronate is effective in treating CRPS. Ex. 1007, 89 (improvement in several symptoms occurred faster with this dose of

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<sup>15</sup> Gatti likewise also suggests administration of 100 mg of neridronic acid by teaching (1) the administration of 100 mg of bisphosphonate and (2) that neridronic is an exemplary bisphosphonate. Ex. 1008, 1308.

neridronate than in groups treated with other drugs). The 250-mg dose of claim 5 falls between these two prior-art values, and there is evidence of record that an ordinarily skilled artisan would have been motivated and able to find an optimum dose of neridronic acid within the prior-art range.

Ex. 1004 ¶¶ 102–103. “[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varena 2011, Gatti, and Muratore teaches or suggests the limitations of claim 5.

g. Claims 6 and 7

Claim 6 depends from claim 2 and adds a limitation requiring that “the neridronic acid [be] administered in divided doses.” Ex. 1002, 90:54–55. Claim 7 depends from claim 6 and adds a limitation requiring that “each division of the divided parenteral dose contain[] about 10 mg to about 150 mg of the neridronic acid.” *Id.* at 90:56–58. Petitioner argues that both Varena 2011 and Muratore teach these limitations. Pet. 43–44. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claims 6 and 7 would have been obvious.

Varena 2011 teaches a divided parenteral dose in which each division falls between 10 mg and 150 mg of neridronate. Ex. 1006, 233 (teaching that neridronate is “administered intravenously at a dosage of 100

mg per four infusions every fourth day”). This teaches dividing a total dose into “four infusions,” thus meeting the limitation of claim 6. *Id.* Regardless of whether the total dose is 100 mg, as is apparent from the text of Varena 2011, or 400 mg, as Petitioner argues, the division into four infusions means that each infusion contains an amount of neridronate between 10 mg and 150 mg as specified in claim 7.

Similarly, Muratore teaches administering 100 mg of neridronate per infusion, with one infusion occurring every four days until four total infusions have been administered. Ex. 1007, 89. This teaches dividing a total dose of 400 mg into four infusions. *Id.* Thus, Muratore teaches both the limitation of claim 6 and, because the divided doses contain 100 mg each, the limitation of claim 7.

Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varena 2011, Gatti, and Muratore teaches or suggests the limitations of claims 6 and 7.

#### h. Claim 8

Claim 8 depends from claim 6 and adds a limitation requiring that “each division of the divided parenteral dose contain[] about 62 mg to about 63 mg of the neridronic acid.” *Id.* at 90:59–61. Petitioner argues that the claimed dose falls within the range of doses that the prior art describes as effective and that a person of ordinary skill in the art would have been motivated and able to arrive at the optimum dose of neridronic acid. Pet. 44–45. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp.

1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 8 would have been obvious.

There is evidence of record that a person of ordinary skill in the art would have been motivated and able to find an optimum dose of neridronic acid. Ex. 1004 ¶¶ 102–105, 110–111. “[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” *Aller*, 220 F.2d at 456. Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varena 2011, Gatti, and Muratore teaches or suggests the limitations of claim 8.

i. Claim 9

Claim 9 depends from claim 1 and adds a limitation requiring that “the complex regional pain syndrome [be] associated with an inciting traumatic event.” Ex. 1002, 90:62–64. Petitioner argues that both Harden and Varena 2011 teach this limitation. Pet. 45–46. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 9 would have been obvious.

Varena 2011 teaches that “approximately half the cases [of CRPS] (from 40 to 65%) recognize[] trauma as the triggering event.” Ex. 1006, 229. Harden teaches that traumatic events caused 73.6% of CRPS cases, with fractures accounting for 41.6% of cases and surgery and crush injuries causing another 32%. Ex. 1009, 269. Thus, a person of ordinary skill in the

art would have expected most cases of CRPS to have resulted from a traumatic triggering event. Because, as discussed above, Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have expected neridronic acid to alleviate changes in skin blood flow associated with CRPS, that person would have been motivated to do so in the majority of CRPS cases resulting from a traumatic initiating event. Ex. 1004 ¶¶ 113–115. Accordingly, Petitioner has shown by a preponderance of the evidence that the subject matter of claim 9 would have been obvious in view of the combined disclosures of Harden and at least one of Varena 2011, Gatti, and Muratore.

j. Claims 10 and 11

Claim 10 depends from claim 1 and adds a limitation requiring that “the human being has suffered from complex regional pain syndrome for at least 6 months.” Ex. 1002, 90:65–67. Claim 11 depends from claim 1 and adds a limitation requiring that “the human being has suffered from complex regional pain syndrome for about 6 months to about 12 months.” *Id.* at 91:1–3. Petitioner argues that these limitations would have been obvious to a person of ordinary skill in the art. Pet. 46–48. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claims 10 and 11 would have been obvious.

The average duration of CRPS symptoms in the study reported in Muratore was 4.1 months, with some patients having suffered from CRPS for at least 6.1 months. Ex. 1007, 89. The disease duration of 6.1 months in Muratore falls within the range recited in claim 10 (“at least 6 months”) and claim 11 (“about 6 months to about 12 months”). Ex. 1002, 89:56–61. The ranges of disease duration recited in claims 10 and 11 fall within the range of 4.1 months to ten years disclosed in the prior art. Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varenna 2011, Gatti, and Muratore teaches or suggests the limitations of claims 10 and 11.

k. Claim 12

Claim 12 depends from claim 1 and adds a limitation requiring that “the human being has suffered from complex regional pain syndrome for about 1 year to about 2 years.” Ex. 1002, 91:4–6. Petitioner argues that this limitation would have been obvious to a person of ordinary skill in the art. Pet. 46–48; Reply 19–21. In particular, Petitioner argues that it would have been obvious to treat patients who had suffered for between one year and two years because Muratore taught treating patients who had suffered for more than six months and other art taught that CRPS could last for longer than one year. Reply 19–21. Patent Owner disagrees, arguing that none of the asserted references teaches using neridronic acid to treat a patient who has suffered from CRPS for between one and two years. PO Resp. 20–24; PO Sur-Reply 13–14. Patent Owner also argues that Petitioner has shown at most that a person of ordinary skill in the art could have treated patients who had suffered from CRPS for between one and two years, not that they would have had a reason to do so. PO Sur-Reply 14. After considering the entire

record, we determine that Petitioner has shown by a preponderance of the evidence that claim 12 would have been obvious.

As discussed above with respect to claims 10 and 11, Muratore teaches treating patients who have suffered from CRPS for up to 6.1 months. Ex. 1007, 89. Varenna 2011 teaches that symptoms of CRPS often last for “ten years from the onset of the disease.” Ex. 1006, 230. Accordingly, we credit the testimony of Dr. Poree that a person of ordinary skill in the art “would have reasonably expected that neridronate could be used to successfully treat symptoms of CRPS . . . in patients having CRPS for up to and including 2 years.” Ex. 1004 ¶ 118. Neither party directs us to evidence that an ordinarily skilled artisan would have considered it more difficult to treat patients who had suffered CRPS symptoms for between one and two years than to treat those who had suffered for shorter periods. Given the disclosures of Muratore and Varenna 2011, as well as the testimony of Dr. Poree, we determine that a person of ordinary skill in the art would have found it obvious to treat patients who had suffered for between one and two years using the same treatment used for those who had suffered for over six months. Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varenna 2011, Gatti, and Muratore teaches or suggests the limitations of claim 12.

#### 1. Claim 13

Claim 13 depends from claim 1 and adds a limitation requiring that “the human being” must have “an age of about 30 years to about 40 years.” Ex. 1002, 91:10–11. Petitioner argues that Muratore teaches this limitation. Pet. 48–49. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and

impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 13 would have been obvious.

Muratore reports the results of a study in which at least one CRPS patient was 39 years old. Ex. 1007, 89 (disclosing that female patients ranged in age from 39 to 57). This falls within the range recited in claim 13. Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varenna 2011, Gatti, and Muratore teaches or suggests the limitations of claim 13.

m. Claims 14 and 15

Claims 14 depends from claim 1 and adds a limitation requiring that “the human being” have “a pain intensity of at least 8 cm on a 10 cm VAS or at least 8 on a 0–10 NRS,” whereas claim 15 (which similarly depends from claim 1) requires a pain intensity “of at least 9 cm on” one of those scales. Ex. 1002, 91:9–14. Petitioner argues that these limitations would have been obvious to a person of ordinary skill in the art. Pet. 49–50. With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claims 14 and 15 would have been obvious.

The Budapest Criteria for diagnosing CRPS include “[c]ontinuous pain disproportionate to the triggering event.” Ex. 1006, 228 (Table I); *see* Ex. 1009, 274 (Appendix II). As discussed above, the events that can trigger CRPS are most often traumatic in nature, including fractures, surgery, and crush injuries. Ex. 1009, 269. Accordingly, “CRPS is characterized and defined by *severe* and continuing pain.” Ex. 1004 ¶ 127. There is evidence of record that “‘severe’ pain includes patients with high VAS scores, such as  $\geq 7$  cm.” *Id.* As discussed above, the combination of Harden and at least one of Varennna 2011, Gatti, and Muratore teaches or suggests treating CRPS with neridronic acid. Thus, the evidence of record shows that a person of ordinary skill in the art “would reasonably [have] expect[ed] that neridronic acid could be successfully used to treat . . . CRPS in patients having VAS scores  $\geq 7$  cm, 8 cm, or 9 cm.” *Id.* Accordingly, Petitioner has shown by a preponderance of the evidence that the combination of Harden and at least one of Varennna 2011, Gatti, and Muratore teaches or suggests the limitations of claims 14 and 15.

*D. Asserted Obviousness of Claims 16–29 over Harden and One or More of Varennna 2011, Gatti, and Muratore*

Petitioner argues that claims 16–29 of the ’774 patent would have been obvious over the combination of Harden and one or more of Varennna 2011, Gatti, and Muratore. Pet. 51–71.

*1. The Asserted Prior Art*

Our description of Harden, Varennna 2011, Gatti, and Muratore provided above in connection with the ground against claims 1–15 applies with equal force here.

2. *Analysis*

a. Reasonable Expectation of Success

As it does with respect to the ground of obviousness challenging claims 1–15, Patent Owner argues that Petitioner fails to show the obviousness of claims 16–29 because it fails to show that a person of ordinary skill in the art would have had “a reasonable expectation of success in treating complex regional pain syndrome by administering neridronic acid.” PO Resp. 24. We disagree with this argument for the same reasons discussed above, which apply with equal force here.

b. Printed-Publication Status

As discussed above, despite Patent Owner’s arguments to the contrary, Petitioner has shown by a preponderance of the evidence that Varena 2011, Gatti, Muratore, and Harden qualify as printed publications. Our reasoning above, regarding the printed-publication status of these references, applies with equal force to our analysis of this ground.

c. Claim 16

Claim 16 recites,

A method of treating abnormal sudomotor activity associated with complex regional pain syndrome, comprising parenterally administering neridronic acid in a salt form or an acid form to a human being suffering from abnormal sudomotor activity associated with complex regional pain syndrome, wherein the human being has a pain intensity of at least 7 cm on the 10 cm visual analogue scale (VAS) or at least 7 on the 0–10 numerical rating scale (NRS).

Ex. 1002, 91:14–21. “‘Sudomotor activity’ refers to stimulation of the sweat glands and sweating.” Pet. 53; Ex. 1004 ¶ 68 (citing Ex. 1039, 1861).

Abnormal sudomotor activity “refers to abnormal sweating changes or sweating asymmetry in the body parts affected by CRPS.” Ex. 1004 ¶ 68.

Petitioner argues that a person of ordinary skill in the art “would have been motivated to administer neridronic acid to [patients suffering from CRPS] based on the disclosures of Varenna 2011, Gatti, and/or Muratore, which teach that neridronic acid is effective for treating CRPS and its symptoms.” Pet. 56–57 (citing Ex. 1004 ¶¶ 81–84). Petitioner argues further that, having been so motivated, the person of ordinary skill in the art would have “look[ed] to other references like Varenna 2011 and Harden, which describe the diagnostic criteria, signs, and symptoms of [CRPS].” *Id.* at 57 (citing Ex. 1004 ¶ 85). Because Varenna 2011 and Harden both teach that abnormal sudomotor activity is a common symptom of CRPS, Petitioner argues that an ordinarily skilled artisan “would have had a reasonable expectation that neridronic acid or one of its salts could successfully be administered to a patient suffering from abnormal sudomotor activity associated with CRPS.” *Id.* (citing Ex. 1004 ¶¶ 81–84).

With the exception of the arguments discussed above with respect to reasonable expectation of success, printed-publication status, and impermissible vagueness due to the use of the phrase “and/or” in the grounds, Patent Owner does not oppose Petitioner’s arguments. PO Resp. 1–24; PO Sur-Reply 1–13. After considering the entire record, we determine that Petitioner has shown by a preponderance of the evidence that claim 16 would have been obvious.

Petitioner is correct that a person of ordinary skill in the art would have been motivated to administer neridronic acid to treat CRPS. As discussed above with respect to claims 1–15, each of Varenna 2011, Gatti,

and Muratore teaches the efficacy of neridronic acid or its salt in treating CRPS, suggesting that a person of ordinary skill in the art would have been motivated to use neridronic acid in treating CRPS. Ex. 1006, 233; Ex. 1007, 89; Ex. 1008, 1305, 1308. In addition, each of these references teaches intravenous administration of neridronic acid. Ex. 1004 ¶ 42; Ex. 1006, 233; Ex. 1007, 89; Ex. 1008, 1308.

We further agree with Petitioner that it would have been “widely known” at the time of the invention “that abnormal sudomotor activity is a sign and symptom of CRPS” and, in fact, was a defining “criteria” used “to identify and diagnose CRPS.” Pet. 52 (citing Ex. 1004 ¶ 48). Varenna 2011 and Harden teach that the Budapest Criteria, which are used as clinical diagnostic criteria for CRPS, include abnormal sudomotor activities, including sweating changes, temperature asymmetry, and sweating asymmetry. Ex. 1006, 228; Ex. 1009, 274 (Appendix II); Ex. 1004 ¶ 78. Further, Harden teaches that CRPS patients were likely to suffer from abnormal sudomotor activity. Pet. 49; Ex. 1009, 271 (Table 2) (43.8% of CRPS patients present with sweating asymmetry on examination). Because each of Varenna 2011, Gatti, and Muratore teaches that neridronic acid is effective in treating CRPS, the combination of any of those references with Harden would have suggested to an ordinarily skilled artisan that neridronic acid would be effective in alleviating abnormal sudomotor activity associated with CRPS.

The combination of Harden and one or more of Varenna 2011, Gatti, and Muratore teaches or suggests the limitations of claim 16. Petitioner has shown sufficiently that a person of ordinary skill in the art would have had reason to combine the teachings of one or more of Varenna 2011, Gatti, and

Muratore with those of Harden in order to determine the symptoms of CRPS that could be improved by the treatment. Ex. 1004 ¶¶ 84–85. Accordingly, we determine that Petitioner has shown by a preponderance of the evidence that claim 16 would have been obvious over the combination of Harden and one or more of Varenna 2011, Gatti, and Muratore.

d. Claims 17–29

Other than their dependency from claim 16 rather than from claim 1, claims 17–29 of the '774 patent are identical to claims 2–14. *Compare* Ex. 1002, 90:41–91:14, *with* Ex. 1002, 91:22–92:29. For the same reasons as discussed above in connection with claims 2–14, we find that Petitioner has shown by a preponderance of the evidence that claims 17–29 would have been obvious over the combination of Harden and one or more of Varenna 2011, Gatti, and Muratore.

*E. Asserted Lack of Written Description*

Petitioner asserts that claims 1–29 lack written description support in “[t]he '774 patent specification.”<sup>16</sup> Pet. 74; *see id.* at 8 (grounds chart). In our Decision on Institution, we concluded that Petitioner had not shown a reasonable likelihood of prevailing on this asserted ground of unpatentability. Dec. Inst. 19–24. After we made that determination,

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<sup>16</sup> The relevant inquiry is whether the subject matter of the challenged claims finds written description support “in the originally filed disclosure.” *Purdue Pharm. L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326–27 (Fed. Cir. 2000). We adopt Petitioner’s convention of referring to the '774 patent specification, rather than Application No. 15/782,480, which matured to issue as the '774 patent. *See* Pet. 72–75 (repeatedly referring to, and citing, the '774 patent specification); Ex. 1002, code (21) (identification of Application No. 15/782,480).

neither party addressed this ground any further. *See generally*, PO Resp.; Reply; PO Sur-Reply. Accordingly, the record after trial remains the same as it was at the time we instituted review, and we repeat our original analysis here, which remains applicable to our consideration of the record after trial.

“[T]he hallmark of written description is disclosure.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). A patent disclosure is sufficient if it “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date,” based on an “objective inquiry into the four corners of the specification.” *Id.* Petitioner argues that the ’774 patent specification “does not specifically describe administration of neridronic acid to human beings to treat changes in skin blood flow” (claims 1–15) or “abnormal sudomotor activity” (claims 16–20) associated with CRPS. Pet. 73, 74.

We find Petitioner’s information on point insufficient for two independent reasons. First, the original claims set forth in the patent application that matured to issue as the ’774 patent are part of the disclosure that we consider when assessing the question of compliance with the written description requirement. *See* Ex. 1036, 145–147<sup>17</sup> (prosecution history, claims as originally filed). It is well settled that “original claims constitute their own description.” *In re Koller*, 613 F.2d 819, 823 (CCPA 1980); *see In re Gardner*, 475 F.2d 1389, 1391 (CCPA 1973) (“[A]n original claim, in itself constituted a description in the original disclosure equivalent in scope and identical in language to the total subject matter now being claimed.”). Original claim 14 (which depends from original claim 1) appears to support

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<sup>17</sup> Regarding Exhibit 1036, we cite to page numbers added by Petitioner not original page numbers assigned during patent prosecution.

adequately the subject matter of claim 1, as issued. *Compare* Ex. 1036, 145, 146 (original claims 1 and 14), *with* Ex. 1002, claims 1 and 14. Similarly, original claim 30 (which depends from original claim 17) appears to support adequately claim 16, as issued. *Compare* Ex. 1036, 146, 147 (original claims 17 and 30), *with* Ex. 1002, claim 16. That circumstance, on this record, appears to us to lay to rest any question that independent claim 1 or 16 lacks written description support.

Petitioner raises no written description argument specific to any limitation of a dependent claim. Pet. 72–75. In any event, a straightforward comparison of original claims 1–30 to claims 1–29, as issued, reveals that they cover essentially identical subject matter. *Compare* Ex. 1036, 145–147 (original claims 1–30), *with* Ex. 1002, claims 1–29. On this record, therefore, the original claims represent “a description in the original disclosure equivalent in scope” to the subject matter of the challenged claims. *In re Gardner*, 475 F.2d at 1391. “Nothing more is necessary for compliance with the description requirement of the first paragraph of 35 U.S.C. § 112.”<sup>18</sup> *Id.*

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<sup>18</sup> We do not mean to suggest that original claims always and inevitably provide their own written description support. When a claim recites a genus and “use[s] functional language to define the boundaries of [the] claimed genus,” it “may simply claim a desired result, and may do so without describing species that achieve that result.” *Ariad*, 598 F.3d at 1349. When that is the case, “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” *Id.* Petitioner does not allege, however, that the claims of the ’774 patent take the form described in *Ariad*.

Second, we find insufficient Petitioner's argument that the '774 patent specification "contains no working examples of neridronic acid administration whatsoever." Pet. 73, 74. Petitioner, in that regard, argues that the rat tibia fracture model discussed in the examples, and which involved administration of zoledronic acid to rats, does not support the claimed feature of claims 1–15 requiring administration of a different bisphosphonate (neridronic acid) to treat a different animal (a human being). *Id.* at 73–74 (asserting that argument in the context of claims 1–15); *compare id.* at 74–75 (nowhere advancing that argument in the context of claims 16–29). Petitioner focuses on those examples in isolation, without adequately accounting for the disclosure of the specification as a whole.

The specification expressly contemplates the use of neridronic acid to treat CRPS and contains disclosure adequate to indicate possession of a method of intravenous administration of neridronic acid to treat the symptoms of CRPS in human patients. *See, e.g.*, Ex. 1002, 3:4–17, 8:38–53, 69:24–36 (Embodiment 79), 69:56–58 (Embodiment 86). The specification repeatedly lists neridronic acid alongside zoledronic acid when identifying bisphosphonate compounds that are suitable for use in the invention. *Id.* at 3:5–6, 3:12–13, 4:20, 8:46, 18:17–18, 18:35, 18:32, 33:28, 42:8. As explained above (*supra* 6), the specification not only mentions neridronic acid alongside zoledronic acid when describing the bisphosphonate compounds useful in the invention, but does so in the context of describing the administration of a bisphosphonate to a human being suffering from CRPS. Ex. 1002, 3:4–16, 8:38–48. Those disclosures, on this record, suggest that the two bisphosphonates behave similarly in the claimed invention. *Id.* Further, the specification repeatedly and consistently

indicates that the inventors were in possession of a treatment applicable to “a human being” or “a human patient.” Ex. 1002, 2:5, 2:33, 7:24, 8:41, 9:21, 9:30, 9:34, 14:6, 14:12, 14:19, 23:46, 23:59, 24:30, 24:49, 31:19, 37:6, 37:67, 38:61, 39:51, 39:58, 39:63, 40:7.

Although, Examples 1–3 contain data keyed to the efficacy of zoledronic acid in a rat tibia fracture model (in which CRPS was induced and evaluated in non-human animals), that fact does not end the inquiry. Pet. 73–74 (discussing rat tibia model in the context of claims 1–15); Ex. 1002, Examples 1–3 (describing the efficacy of zoledronic acid in rat tibia fracture model of CRPS). Each of those examples includes disclosure that explains how to extrapolate starting dosages for animals to dosages appropriate for human patients, by reference to FDA guidelines. Ex. 1002, 49:49–55, 50:23–31 (Example 1), 51:20–24 (Example 2), 52:64–67 (Example 3).

Example 3 goes further, citing prior research demonstrating that the rat tibia fracture model, referenced in the working examples, replicates CRPS as “observed in human[s].” *Id.* at 51:30–40 (Example 3, citing a prior publication). Moreover, “Embodiment 79” in the specification expressly refers to “[a] method of treating complex regional pain syndrome, comprising administering neridronic acid to a human being in need thereof.” Ex. 1002, 69:34–38. As to the limitations that require a patient suffering a particular intensity of pain, the specification expressly describes VAS and NRS pain intensity scores required by the claims and, moreover, includes “Embodiment 86,” which expressly discloses “[a] method of treating pain, comprising administering neridronic acid to a human being in need thereof.” *Id.* at Figs. 10–12, 3:56–67, 10:9–59, 69:56–58 (Embodiment 86).

Petitioner acknowledges, moreover, that the specification describes “[s]ome embodiments” that “include administering an osteoclast inhibitor, such as a bisphosphonate, including zoledronic acid, neridronic acid, etc. to inhibit the development of pain, unweighting, and abnormal sudomotor activity when administered early such as when a precipitating event such as fracture occurs, wherein the precipitating event is associated with CRPS.” Pet. 74–75 (quoting Ex. 1002, 3:4–10). We find this express disclosure, in combination with other disclosures discussed above, adequately supports the administration of “neridronic acid” in a human patient suffering from “abnormal sudomotor activity” that “is associated with CRPS.” *Id.* Petitioner’s attempt to narrowly read that disclosure as relating only to an administration of neridronic acid that occurs “‘early’ after a bone fracture” not only reads out of the disclosure the words “such as,” but also myopically focuses on a phrase in isolation without taking fair account of the totality of disclosure in the specification. *Id.* at 75.

In sum, on this record, we find that the claims as originally filed provide written description support for the claims as issued in the ’774 patent. *Compare* Ex. 1036, 145–147 (claims 1–30, as originally filed), *with* Ex. 1002, claims 1–29 (as issued). But even if we set aside that circumstance, other disclosures, discussed above, provide written description support for the claims—support that is addressed inadequately, if at all, by Petitioner and Dr. Poree. Pet. 72–75 (including citations to Ex. 1004). Accordingly, we find that Petitioner fails to show that any challenged claim is more likely than not invalid for lack of written description support.

*F. Motion to Exclude*

Patent Owner's motion to exclude evidence seeks to exclude all or parts of Exhibits 1004, 1006–1010, 1038, 1040, and 1043–1046. Mot. Exclude 1. We consider the arguments for each exhibit separately.

*1. Exhibit 1004: Declaration of Dr. Poree*

Patent Owner moves to exclude any portion of Dr. Poree's declaration that relies on Exhibits 1006, 1007, 1008, 1009, or 1010. Mot. Exclude 1–2. Patent Owner relies on the argument, discussed below, that each of Exhibits 1006–1010 is itself inadmissible. *Id.* As discussed below, however, we are not persuaded that Exhibits 1006–1010 should be excluded as inadmissible. Accordingly, we deny Patent Owner's motion to exclude Dr. Poree's testimony.

*2. Exhibit 1006: Varenna 2011*

Patent Owner moves to exclude the phrases "OTTOBRE 2011," "ARTICOLO ORIGINALE," "Ricevuto il 15 luglio 2011," and "Accettato il 30 agosto 2011," as they appear on the face of Varenna 2011. Mot. Exclude 2. The English translations of these phrases are, respectively, "October 2011," "Original Article," "Received on July 15, 2011," and "Accepted on August 30, 2011." Ex. 1006, 227. According to Patent Owner, each of these phrases is hearsay and should be excluded. Mot. Exclude 2; Reply Mot. 1–3.

We are not persuaded that "October 2011" should be excluded. Assuming that "October 2011" is hearsay, it is still admissible evidence under Rule 807 of the Federal Rules of Evidence. *See* Opp. Mot. 3–4 (asserting this hearsay exception). Under Rule 807, a statement "is not excluded," even if it is hearsay, if it meets two requirements. First, the

statement must be “supported by sufficient guarantees of trustworthiness—after considering the totality of circumstances under which it was made and evidence, if any, corroborating the statement.” Fed. R. Evid. 807(a)(1).

Second, the statement must be “more probative on the point for which it is offered than any other evidence that the proponent can obtain through reasonable efforts.” *Id.* at 807(a)(2). Here, both requirements are satisfied.

The statement “October 2011” on the face of Varena 2011 is offered to prove that Varena 2011 was published in October 2011. This statement is accompanied by several guarantees of trustworthiness. The statements “Received on July 15, 2011” and “Accepted on August 30, 2011,” when offered as corroboration of the October 2011 publication date, are not hearsay. Fed. R. Evid. 801 (statement is hearsay only if offered in evidence “to prove the truth of the matter asserted in the statement”). Accordingly, they may be admitted for this purpose, and they corroborate a publication in October 2011. Moreover, Exhibits 1038 and 1040 also provide some evidence that Varena 2011 was published in October 2011. Ex. 1038, 1 (article with same title as Varena 2011 published in “Fascicolo 5 2011”); Ex. 1040, 1 (“Fascicolo 5 2011” published in 2011). Thus, the record contains sufficient guarantees of trustworthiness of Varena 2011’s statement that Varena 2011 was published in October 2011. *See* Opp. Mot. 3 (citing Ex. 1004 ¶¶ 39–40).

We find that Varena 2011’s statement, indicating that the reference was published in October 2011, is “more probative on the point for which it is offered than any other evidence that the proponent can obtain through reasonable efforts.” Fed. R. Evid. 807(a)(2). It is difficult to imagine evidence more probative of the publication date of a journal article than the

article's own contemporaneous statement about when it was published.<sup>19</sup> See Opp. Mot. 2–4 (for well-supported arguments on point). Accordingly, we determine that the exception of Rule 807 applies, and we conclude that the statement “October 2011” in Varenna 2011 should not be excluded.

As discussed above, the statements “Received on July 15, 2011,” and “Accepted on August 30, 2011” in Varenna 2011 are not hearsay, because they are offered not to prove the date when the article was received or accepted but, rather, to corroborate the October 2011 publication date. Accordingly, we conclude that these statements should not be excluded.

In reaching our decision on the unpatentability of the challenged claims, as well as on the admissibility of the evidence Patent Owner seeks to exclude, we do not rely on the statement “Original Article” on the face of “Varenna 2011.” Accordingly, we dismiss Patent Owner's motion to exclude this statement as moot.

### 3. *Exhibit 1007: Muratore*

Patent Owner moves to exclude the statements “S/2004,” “2004-07-19,” “Volume 5,” “Supplemento 1/2004,” “2004 ISSUE 1 SUPPLEMENT,” and “Maratea (PZ), 16-18 aprile 2004,” as they appear on the face of Muratore. Mot. Exclude 2–3. According to Patent Owner, each phrase is hearsay and should be excluded. *Id.*; Reply Mot. 1–3.

As with the statements discussed above on the face of Varenna 2011, the statements Patent Owner moves to exclude in Muratore include the statement of the publication date (“Maratea (PZ), 16-18 aprile 2004”) as

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<sup>19</sup> The authenticity of Varenna 2011 is not in dispute. Paper 8, 4–6 (objections to Ex. 1006, including no objection based on authenticity); Mot. Exclude 2 (declining to preserve any objection based on authenticity).

well as several statements offered to corroborate that date. The statements offered as corroboration are not hearsay, because they are not offered to prove their own truth. The corroborating statements, moreover, provide sufficient guarantees of trustworthiness of the reference's publication date. Muratore's own statement about its publication date, "affixed . . . long before the instant dispute began by wholly disinterested parties," is more probative than any other evidence of record. Opp. Mot. 3 (citation omitted). Accordingly, we conclude that none of the challenged statements in Muratore should be excluded.

4. *Exhibit 1008: Gatti*

Patent Owner moves to exclude two statements appearing on the face of Gatti: "Published online: 17 Sep 2009" and "© 2009 Informa UK Ltd." Mot. Exclude 3–4. According to Patent Owner, each of these statements is hearsay and should be excluded. *Id.*; Reply Mot. 1–3.

The statement regarding the copyright date is offered as corroboration of the September 17, 2009, publication date, rather than as proof of the date when copyright attached, so it is not hearsay. The statement that the article was published on September 17, 2009, satisfies the hearsay exception of Rule 807 for the same reasons discussed above with respect to similar statements in Varenna 2011 and Muratore. The record contains sufficient guarantees of the trustworthiness of the statement. Ex. 1008, 1305 (copyright date); Ex. 1044 ¶¶ 3–6 (testimony regarding publication process). In addition, an article's own statement regarding its publication date is more probative than any other evidence. Accordingly, we conclude that none of the challenged statements in Gatti should be excluded.

5. *Exhibit 1009: Harden*

Patent Owner moves to exclude several statements appearing on the face of Harden: “PAIN 150 (2010) 268-274,” “Received 18 November 2009,” “Received in revised form 19 March 2010,” “Accepted 20 April 2010,” and “© 2010 International Association for the Study of Pain.” Mot. Exclude 4–5. According to Patent Owner, each of these statements is hearsay and should be excluded. *Id.*; Reply Mot. 1–3.

The statement “PAIN 150 (2010) 268-274” may be considered to include a statement that Harden was published in 2010 that is offered to prove that Harden was published in 2010. Even if we interpret the statement as being offered for this hearsay purpose, however, it is admissible under Rule 807 for the same reasons discussed above with respect to the statements in Varenna 2011, Muratore, and Gatti. *See* Opp. Mot. 2–4 (Petitioner’s persuasive arguments on point). The remaining statements, all of which are offered for the non-hearsay purpose of corroborating the 2010 publication date, provide sufficient guarantees of trustworthiness, and there is no more probative evidence of an article’s publication date than the article’s own statement on that point. Accordingly, we conclude that none of the challenged statements in Harden should be excluded.

6. *Exhibit 1010: Drummond*

Patent Owner moves to exclude the statement “Pain Medicine 2010” as it appears on the face of Drummond. According to Patent Owner, this statement is hearsay and should be excluded. Mot. Exclude 5; Reply Mot. 1–3.

As noted above (*supra* 27 n.14), we do not rely on Drummond in reaching our decision in this case. Accordingly, we dismiss Patent Owner's motion to exclude a portion of Drummond as moot.

7. *Exhibit 1038: Relevance*

Patent Owner moves to exclude the entirety of Exhibit 1038 as irrelevant because, given the 2015 and 2019 dates on its face, "it has no bearing upon the determination of what a [person of ordinary skill in the art] would have known before the priority date of May 14, 2012." Mot. Exclude 6.

Evidence is relevant if "it has any tendency to make a fact more or less probable than it would be without the evidence," and "the fact is of consequence in determining the action." Fed. R. Evid. 401. Here, the fact in question is whether Varena 2011 was published before May 14, 2012. Patent Owner points to the date "1/2/2019" on the face of Exhibit 1038 (apparently the date the exhibit was printed), as well as the year 2015 in a URL appearing on page 3 of the exhibit, as evidence that the exhibit cannot bear any relevance to what happened before May 14, 2012. Mot. Exclude 5–6. But Exhibit 1038 also states multiple times that Varena 2011 was a part of "Fascicolo 5 2011." Ex. 1038, 1–3. Accordingly, we do not agree with Patent Owner that the exhibit does not tend to make a 2011 publication date any more likely. On the contrary, "[r]egardless of when the websites were retrieved or when the content was uploaded" for purposes of preparing Exhibit 1038 for this proceeding, the document nonetheless contains "independent evidence tending to support the fact that Varena 2011 was, in fact, published in October 2011." Opp. Mot. 10–11. Thus, we are not persuaded that Exhibit 1038 should be excluded as irrelevant.

8. *Exhibits 1040, 1043–1046: Reply Evidence*

Patent Owner argues that Exhibits 1040 and 1043–1046 should be excluded as untimely because Petitioner could have submitted them with the Petition but, instead, elected to submit them with the Reply. Mot.

Exclude 6–10. Each of these exhibits supports the printed-publication status of Petitioner’s asserted prior-art references, and Petitioner is permitted to file such evidence with its Reply when responding to an argument in Patent Owner’s Response, regarding the status of the asserted references as printed publications. *Hulu*, IPR2018-01039, Paper 29 at 15 (precedential). Here, Patent Owner raised such an argument, Response 4–17, so Petitioner’s submission of Exhibits 1040 and 1043–1046 with the Reply was timely. We deny Patent Owner’s motion to exclude these references as untimely.

9. *Exhibit 1040: Relevance*

Patent Owner moves to exclude the entirety of Exhibit 1040 as irrelevant. Mot. Exclude 10–11. Here, as with Exhibit 1038, the fact in question is whether Varenna 2011 was published before May 14, 2012. Patent Owner argues that Exhibit 1040 does not make such a publication date more or less likely. We disagree. Exhibit 1040 lists “Fascicolo 5 2011” under the heading “2011” on a page with headings for other years from 2012 through 2019. Ex. 1040, 1. Taken together with the evidence that Varenna 2011 was published as part of “Fascicolo 5 2011,” Ex. 1038, 1–3, this supports a finding that Varenna 2011 was published in 2011. Accordingly, we are not persuaded that Exhibit 1040 should be excluded as irrelevant.

*10. Exhibit 1043: Relevance*

Patent Owner moves to exclude the entirety of Exhibit 1043 as irrelevant. Mot. Exclude 11–13. Here, the fact in question is whether Muratore was published before May 14, 2012. Patent Owner argues that Exhibit 1043 does not make such a publication date more or less likely. We disagree. Exhibit 1043 contains the declaration testimony of David E. Cannady, who testifies that he has “nearly forty years of experience retrieving articles from the [National Library of Medicine],” that the copy of Muratore he retrieved from the library bore “a date/time stamp of ‘2004-07-19 10:33:34,’” and that, based on his experience, this stamp “represents the date/time Muratore was received by the [library].” Ex. 1043 ¶¶ 1, 7. This testimony tends to establish a publication date before May 14, 2012, because the article likely was printed and published near the time it was received by the National Library of Medicine in 2004. Accordingly, we are not persuaded that Exhibit 1043 should be excluded as irrelevant.

*11. Exhibit 1043: Personal Knowledge*

Patent Owner also seeks to exclude the statement in Exhibit 1043 that materials received by the National Library of Medicine are “added to the [library’s] General Collection—and therefore available and accessible to the public . . . within 7-10 days of receipt of the publication.” Mot. Exclude 12–13. Patent Owner argues that this statement is beyond the witness’s personal knowledge and, therefore, is not admissible under Fed. R. Evid. 602. *Id.* We do not rely on this testimony in reaching our decision in this case, so we dismiss this portion of Patent Owner’s motion to exclude as moot.

*12. Exhibit 1044: Relevance*

Patent Owner moves to exclude the entirety of Exhibit 1044 as irrelevant. Mot. Exclude 12–13. Here, the fact in question is whether Gatti was published before May 14, 2012. Patent Owner argues that Exhibit 1044 does not make such a publication date more or less likely. We disagree. Exhibit 1044 contains the declaration testimony of Corinne Militello, Esq., who testifies that she investigated the process her employer undertook to publish Gatti and that her investigation revealed dates for various steps in the publication process that are consistent with a publication date of September 17, 2009. Ex. 1044 ¶¶ 1–6. This testimony tends to establish a publication date before May 14, 2012. Accordingly, we are not persuaded that Exhibit 1044 should be excluded as irrelevant.

*13. Exhibits 1045 and 1046: Relevance*

Patent Owner moves to exclude the entirety of Exhibit 1045 and its English translation, Exhibit 1046, as irrelevant. Mot. Exclude 14–15. Here, the fact in question is whether Varenna 2011 was published before May 14, 2012. Patent Owner argues that Exhibits 1045 and 1046 do not make such a publication date more or less likely. We disagree. These exhibits provide testimony that some copies of Varenna 2011 were distributed to conference attendees on September 26, 2011, and that other copies were sent to subscribers in October 2011. Ex. 1046, 3. This testimony tends to establish a publication date before May 14, 2012, because no copies of an article published after May 14, 2012, could have been distributed either on September 26, 2011, or in October 2011. Accordingly, we are not persuaded that Exhibits 1045 and 1046 should be excluded as irrelevant.

*14. Exhibit 1046: Hearsay*

Patent Owner moves to exclude the entirety of Exhibit 1046 as hearsay. Mot. Exclude 15. We are not persuaded that Exhibit 1046 is hearsay. The exhibit is offered to corroborate a publication date of October 2011 for Varenna 2011, rather than as proof of the content of the statements it contains (that some copies of the article were distributed on September 26, 2011, or that other copies were sent to subscribers in October 2011). Reply 11. Accordingly, we are not persuaded that Exhibit 1046 should be excluded as hearsay.

*15. Conclusion as to Motion to Exclude*

We dismiss as moot those portions of Patent Owner's motion to exclude that seek to exclude exhibits on which we do not rely in reaching our decision. Specifically, as discussed above, we deny as moot Patent Owner's request to exclude portions of Exhibit 1006 for hearsay and portions of Exhibit 1010 and Exhibit 1043 for lack of personal knowledge. We deny the remainder of Patent Owner's motion to exclude.

CONCLUSION<sup>20</sup>

Upon consideration of the papers and evidence before us, we determine that Petitioner has proven by a preponderance of the evidence that

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<sup>20</sup> Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

claims 1–29 are unpatentable as obvious over the combination of Harden and one or more of Varenna 2011, Gatti, and Muratore. We also determine that Petitioner has not shown that any claim of the '774 is unpatentable for lack of written description. Finally, we partially deny and partially dismiss Patent Owner's motion to exclude evidence.

| <b>Claims</b>              | <b>35<br/>U.S.C. §</b> | <b>Reference(s)/Basis</b>                                | <b>Claims<br/>Shown<br/>Unpatentable</b> | <b>Claims<br/>Not Shown<br/>Unpatentable</b> |
|----------------------------|------------------------|----------------------------------------------------------|------------------------------------------|----------------------------------------------|
| 1–15                       | 103                    | Harden, Varenna<br>2011, Gatti,<br>Muratore,<br>Drummond | 1–15                                     |                                              |
| 16–29                      | 103                    | Harden, Varenna<br>2011, Gatti,<br>Muratore              | 16–29                                    |                                              |
| 1–29                       | 112                    | Written<br>Description                                   |                                          | 1–29                                         |
| <b>Overall<br/>Outcome</b> |                        |                                                          | 1–29                                     |                                              |

### ORDER

It is hereby

ORDERED that Petitioner has proven by a preponderance of the evidence that claims 1–29 of U.S. Patent No. 10,039,774 B2 are unpatentable;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 318(b), upon expiration of the time for appeal of this decision, or the termination of any such appeal, a certificate shall issue canceling claims 1–29 of U.S. Patent No. 10,039,774 B2;

FURTHER ORDERED that Patent Owner's motion to exclude portions of Exhibit 1006 for hearsay and portions of Exhibit 1010 and Exhibit 1043 for lack of personal knowledge is dismissed as moot;

FURTHER ORDERED that Patent Owner's motion to exclude is otherwise denied; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

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