2020 Pat. App. LEXIS 12114

Patent Trial and Appeal Board Representative Orders, Decisions and Notices

December 22, 2020, Decided

PGR2018-00092, Paper 31 ; Patent 9,820,999 B2

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

Reporter
2020 Pat. App. LEXIS 12114 *

GRÜNENTHAL GMBH,
Petitioner,
v.
ANTECIP BIOVENTURES II LLC,
Patent Owner.

Notice:

[*1] ROUTINE OPINION. Pursuant to the Patent Trial and Appeal Board Standard Operating Procedure 2, the opinion below has been designated a routine opinion.

Core Terms

patent, neridronic, patient, pain, acid, was, bone fracture, trigger, prior art, dose, anticipate, fracture, human being, filing date, bisphosphonate, syndrome, skill, disclosure, disease, has, clinical, unpatentability, precipitate, regional, printed, invent, regimen, routine, month, predispose

Counsel

FOR PETITIONER:

Daniel Minion

Bruce Haas

VENABLE LLP

dminion@venable.com

bchaas@venable.com

FOR PATENT OWNER:

Brent Johnson

Parrish Freeman

MASCHOFF BRENNAN

bjohnson@mabr.com

pfreeman@mabr.com

Panel: Before GRACE KARAFFA OBERMANN, SHERIDAN K. SNEDDEN, and CHRISTOPHER M. KAISER, Administrative Patent Judges.

Opinion By: SHERIDAN K. SNEDDEN

Opinion

SNEDDEN, *Administrative Patent Judge*.

JUDGMENT

Final Written Decision

Determining All Challenged Claims Unpatentable

35 U.S.C. § 328(a)

I. INTRODUCTION

We issue this revised Final Written Decision after our decision to grant Petitioner's Request for Rehearing (Paper 29) and vacate our original Final Written Decision (Paper 25).

This Final Written Decision is issued pursuant to 35 U.S.C. § 328(a) and 37 C.F.R. § 42.73. Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden of persuasion never shifts to Patent Owner. Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015). The evidentiary standard is a preponderance of the evidence. *See* 35 U.S.C. § 326(e) (2012); 37 C.F.R. § 42.1(d) (2018).

For the reasons that follow, we determine that Petitioner has established by a preponderance of the evidence that claims 1-30 of U.S. Patent No. 9,820,999 B2 (Ex. 1001, "the '999 patent ") are unpatentable.

A. Procedural Background

Petitioner filed a Petition requesting **[*2]** *inter partes* review of claims 1-30 ("the challenged claims") of the '999 patent . Paper 2 ("Pet."). Patent Owner did not file a Patent Owner Preliminary Response. Upon consideration of the information presented in the Petition, we instituted an *inter partes* review of claims 1-30 of the '999 patent on each ground of unpatentability set forth in the Petition. *See infra* Section I.E.

Subsequently, Patent Owner filed a Patent Owner Response (Paper 10; "PO Resp."), Petitioner filed a Reply (Paper 11; "Reply"), and Patent Owner filed a Sur-Reply (Paper 18; "Sur-Reply").

The Petition is supported by the Declaration of Lawrence Poree, M.D., Ph.D. Ex. 1003. In its Reply, Petitioner relies on the Declaration of Dr. Philip Robinson, MBChB, PhD, FRACP (Ex. 1044).

Oral argument was conducted on November 21, 2019. A transcript is entered as Paper 23 ("Tr.").

Petitioner timely filed a Request for Rehearing (Paper 26, "Req. Reh'g.") requesting rehearing of our original Final Written Decision (Paper 25). We granted Petitioner's request for rehearing and vacated our original Final Written Decision. Paper 29.

In this revised, corrected Final Written Decision, we address all arguments and evidence set forth in the Papers to the extent **[*3]** necessary to resolve the dispute between the parties.

B. The '999 Patent (Ex. 1001)

The '999 patent is titled "Neridronic Acid for Treating Complex Regional Pain Syndrome." Ex. 1001, [54]. The specification of the '999 patent describes "[o]steoclast inhibitors, such as neridronic acid, in an acid or salt form" for treating or alleviating "pain or related conditions, such as complex regional pain syndrome" ("CRPS"). *Id.*, [57]. Two bisphosphonates specifically discussed in the specification are zoledronic acid and neridronic acid. *See* Ex. 1001, Figs. 1-16, 2:64-4:3 (figures and descriptions of figures, all pertaining to a method that employs zoledronic acid); *see also id.* at 2:50-60, 4:8 (identifying both zoledronic acid and neridronic acid as useful for treating CRPS triggered by bone fracture).

The '999 patent specification discusses a method of administering bisphosphonates--and, in particular, zolendronic acid or neridronic acid--for treating "bone fractures or to enhance the healing of bone fractures" in "a human being that is treated for CRPS, suffered from a precipitating injury such as a bone fracture." *Id.* at 8:27-37. The specification, moreover, states that "[a]n oral dosage form of bisphosphonate such as zoledronic acid may be used **[*4]** to treat, or provide relief of, any type of pain including, but not limited to," for example, CRPS. *Id.* at 7:43-52. The specification identifies "bisphosphonate" compounds generally, and neridronic acid in particular, as useful for mitigating "pain associated" with, for example, "vertebral crush fractures" in a human being. Ex. 1001, 7:66-8:19, 8:64-67, 15:25-37, 91:5-7 (Embodiment 282), 93:50-94:5-32 (Embodiments 314-318).

Example 3 relates to "[t]he effect of orally administered zoledronic acid" in a "rat tibia fracture model of" CRPS. *Id.* at 51:28-30. Example 3 reports that zoledronic acid mitigates pain associated with CRPS, where that condition is induced in "rats by fracturing the right distal tibias of the animals." *Id.* at 51:30-31. Example 3 discusses pain assessment methods and pain reduction achieved in the rat tibia fracture model when zoledronic acid is selected as the bisphosphonate. *Id.* at 51:47-52:11. In addition, Example 3 explains that "[t]his animal model has been shown to replicate the inciting trauma" (for example, a bone "fracture") that is "observed in human CRPS patients." *Id.* at 51:33-38.

The '999 patent includes no working example using neridronic acid as the bisphosphonate. **[*5]** The general disclosure provides dosing information pertaining to neridronic acid when that compound is selected for use in the claimed method. *See, e.g., id.* at 26:30-43.

C. Illustrative Claim

Claim 1, the only independent challenged claim, is illustrative and reproduced below:

1. A method of treating pain associated with complex regional pain syndrome (CRPS) comprising selecting *a human being having CRPS triggered by bone fracture* and administering neridronic acid or a pharmaceutically acceptable salt thereof to the human being, wherein the treatment is effective in reducing pain.

Ex. 1001, 106:25-30 (emphasis added).

The other challenged claims (namely, claims 2-30) depend directly or indirectly from claim 1 and specify additional limitations that pertain to the type of CRPS, the form of neridronic acid, the method of administration, the age of the treated human being, baseline pain intensity, and dosing regimens. *See id.* at 106:31-107:26.

D. Asserted Prior Art

The Petition identifies the following references as prior art in the grounds of unpatentability:

(1) M. Varenna et al., *Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study*, RHEUMATOLOGY 52:534-42 (NOV. 2012) (Ex. 1005, "Varenna 2012");

(2) M. Varenna et al., *Predictors of responsiveness to bisphosphonate treatment in patients with complex regional pain syndrome type I: A retrospective chart analysis*, PAIN MED. 18:1131-38 (2017) (Ex. 1015, "Varenna 2016");

(3) Manara et al., *SAT0524 Predictors of a Clinical Response to Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I*, ANNALS OF **[*6]** THE RHEUMATIC DISEASES, 73 (Suppl. 2) (2014) (Ex. 1037, "Manara");

(4) S. Bruehl, " *How common is complex regional pain syndrome-Type I*?," PAIN 129:1-2 (2007) (Ex. 1006, "Bruehl");

(5) D. Gatti et al., *Neridronic acid for the treatment of bone metabolic diseases*, EXPERT OP. ON DRUG METABOLISM & TOXICOLOGY 5(10): 1305-11 (Sept. 2009) (Ex. 1007, "Gatti");

(6) G. La Montagna et al., *Successful neridronate therapy in transient osteoporosis of the hip*, CLIN. RHEUMATOL. 24: 67-69 (Aug. 2004) (Ex. 1008, "La Montagna");

(7) D. Manicourt et al., *Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity*, ARTHRITIS & RHEUMATISM 50(11): 3690-97 (Nov. 2004) (Ex. 1009, "Manicourt");

(8) M. Muratore et al., *Il neridronato nel trattamento dell'algodistrofia simpatica riflessa dell'anca: confronto in aperto con il clodronato*, PROGRESSI IN RHEUMATOLOGIA, ABSTRACT BOOK VII CONGRESSO NAZIONALE COLLEGIO DEI REUMATOLOGI OSPEDALIERI 5 (Suppl. 1): 89 (April 16-18, 2004) (certified English translation) (Ex. 1010, "Muratore"); and

(9) Schwarzer & Maier, *Complex regional pain syndrome, in* GUIDE TO PAIN MANAGEMENT IN LOW-RESOURCE SETTINGS 249-254 (Kopf & Patel eds. 2010) (Ex. 1020, "Schwarzer").

E. Asserted Grounds of Unpatentability

We instituted review of claims 1-30 of the '999 patent as follows. Paper 7.

Claims	**35 U.S.C. §** [1]	**Reference(s)/Basis**

[1] The Leahy-Smith America Invents Act ("AIA"), ***Pub. L. No. 112-29*** , ***125 Stat. 284*** , 287-88 (2011), amended *35 U.S.C. §§ 102* and *103* . Because the '514 patent was filed before March 16, 2013 (the effective date of the relevant amendment), the pre-AIA version of § 103 applies.

Claims	35 U.S.C. § [1]	Reference(s)/Basis
1-4, 9, 10, 12, 14, 16-18, 23-25, 27-29	102(a)	Varenna 2012 **[*7]**
1-4, 9, 10, 12, 14, 16-18, 23-25, 27-28	02(a)	Varenna 2016
1-4, 9, 10, 12, 14, 16-18, 24-25, 27-28	02(a)	Manara Varenna 2012, Varenna 2016, Manara, Bruehl
1-4, 9-20, 22-29	103(a)	Gatti, La Montagna, Muratore
5-8, 21	103(a)	Varenna 2012, Varenna 2016, Manara, and Manicourt
30	103(a)	Varenna 2012, Varenna 2016 Manara, Schwarzer, Bruehl, Gatti, La Montagna, Muratore
1-30	112(a), Enablement	

II. ANALYSIS

A. Level of Ordinary Skill in the Art

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art ("POSA") at the time of the invention. Petitioner argues that an ordinarily skilled artisan would have had "an M.D. or a Ph.D. in a pain-medicine-relevant discipline, such as clinical health psychology or neuroscience, and at least 3-5 years of experience in the treatment of CRPS or related chronic pain conditions, or in the study of CRPS or related types of chronic pain." Pet. 13-14 (citing Ex. 1003 P 20).

Patent Owner disputes Petitioner's definition for a person of ordinary skill in the art. PO Resp. 2. Patent Owner contends that the "claims are directed to methods of treating pain associated with CRPS using a medication, i.e. neridronic acid," and as such, "a POSA would have an **[*8]** M.D. or a Ph.D. in a discipline related to the interaction of drugs with a human body, such as biology, pharmacology, etc., and experience in supervising, carrying out, or collaborating in animal or human testing, including off-label treatment of patients related to drug development in the pain area." *Id.* at 2-3.

Having considered the parties' positions and evidence of record, summarized above, we agree with Patent Owner that the claims are limited to methods of treating pain associated with CRPS and agree that the definition of a person of ordinary skill in the art should likewise include those persons having the relevant education and sufficient clinical expertise in treating patients with pain associated with CRPS. That said, we discern no material differences between the parties' respective definitions that would alter the outcome of our decision based on our acceptance of one over the other.

We further note that prior art may also demonstrate the level of skill in the art at the time of the invention. *See* *Okajima v. Bourdeau, 261 F.3d 1350, 1355 (Fed. Cir. 2001)* (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") **[*9]** (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp., 755 F.2d 158, 163 (Fed. Cir. 1985))*.

B. Claim Construction

For petitions filed before November 13, 2018, we interpret the claims of an unexpired patent that will not expire before issuance of a final written decision using the broadest reasonable interpretation in light of the specification. *See* 37 C.F.R. § 42.100(b) (2018) [2]; *Cuozzo Speed Techs., LLC v. Lee, 136 S. Ct. 2131, 2144-46 (2016)*. Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007)*. Only terms that 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)*.

Petitioner proposes claim constructions for the claim terms set forth in the table below. Pet. 14-18.

Term	Claims	Petitioner's Proposed Construction
"A method of treating pain associated with complex regional pain syndrome (CRPS) comprising selecting a human being having CRPS"	1-30	Requires that neridronic acid be administered to a human being having CRPS for the purpose of diagnosing, curing, mitigating, or preventing pain associated with CRPS, or for activity that otherwise affects the structure or any function of the body in a human being with CRPS.
"triggered by bone fracture"	1-30	Synonymous with **[*10]** fracture as a "precipitating event" or "predisposing event," i.e., a bone fracture causes or contributes to the occurrence or onset of CRPS.
"wherein the treatment is effective in reducing pain"	1-30	The treatment actually results in an observed and/or measured reduction in pain in a patient.

We have considered Petitioner's claim constructions and adopt Petitioner's undisputed construction for the terms "triggered by bone fracture" and "wherein the treatment is effective in reducing pain." Petitioner's construction of those terms aligns with the plain words of the claim, finds support in the uncontroverted testimony of Dr. Poree, and is not contested by Patent Owner. Pet. 14-15; Ex. 1003 PP 35-41; *see* PO Resp. 3-4 (Patent Owner, nowhere opposing that construction).

Patent Owner disputes Petitioner's construction for "[a] method of treating pain associated with complex regional pain syndrome (CRPS) comprising selecting a human being having CRPS" in claim 1 of the '999 patent . PO Resp. 3-4. Patent Owner first notes that the term "comprising" transitions from the preamble "[a] method of treating pain associated with complex regional pain syndrome (CRPS)" to the body of the claim, which begins with the verb "selecting." Next, Patent Owner contends that the first element in the body of the claims is "selecting a human being having CRPS triggered by a bone fracture," and that Petitioner's proposed construction reads the term "selecting" out of the claim. *Id.*

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[2] An amendment to this rule does not apply here, because the Petition was filed before November 13, 2018. *See* *Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018)* (amending *37 C.F.R. § 42.200(b)* effective November 13, 2018) (now codified at *37 C.F.R. § 42.100(b) (2019)*).

We agree with Patent Owner the term "selecting" appears in the body of the claim and that "selecting a human being having CRPS triggered by bone fracture" is a required element of the claims. To the extent further **[*11]** discussion of the meaning of this term is necessary to our decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

We determine that no express construction of any other claim term is necessary to determine whether Petitioner has shown by a preponderance of the evidence that the claims are unpatentable in this case.

C. Effective Filing Date of the '999 Patent

We next resolve the effective filing date of the '999 patent . When discussing the prior art status of Varenna 2012, Petitioner indicates that the effective filing date of the '999 patent is "May 14, 2013--the filing date of U.S. Patent Application No. 13/894,274" ("the '274 application"). Pet. 32; *see* Ex. 1001, [63] (identifying the '274 application as a priority document). Elsewhere in the Petition, however, Petitioner repeatedly asserts that the earliest possible effective filing date is December 7, 2016--that is, the filing date of Provisional Application No. 62/431,287 ("the '287 application"), which is the third-filed of three provisional applications identified on the face of the '999 patent . Pet. 9, 11-12, 16, 20, 24 n.1, 45-46; *see* Ex. 1001, [60] (claiming priority through three provisional applications, including the '287 application). **[*12]** For reasons explained below, we find that the effective filing date of the '999 patent is May 14, 2013, the filing date of the '274 application. *See* Ex. 1001, [63] (identifying chain of priority from May 14, 2013, the filing date of the '274 application).

Petitioner acknowledges that the '999 patent claims the benefit of priority not only from the filing date of the '274 application, but also from the filing date of Provisional Application No. 61/646,538 ("the '538 application"), which is the first-filed provisional application identified on the face of the '999 patent . Pet. 32; *see* Ex. 1001, [60] (identifying the '538 application, filed May 14, 2012); *see id.* at [63] (claiming priority also through the '247 application, filed May 14, 2013). The '538 application was filed on May 14, 2012. Petitioner argues that the disclosure of the '538 application, however, does not support the challenged claims because that application nowhere refers to the claim 1 limitation that requires "bone fracture as a triggering event for CRPS." *Id.* [3]

We find that Petitioner shows sufficiently that the disclosure of the '538 application does not support the claims of the '999 patent . *See* Pet. 20-24 (and evidence cited therein). Petitioner's **[*13]** information on that point is not challenged. On this record, we agree with Petitioner that the '538 application nowhere mentions any triggering events for CRPS and, further, that a person of ordinary skill in the art "would not have understood that administering neridronic acid to treat CRPS specifically triggered by bone fracture was an aspect of the alleged invention." Pet. 20; Ex. 1003 P 45 (Dr. Poree's assertion that "[t]he terms 'bone,' 'fracture,' and 'triggered' do not appear anywhere in the ['538] application"), P 46 (Dr. Poree's further assertion that "[n]othing in the '538 application suggests that the patentee was in possession of a method of treating pain associated with CRPS triggered by bone fracture" or "that this was even an aspect of the alleged invention"); *see* Ex. 1016, 4-6 (disclosure from the '538 application, nowhere mentioning bone fracture as a triggering event for CRPS).

Petitioner does not show adequately, however, that the '999 patent is not entitled to claim the benefit of the filing date of the '274 application, which was filed on May 14, 2013. Ex. 1001, [63] (the '999 patent , identifying the '274 application as a priority document); *see, e.g.*, Pet. 9, 11-12, 16, 20, 24 n.1, 45-46 (Petitioner, **[*14]** asserting that the earliest possible effective priority date is December 7, 2016, but failing to account adequately for the claim of priority that derives from the filing date of the '274 application). On that point, Petitioner argues only that the '274

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[3] Elsewhere in the Petition, Petitioner asserts that the '999 patent claims are not entitled to the benefit of the filing date of the second-filed Provisional Application No. 62/378,140 ("the '140 application"), which was filed on August 22, 2016. Pet. 29. We agree with Petitioner that the '140 application "does not even mention neridronic acid at all." *Id.*; *see generally* Ex. 1029, 9-35 (the '140 application). We disagree with Petitioner's further contention, however, that the '140 application does not support the limitation that requires bone fracture as a triggering event for CRPS. Pet. 46. In that regard, the '140 application discloses "[t]he therapeutic efficacy of bisphosphonate treatment in the rat CRPS fracture model"--including data pertaining to a rat tibia fracture study, which demonstrates "that bisphosphonate therapy inhibits pain . . . in the rat fracture model of CRPS." Ex. 1029, 9, 11, 23.

application contains no "additional information about how to treat CRPS with neridronate other than the limited information in the '999 patent specification." Pet. 29. Significantly, however, the '274 application identifies "neridronate or neridronic acid" as "another bisphosphonate" that "may also be useful to treat complex regional pain syndrome" and "acute vertebral crush fracture." Ex. 1024 PP 23, 37, claim 79. The '274 application expressly defines "[t]he term 'treating' or 'treatment'" to "broadly include any kind of treatment activity, including . . . mitigation or prevention of disease in man . . . or any activity that otherwise affects the structure or any function of the body of man." *Id.* P 24. The '274 application also discloses data, in Example 3, which specifically addresses the efficacy of administering a bisphosphonate compound, and reports the results of a rat tibia fracture model study, which includes pain assessments performed on rats having CRPS triggered by bone fractures. *Id.* PP 97-101.

On this record, we reject Petitioner's contention that the '274 application fails to support the limitation of claim 1 that requires the effective treatment of pain associated with CRPS triggered by bone fracture. Pet. 32. Accordingly, we assign the '999 patent an effective filing date of May 14, 2013--the date of filing of the '274 application. Ex. 1001, [63].

D. Varenna 2012 is a Prior Art Printed Publication

Inter partes review may be requested only "on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. 311(b) . There is no presumption in favor of finding that a reference is a printed publication. *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 12-14 (PTAB Dec. 20, 2019) (precedential). To qualify as a "printed publication" within the meaning of § 102, a reference "must have been sufficiently accessible **[*15]** to the public interested in the art" before the critical date. *In re Cronyn, 890 F.2d 1158, 1160 (Fed. Cir. 1989)*. Whether a reference is publicly accessible is determined on a case-by-case basis based on the "facts and circumstances surrounding the reference's disclosure to members of the public." *In re Lister, 583 F.3d 1307, 1311 (Fed. Cir. 2009)*.

A reference is 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.*; *see also Acceleration Bay, LLC v. Activision Blizzard Inc., 908 F.3d 765, 772 (Fed. Cir. 2018)* ("A reference is 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.'").

In the present case, Patent Owner argues that Petitioner cites to no evidence to support its contention that Varenna 2012 was publicly accessible before the effective filing date of the invention and therefore prior art to the '999 patent . PO Resp. 4-13. Patent Owner contends that the only evidence entered in support of the Petition is Ex. 1005, "a .pdf file downloaded from the Internet on December 6, 2017." PO Resp. 4-5; Ex. 1005. Patent Owner contends that **[*16]** "[s]omething downloaded from the Internet on December 6, 2017, is obviously not prior art to something having a priority date of May 14, 2013, such as the '999 patent ." *Id.* at 5; Sur-Reply 6-7. Patent Owner further contends that a copyright notice standing alone does not constitute evidence demonstrating that Varenna 2012 was in fact publicly accessible before the priority date of May 14, 2013. PO Resp. 5-6; Sur-Reply 12-13.

In its Reply, Petitioner contends that it has provided sufficient evidence demonstrating that Varenna 2012 is a prior art printed publication to the '999 patent . Reply 5-11. Specifically, Petitioner argues that

> Varenna 2012 was plainly published, i.e. made publicly available, before [earliest possible priority date of May 14, 2013]. At the top of the first page, Varenna 2012 expressly states that it is an article from the journal *Rheumatology* published on November 30, 2012. Ex. 1005 at 534. Moreover, the copyright line at the bottom of the first page reads: "(c) The Author 2012. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: *journals.permissions@oup.com*." *Id.* This indicates that Varenna 2012 was published in 2012 by a well-known and reputable publisher.

Id. at 5. In its Reply, Petitioner additionally relies on the Declaration of Dr. Philip Robinson, who testifies that he accessed, reviewed, and posted about Varenna 2012 on the social media site Twitter in February 2013, which is before the May 14, 2013 priority date of the '999 patent . Ex. 1044; Reply 11.

We have considered the parties' positions, summarized above, and find Petitioner to have the better position. In reaching our determination, we weigh the totality of the evidence currently **[*17]** in the record to resolve the dispute between the parties of whether Varenna 2012 is a prior art printed publication. On one hand, we weigh the evidence supporting Petitioner's position that Varenna 2012 was published and made available to the interested scientific community via the journal Rheumatology prior to the priority date of the '999 patent , summarized above. Reply 7-11; Ex. 1005 (indicia on the face of the document); Ex. 1044. To that point, we are persuaded that the information pertaining to the publication of Varenna 2012 on the face of the document is sufficient to establish Varenna 2012 as a printed publication. *See, e.g.,* *Telefonaktiebolaget LM Ericsson v. TCL Corp., 941 F.3d 1341, 1344, 1347 (Fed. Cir. 2019)* (holding that "the date on the face of the journal" was part of the substantial evidence supporting PTAB's finding that a journal article was prior art); *Hulu*, at 17-20 ("[T]he indicia on the face of a reference, such as printed dates and stamps, are considered as part of the totality of the evidence.").

In particular, Varenna 2012 bears several hallmarks suggesting it was published in 2012 as part of a regularly distributed medical journal. These hallmarks include the name of the journal ("Rheumatology"); citation information reflecting the date, the volume number, and the pertinent page numbers of the journal ("2013; 52:534-542"); the dates the article was available to the public ("Advance Access publication 30 **[*18]** November 2012"); a link to the website of the journal ("*www.rheumatology.oxfordjournals.org*"); the publisher of the journal ("(c) The Author 2012. Published by Oxford University Press on behalf of the British Society for Rheumatology"); and where readers interested in learning more about the topic of Varenna 2012 can make inquiries ("Correspondence to: Silvano Adami, Rheumatology Unit, Policlinico GB Rossi, Piazzale Scuro, 37121 Verona, Italy"). Ex. 1005.

On the other hand, we consider the lack of evidence supporting Patent Owner's position that Varenna 2012 is not a printed publication. In this regard, we note that Patent Owner provides no evidence to counter the indicia on the face of Varenna 2012 or the testimony of Dr. Philip Robinson. PO Resp. 4-13; Sur-Reply 5-13. Indeed, Patent Owner does not even contest that Oxford University Press is a known publisher or that Rheumatology is an established journal. Tr. 30:13-21. Rather, Patent Owner's position is that Petitioner has failed to meet its burden of establishing Varenna 2012 as a prior art printed publication--that is, the indicia of publication on the face of the document are insufficient to establish the Varenna 2012 as a **[*19]** prior art printed publication. PO Resp. 8-10.

We also consider Patent Owner's attorney argument in response to the declaration evidence of Dr. Robinson, that

> This testimony does not show accessibility by interested POSAs. The declarant does not say, for example, whether he "accessed [and] reviewed" Varenna 2012 after a reasonably diligent search, or whether someone simply directed him to it. Nor does the declarant provide any information that would allow a conclusion that his mere possession of Varenna 2012 can be extrapolated to legally significant accessibility by interested POSAs at large. The declarant likewise says nothing about his Twitter following, that is, about whether some or all of his followers qualify as POSAs. Further diluting things, the declarant also attaches two versions of Varenna 2012 he purports are the same as they were on February 3, 2013, but that testimony defies belief. It would require a photographic and infallible memory of things seen and read over six years ago. At best it shows merely that the two articles may or may not be similar or identical to something the declarant saw or thinks he saw six years ago. Hyperlinks on the Internet are not static, **[*20]** so retrieving an article from a URL today does nothing to prove that article was there yesterday, or what it looked like yesterday. This evidence fails to establish the public accessibility of Varenna 2012 to the level the law requires.

Sur-Reply 23. It is well established that such bare attorney arguments cannot take the place of objective evidence and, thus, we accord them little evidentiary weight. *In re Payne, 606 F.2d 303, 315 (CCPA 1979)*; *In re Pearson, 494 F.2d 1399, 1405 (CCPA 1974)* ("Attorney's argument in a brief cannot take the place of evidence"). That bare attorney argument does not outweigh the objective proof advanced by Dr. Robinson showing that he accessed, reviewed, and posted about Varenna 2012 on the social media site Twitter in February 2013, which is before the

May 14, 2013 priority date of the '999 patent . *See* Ex. 1044 PP 5-7 (directing us to Exhibits A, B, and C, which tend to establish the veracity of Dr. Robinson's testimony on point). [4]

Having considered the parties' positions and evidence of record, summarized above, we determine the totality of the evidence--the indicia of publication on the face of the document and testimony of Dr. Robinson--supports a finding that Varenna 2012 was publicly available as of November 30, 2012, the "Advance Access" publication date on the face of the journal. We further credit the testimony of Dr. Robinson and are not persuaded by Patent Owner's **[*21]** bare attorney argument to the contrary. Attorney argument cannot take the place of evidence lacking in the record. *In re Pearson, 494 F.2d at 1405*.

In view of the above, we determine that Varenna 2012 qualifies as a prior art printed publication to the '999 patent .

E. The Asserted Grounds of Unpatentability

In this section, we address in turn the following grounds of unpatentability advanced in the Petition: (1) anticipation; (2) obviousness; and (3) lack of enablement. Pet. 8-9.

1. The Grounds Based on Anticipation

Petitioner asserts three anticipation grounds against claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29 based on, respectively, the disclosures of Varenna 2012, Varenna 2016, and Manara. Pet. 8. We address the three anticipation grounds in turn below.

a. Anticipation by Varenna 2012

Petitioner asserts that claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29 are anticipated by Varenna 2012. Pet. 31-44. We first address independent claim 1, then turn to the dependent challenged claims.

(i) Claim 1

The parties do not dispute that Varenna 2012 discloses administration of neridronic acid to human beings having CRPS as recited in claim 1. Pet. 33-34; Ex. 1003 P 87; PO Resp. 14-20. The dispute between the parties is whether Varenna 2012 expressly or inherently discloses the recited elements of 1) "selecting a human being **[*22]** having CRPS triggered by bone fracture" and 2) "wherein the treatment is effective in reducing pain" in patients with CRPS triggered by bone fracture. PO Resp. 14; Pet. 31-37 (information directed to anticipation of claim 1 by Varenna 2012); Ex. 1001, 106:25-30 (claim 1). For the reasons that follow, we determine that Varenna 2012 discloses each of the disputed elements of claim 1 and that Varenna 2012 anticipates claim 1.

(a) "selecting a human being having CRPS triggered by bone fracture"

With regard to the element of "selecting a human being having CRPS triggered by bone fracture," Petitioner contends that "this limitation should be construed as requiring the human being treated to have CRPS wherein a bone fracture caused or contributed to the occurrence or onset of CRPS, and is synonymous with bone fracture as a precipitating or predisposing event." Pet. 34. On this point, Petitioner contends that Varenna 2012

> discloses that 11 of the 41 patients enrolled in the neridronate arm of the study (26.8%) had fracture as a precipitating event for CRPS. Ex. 1005 at 536, Table 1; Ex. 1003 P 89. Of the 41 patients enrolled in the placebo arm, 17 had fracture as a precipitating event for CRPS (41.4%). Ex. 1005 at 536, Table 1; Ex. 1003 P

[4] Patent Owner moved to strike Dr. Robinson's Declaration and related portions of Petitioner's Reply, which we denied. Papers 11 and 24. Even if we set aside Dr. Robinson's Declaration, however, we are persuaded that the indicia of publication on the face of Varenna 2012 are sufficient to establish that Varenna 2012 was "sufficiently accessible to the public interested in the art" and "disseminated or otherwise made available" to the interested public before the critical date, and consequently, a printed publication. *Blue Calypso, LLC v. Groupon, Inc., 815 F.3d 1331, 1348 (Fed. Cir. 2016)*.

> 89. After the double-blind phase of **[*23]** the study concluded, the patients that had been on placebo were given neridronate following the same regimen (four 100-mg infusions over 10 days) as in the double-blind phase. Ex. 1005 at 535; Ex. 1003 P 90.

Pet. 34-35 (citing Ex. 1005, 534, 535; Ex. 1003 PP 87-90).

Petitioner further relies on Dr. Poree's declaration, wherein Dr. Poree specifically opines that the limitation "comprising selecting a human being having CRPS triggered by bone fracture" is disclosed in Varenna 2012. Ex. 1003 PP 86-90. Dr. Poree explains that "[t]his limitation requires the human being treated to have CRPS wherein a bone fracture caused or contributed to the occurrence or onset of CRPS, and has the same meaning as bone fracture as a precipitating or predisposing event for CRPS." *Id.* at P 86. Thus, according to Petitioner, "Varenna 2012 discloses selecting and treating a human being having CRPS triggered by bone fracture as required by claim 1." Pet. 35 (citing Ex. 1003 P 87).

Patent Owner contends that Varenna 2012 does not expressly disclose the claim requirement for "selecting a human being having CRPS triggered by bone fracture." PO Resp. 14. In short, Patent Owner argues that the study reported by Varenna 2012 did not select patients on the basis of having CRPS triggered by bone fracture, the study only happened to include such patients. PO Resp. 14-20; Sur-Reply 14-17. Specifically, Patent Owner contends that

> Varenna 2012 does not disclose deliberately selecting humans suffering from CRPS because their CRPS was caused by bone fracture. "Selecting" requires deliberation. It is not enough to simply apply the claimed method to people who happen to have CRPS that happens to have been caused by bone fracture; the selection must have been deliberately made based on those criteria. Varenna 2012 does not disclose "selecting" in this way.

Sur-Reply 14 (emphasis omitted).

To support its position, Patent Owner directs our attention to the section of Varenna **[*24]** 2012 that provides detail on the methods and criteria used to select patients for the study. *Id.* at 14-15 (citing Ex. 1005, 535). With reference to that section of Varenna 2012, Patent Owner contends that Varenna 2012 used at least 15 criteria to select patients for the study, however, "CRPS triggered by bone fracture" is not among the criteria used. *Id.* at 14-15 (citing Ex. 1005, 535). Specifically, Patent Owner contends that Varenna 2012

> contains at least 15 examples of "to choose from a number or group: pick out." These are at least: 1) patients fulfilled the Budapest criteria, 2) patients had involvement of hands or feet, 3) patients had an age of at least 18 years, 4) patients had disease duration no longer than 4 months, 5) patients had a VAS of at least 50 mm, 6) patients had abnormal uptake of the bone seeking agent in three-phase bone scintigraphy in both early and late phases, 6)[*sic*] female patients of childbearing age had a negative pregnancy test, 7) patients had no hepatic disease, 8) patients had no renal disease, 9) patients had no endocrine disease, 10) patients had no haematological disease, 11) patients had no cardiac disease, 12) patients had no pulmonary disease, 13) patients had no neurological disease, 14) patients had no routine laboratory abnormalities, and 15) patients had no prior treatment with bisphosphonates. Thus, Varenna 2012 did a great deal of selecting, but none that had to do with "selecting a human being having CRPS triggered by bone fracture."

Id. at 15 (emphasis omitted).

Patent Owner contends that Dr. Poree's **[*25]** declaration does not provide factual support for Petitioner's assertion that Varenna 2012 discloses selecting patients on the basis of having CRPS triggered by fracture. *Id.* at 17 (citing Ex. 1003 P 87). In particular, Patent Owner contends that Dr. Poree makes no express statement supporting Petitioner's notion that Varenna 2012 discloses selecting patients having CRPS triggered by fracture. *Id.* Thus, according to Patent Owner, Petitioner has "offered absolutely no evidence that Varenna 2012 discloses

selecting a human being having CRPS triggered by bone fracture, either expressly or inherently." *Id.*; Ex. 1003 PP 86-90.

Patent Owner further contends that

> [t]he only place where *Varenna 2012* even mentions bone fracture is in Table 1, and *Varenna 2012* makes it clear that patients were not selected for fracture as a precipitating event because assignment to neridronic acid treatment was random. *Varenna 2012* states that "[a] centrally computer-generated table of ***random*** numbers was used for the ***treatment assignment*** . Patients were treated with either neridronate . . . or placebo with an identical appearance in a 1:1 ratio . . . Neither patients nor investigators knew whether the assignment would be the placebo or the neridronate group." (Ex. 1005 at 535 (emphasis added).) Therefore, the element "selecting a human being having CRPS triggered by bone fracture" is not expressly or inherently found in *Varenna 2012*, and claims 1-30 are not anticipated by the reference.

PO Resp. 14-15.

Thus, according to Patent Owner, Varenna 2012 does not in fact disclose deliberate "selecting" based on CRPS having been caused by bone fracture. PO Resp. 14-20; Sur-Reply 14-17. "Rather, the Petition simply addresses **[*26]** the clause as if the word 'selecting' has no effect at all upon its meaning." Sur-Reply 16 (citing Pet. 34-35).

Having considered the parties' positions and evidence of record, summarized above, we determine that Varenna 2012 inherently discloses the required element of selecting a human being having CRPS triggered by bone fracture. Varenna discloses that a subset of the patients included in the human clinical study experienced bone "fracture" as a "[p]recipitating event" for CRPS. Ex. 1005, 536 (Table 1). Additionally, Varenna 2012 shows that the data collected was analyzed on the basis of precipitating events--that is, predisposing factors were among the variables analyzed. Ex. 1005, 536. Those precipitating events include fracture, trauma, and surgery. *Id.* at 536 (Table 1). While Varenna 2012 does not expressly disclose that those patients were selected because they have CRPS triggered by bone fracture, the study was designed to assess predisposing factors as a distinct variable in order "to assess the potential influence of baseline variables on treatment effect." *Id.* at 536 ("Multivariate regression analysis was performed to assess the potential influence of baseline variables on treatment effect [site of disease: (upper/lower limb), disease duration and precipitating event (none/trauma, surgery)].").

Additionally, Dr. Poree testifies that Varenna 2012 shows that patients having fracture-induced CRPS were selected for inclusion in the neridronate treatment study. Ex. 1003 P 89. More specifically, he testifies that 11 of the 41 patients included in the neridronate arm and 17 of 41 patients included in the placebo arm had fracture-induced CRPS. *Id.* at PP 88-90. We see no meaningful distinction between including a patient in a study, which involves **[*27]** treating that patient with neridronate, and selecting a patient for treatment with neridronate. Thus, in our view, the 11 patients included in the neridronate arm of the study were, in essence, selected for treatment with neridronate. Further, as Dr. Poree testifies, all of the patients in the placebo arm, including the 17 fracture-induced CRPS patients, who had initially been given placebo were then put into the open-extension phase of the study, in which they were given neridronate using the same regimen given to those patients initially in the treatment group. *Id.* at P 90. In other words, those 17 fracture-induced CRPS patients were included in the open-extension phase of the study (and, thereby, were selected for treatment with neridronate).

When we consider Dr. Poree's testimony with the results disclosed by Varenna 2012, we are persuaded that the totality of the evidence shows that Varenna 2012 discloses that CPRS triggered by bone fracture was among the criteria used to select patients and to determine treatment outcomes. That is, selecting a patient having CRPS triggered by bone fracture is inherent to the study design as evidence by the presentation of the results and statistical **[*28]** analysis based on predisposing factors in Varenna 2012.

(b) "wherein the treatment is effective in reducing pain"

With regard to the element of "wherein the treatment is effective in reducing pain," we are not persuaded by Patent Owner's argument that Varenna 2012 does not disclose that neridronic acid is effective in reducing pain in human patients having CRPS triggered by bone fracture. PO Resp. 14-16; Sur-Reply 17-22. Rather, we are persuaded that Petitioner advances information that sufficiently supports that factual contention. Pet. 36-37 (citing Ex. 1005, 534-538, Table 1; Ex. 1003 PP 95-100). In particular, we note that Varenna 2012 reports "the efficacy of the amino-bisphosphonate neridronate in patients with" CRPS, including "clinically relevant and persistent benefits" associated with the administration of neridronate. *Id.* at 33 (citing Ex. 1005 at 534; Ex. 1003 PP 83-84). Significantly, Varenna expressly teaches that neridronate effectively mitigates pain associated with CRPS in patients presenting with "bone fracture" as "a predisposing event for" that condition. Ex. 1001, 84:61-62; *see* Pet. 34-35 (citing, for example, Ex. 1005, 535-36, 538-39, Table 1; Ex. 1003 PP 87-90). Of particular significance is Varenna's identification of a subset of patients in a human clinical study that experienced bone "fracture" as a "[p]recipitating event" for CRPS. Ex. 1005, 536 (Table 1). Varenna reports that, in that subset of patients, the administration of neridronate effectively mitigated pain. Pet. 32-33, 37-39 (and evidence cited therein); Ex. 1005, 534, 536; Ex. 1003 PP 95-100.

Further to that point, we agree with Petitioner that Varenna 2012 discloses that "the particular type of precipitating event did not influence outcomes in the study, indicating that patients with all types of precipitating events, including fractures, benefited from the neridronate treatment." Pet. 37, 63 (citing Ex. 1003 PP 100, 234); *see* Ex. 1005, 538 (Varenna 2012, explaining, "[i]n multivariate regression analysis," no "baseline variables except treatment assignment" "appeared to influence outcome measures"). Here, we credit Dr. Poree's testimony on that point. Specifically, Dr. Poree states in his declaration that:

> A "[m]ultivariate regression analysis was performed to assess the potential influence of baseline variables on treatment effect [site of disease: (upper/lower limb), disease duration and precipitating event (none/trauma, surgery)]." Exhibit 1005, Varenna 2012 at 536. In the multivariate regression analysis, *baseline variables other than treatment assignment did not appear to influence outcome measures*.

Ex. 1003 P 99 (emphasis added).

Several other facts confirm our above analysis. Varenna informs, "[i]n patients with acute CRPS-I," the intravenous administration of neridronate is "associated with clinically relevant and persistent benefits." Ex. 1005, 534; *see* Pet. 36-39 (and evidence cited therein). Varenna reports results that provide "conclusive evidence that the use of bisphosphonates . . . is the treatment of choice for CRPS-I." Ex. 1005, 534. CRPS was known in the prior art as "a severely debilitating pain syndrome that sometimes develops after trauma such as a bone fracture." Pet. 1. Varenna discloses with anticipatory specificity the mitigation of pain in patients suffering from CRPS (including those in which that pain syndrome was triggered by bone fracture) by treatment with neridronate. Pet. 33-34, 36-37; Ex. 1005, 534, 536; Ex. 1003 PP 95-100. In addition, these facts are similar to *Montgomery* where the drug ramipril was administered to patients in need of stroke prevention and our reviewing court found that "efficacy is inherent in carrying out the claim steps." *In re Montgomery, 677 F.3d 1375, 1381 (Fed. Cir. 2012)*.

Accordingly, we determine, on this record, Petitioner shows sufficiently that pain was mitigated effectively in those patients by administration of neridronate. Pet. 33-34, 36-37 (and evidence cited therein).

(ii) Dependent Claims

Our analysis pertaining to claim 1 applies with equal force to dependent claims 2-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29, each of which depends directly or indirectly from claim 1.

Petitioner contends that Varenna 2012 anticipates the subject matter of dependent claims 2-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29. Pet. 39-46. To support its position, **[*29]** Petitioner provides a detailed discussion explaining how each claim limitation is disclosed in Varenna 2012. *Id.*

Patent Owner raises no new argument directed to any of those dependent claims. PO Resp. 14-20; Sur-Reply 14-22. Instead, Patent Owner relies on argument presented in the context of claim 1. *Id.*

Having considered the parties' positions and evidence of record, we are persuaded by Petitioner that Varenna 2012 discloses each element of claims 2-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29 for the reasons set forth in the Petition. *See* Pet. 39-46 (including substantial evidence cited therein). Accordingly, we determine that Varenna 2012 anticipates dependent claims 2-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29.

b. Anticipation by Varenna 2016

Petitioner asserts that claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27, 28 are anticipated by Varenna 2016. For reasons explained above, on this record, we find that the effective filing date of the '999 patent is May 14, 2013. Petitioner asserts that, "[a]lthough the issue of the journal" in which the reference appears "is dated June 2017, Varenna 2016 was first published on September 20, 2016." Pet. 45 (citing Ex. 1003 P 133). Even if we accept that contention, Varenna 2016 does not **[*30]** qualify as prior art against the '999 patent claims, because the reference was published after the effective filing date of the patent. Accordingly, on this record, we find that Petitioner has not shown that any challenged claim is anticipated by Varenna 2016.

c. Anticipation by Manara

Petitioner asserts that claims 1-4, 9, 10, 12, 14, 16-18, 24-25, and 27, 28 are anticipated by Manara. For reasons explained above, on this record, we find that the effective filing date of the '999 patent is May 14, 2013. Petitioner asserts that Manara was first published in June of 2014. Pet. 55-56. Even if we accept that contention, Manara does not qualify as prior art against the '999 patent claims, because the reference was published after the effective filing date of the patent. Accordingly, on this record, we find that Petitioner has not shown that any challenged claim is more likely than not anticipated by Manara.

2. The Grounds Based on Obviousness

a. Obviousness Grounds Relying on Varenna 2016 and Manara

Petitioner asserts a plurality of alternative obviousness grounds that depend on the contention that Varenna 2016 and Manara constitute prior art. Pet. 8, 62-79 (and evidence cited therein). For reasons explained above, we find that Petitioner fails to show sufficiently that those references are prior art against the **[*31]** '999 patent claims. *See supra*. Accordingly, for that reason, we find also that Petitioner fails to show that it is more likely than not that any challenged claim is unpatentable based on the obviousness grounds relying on Varenna 2016 and/or Manara. *See* Pet. 62-79 (obviousness grounds).

b. Obviousness Grounds Relying on Varenna 2012

It is axiomatic patent law that a disclosure that anticipates under *35 U.S.C. § 102* also may render the claim unpatentable under *35 U.S.C. § 103*, because anticipation is the epitome of obviousness. *See In re McDaniel, 293 F.3d 1379, 1385 (Fed.Cir.2002)* ("It is well settled that 'anticipation is the epitome of obviousness.'") (*quoting Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed.Cir.1983))*. In that regard, the Board is allowed to rely on findings regarding whether a reference anticipates a limitation in its obviousness analysis. *See Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc., 853 F.3d 1272, 1278 (Fed. Cir. 2017)* (stating approvingly in a footnote that the "Board noted that Oselin rendered [the challenged claims] obvious by virtue of its anticipation of them.").

Petitioner contends that claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29 are anticipated by Varenna 2012. Petitioner also relies on Varenna 2012 to assert three alternative obviousness grounds of unpatentability that, taken together, challenge the patentability of claims 1-30 of the '999 patent . Pet. 62-79. Thus, Petitioner relies on Varenna 2012 to argue separately that **[*32]** claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29 would have been obvious. We rely on our anticipation findings above to determine that determining that Varenna 2012 renders obvious claims 1-4, 9, 10, 12, 14, 16-18, 23-25, and 27-29.

We address below Petitioner's obviousness challenges to claims 5-8, 11, 13, 15, 19-22, 26, and 30 of the '999 patent to the extent those grounds rely on Varenna 2012.

(i) Obviousness of claims 11, 13, 15, 19-20, 22, 26, and 30 over the combination of Varenna 2012, Bruehl, Gatti, La Montagna, and Muratore

Dependent claims 11, 13, 15, 19-20, 22, and 26 all recite limitations that relate to specific neridronic acid dosing amounts, frequencies, and/or durations for the treatment of pain associated with CRPS triggered by bone fracture. Claims 11, 13, 15, 19-20, 22, and 26 are reproduced below (parenthetical text added):

> 11. The method of claim 9 [(reciting parenteral administration)], wherein a total of about 5 mg to about 200 mg of the neridronic acid is administered within one month.
>
> 13. The method of claim 9 [(reciting parenteral administration)], wherein a total of about 100 mg to about 300 mg of the neridronic acid is administered within one month.
>
> 15. The method of claim 1, wherein a total of about 100 mg to about 300 mg of the neridronic acid is administered.
>
> 19. The method **[*33]** of claim 4 [(reciting intravenous administration)], wherein each dose contains about 50 mg to about 65 mg of the neridronic acid.
>
> 20. The method of claim 19, wherein the neridronic acid is administered about every three days.
>
> 22. The method of claim 3 (reciting salt form of neridronic acid), wherein each dose contains an equivalent of about 50 mg to about 60 mg of the neridronic acid in an acid form.
>
> 26. The method of claim 1, wherein the neridronic acid is administered weekly for about four to about six weeks.

Ex. 1001, 106:50-107:25.

Petitioner acknowledges that "Varenna 2012 does not expressly disclose the additional limitations of these claims because in its clinical study, a total of 400 mg neridronate was administered within one month over a period of ten days." Pet. 71 (citing Ex. 1003 P 256). For the claim elements related to neridronic acid dosing amounts, frequencies, and/or durations, Petitioner relies on Gatti, La Montagna, and Muratore. Specifically, Petitioner contends that

> Gatti, Muratore, and La Montagna confirm to a POSA that neridronic acid can be used to treat patients with CRPS. La Montagna further teaches that patients with transient osteoporosis of the hip, **[*34]** which is associated with fracture, can be successfully treated with neridronic acid.

Pet. 67. Petitioner contends that "it would have been obvious, routine, and within the skill of a POSA to determine the dosing regimen of neridronic acid to administer for treatment of pain associated with CRPS triggered by fracture for a particular patient." *Id.* 71 (citing Ex. 1003 P 257). [5]

We now turn to the disclosures of Gatti, Muratore, and La Montagna and to the relevance of each of these references to claims 11, 13, 15, 19-20, 22, and 26. Gatti [6] reports that "[i]ntravenous high doses of bisphosphonates are increasingly used for the treatment of reflex sympathetic dystrophy syndrome or algodystrophy." [7] Ex. 1007, 1308. According to Gatti, "the most effective dose is 100 mg diluted in 250 ml of saline

[5] We find that Dr. Poree's testimony is conclusory and largely parrots the attorney argument in the Petition. Ex. 1003 PP 256-257.

[6] Gatti originally was written in Italian, but we refer to the English translation Petitioner submitted.

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%." *Id. at 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 **[*35]** syndrome has been designed and is underway." *Id.* Accordingly, we find that Gatti discloses intravenous administration of 100 mg neridronate administered within 4 days. That dosage regimen falls within the scope of claim 11 (about 5-200 mg of neridronic acid within one month), claim 13 (about 100-300 mg of neridronic acid within one month), and claim 15 (total of about 100-300 mg of neridronic acid).

Muratore reports the results of a comparison of neridronate and clodronate "in the treatment of reflex sympathetic hip algodystrophy." Ex. 1010, 89, 90. The purpose of the study was "[t]o evaluate the therapeutic 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 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. Accordingly, we find that Muratore discloses intravenous administration of 100 mg **[*36]** neridronate every 4 days 4 times, or 400 mg neridronate administered intravenously within about 2 weeks. We find Muratore's teaching of administering neridronate every 4 days to be particularly relevant to element of claim 20 (about every three days).

La Montagna reports a case study of a patient with "an uncommon case of bilateral transient osteoporosis of the hip (TOH)" who was "successfully treated" with 25 mg/month neridronate sodium for 6 months. Ex. 1008, 67-68. TOH "is a rare clinical syndrome characterized by transient osteopenia, rapidly or gradually increasing pain, and disability without deformity." *Id.* at 67.

Petitioner contends that the recited doses would have been obvious because "[t]he doses recited in claims 11, 13, 15, 19, and 22 are lower than the 400 mg total neridronic acid that was administered in the study reported in Varenna 2012." Pet. 71. Petitioner further contends that

> A POSA would be motivated to use the lowest dose that provides efficacy in a particular patient due to safety and side effect concerns. Ex. 1003 P 259. For example, in La Montagna, a dose of only 25 mg per month [of neridronate sodium] for six months was effective for treating transient osteoporosis of **[*37]** the hip, a type of CRPS. Ex. 1008 at 67-68; Ex. 1003 P 260. And, according to Varenna 2012, although the 400 mg neridronate dose had the best results, some degree of efficacy in certain patients was previously observed with smaller doses of 200 and 300 mg i.v. neridronate. Ex. 1005 at 540; Ex. 1003 P 260.

Id. at 71-72.

Petitioner further contends that the '999 patent specification 1) "lists dozens of different dosage ranges and states that any suitable amount of a bisphosphonate may be used;" 2) "attaches no criticality to any particular dosing regimen for any condition;" and 3) "does not suggest any critical dosing regimen for treating pain associated with CRPS triggered by fracture." *Id.* at 73. Thus, according to Petitioner, "it would have been within the level of ordinary skill in the art to determine the optimal dosing regimen of neridronic acid to use as claimed in challenged claims 11, 13, 15, 19-20, 22, and 26." *Id.* at 73-74. Petitioner further contends that "routine determination of the appropriate dose of a known drug is not inventive" and, more specifically, that "mere differences in concentration, proportions, or degree will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating **[*38]** such concentration, proportion, or degree is critical." *Id.* at 72-73 (citing *In re Williams, 17 C.C.P.A. 718, 722 (C.C.P.A. 1929)*; *In re Hoeschele, 406 F.2d 1403, 1406 (C.C.P.A. 1969)*; *Merck & Co., Inc. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989)* (describing "routine procedures" used to

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[7] According to Petitioner, "CRPS is also referred to as algodystrophy or reflex sympathetic dystrophy syndrome." Pet. 65, n.5 (citing Ex. 1007, 1308; Ex. 1003 P 243).

determine appropriate dose of drugs and finding that "experimentation needed to arrive at the claimed dosages was nothing more than routine")); *see also* Eli Lilly and Co. v. Actavis Elizabeth LLC, 435 Fed. Appx. 917, 922 (Fed. Cir. 2011) ("The optimum dose for each patient, as always, must be set by the physician in charge of the case, taking into account the patient's size, other medications which the patient requires, severity of the disorder and all of the other circumstances of the patient.").

Patent Owner presents no additional arguments regarding the obviousness challenge to these claims, except for the previously-discussed arguments addressed to claim 1. *See generally* PO Resp. and PO Sur-Reply.

Based on our review of Petitioner's unopposed argument and evidence, summarized above, which we adopt as our own findings, we conclude that the claimed neridronic acid dosing amounts, frequencies, and/or durations to be encompassed by or substantially similar to the treatment ranges and conditions disclosed in Varenna 2012, Gatti, La Montagna, and Muratore. That is, the combination of Varenna 2012, Gatti, La Montagna, and Muratore teaches or suggests general dosing **[*39]** regimens for neridronic acid for the treatment of CRPS or similar conditions and that a person of ordinary skill in the art would have reasonably expected the claimed dosing parameters to be achieved with routine optimization. Accordingly, we determine Petitioner has proven by a preponderance of evidence that claims 5-8 and 21 would have been obvious over the combination of Varenna 2012, Gatti, La Montagna, and Muratore.

(ii) Obviousness of claims 5-8 and 21 over the combination of Varenna 2012 and Manicourt

Claims 5-8 and 21 require oral administration of neridronic acid. Petitioner acknowledges that Varenna 2012 does not expressly disclose oral administration of neridronic acid. Pet. 74. Petitioner contends, however, that "it would have been obvious to a POSA to orally administer neridronic acid for the treatment of pain associated with CRPS triggered by fracture based upon the combination of Varenna 2012 . . . with Manicourt." *Id.*

Manicourt reports the results of a clinical study designed "[t]o evaluate the effects of the antiresorptive agent alendronate [8] at a daily oral dose of 40 mg in patients with posttraumatic complex regional pain syndrome type I (CRPS I) of the lower extremity." Ex. 1009, Abstr. The patients in the study exhibited various clinical characteristics **[*40]** of CRPS, including severe spontaneous pain, allodynia and hyperalgesia of the diseased area, and skin swelling and discoloration. *Id.* at 3691. The treatment group received daily doses of tablets containing 40 mg alendronate sodium for 8 weeks. *Id.* at 3691-92. Manicourt reports that "oral alendronate taken at a daily dose of 40 mg was well tolerated and appeared to be a very effective tool in the management of CRPS I." *Id.* at 3696.

Petitioner contends that a person of ordinary skill in the art would have had motivation to combine Varenna 2012 with Manicourt because

> As of at least 2012, the use of oral bisphosphonates would have been well-known to a POSA. Multiple bisphosphonates were marketed and prescribed orally, including Fosamax(R) (alendronate sodium) Tablets and Oral Solution, and Boniva(R) (ibandronate sodium) Tablets. Ex. 1018 at 1, 3; Ex. 1019 at 1-2; Ex. 1003 P 272. Therefore, a POSA reading Varenna 2012 . . . would have been motivated to look to other prior art examples of orally administered bisphosphonates, like Manicourt. Ex. 1003 P 272. A POSA would have been motivated to combine the disclosures of Varenna 2012 . . . with Manicourt to administer neridronic acid in an oral formulation because all of these references concern clinical trials investigating the use of bisphosphonates to treat CRPS, and both included patients with fracture as a predisposing or triggering event. *Id.* P 271. Manicourt teaches a POSA that a pharmaceutically acceptable oral formulation of alendronate, one which was "well **[*41]** tolerated" and "effective," was possible. Therefore a POSA would have been motivated to administer neridronic acid orally. *Id.* P 272.

Pet. 75-76.

[8] Alendronate is another bisphosphonate compound, like neridronic acid. Ex. 1003 P 265; Ex. 1001, 4:6-13.

Patent Owner presents no additional arguments regarding the obviousness challenge to these claims, except for the previously-discussed arguments addressed to claim 1. *See generally* PO Resp. and PO Sur-Reply.

Based on our review of Petitioner's argument and evidence, summarized above, which we adopt as our own findings, we conclude that Petitioner has proven by a preponderance of evidence that claims 5-8 and 21 would have been obvious over the combination of Varenna 2012 and Manicourt.

(iii) Obviousness of claim 30 over the combination of Varenna 2012, Schwarzer, Bruehl, Gatti, La Montagna, and Muratore

Claim 30 depends from claim 1 and further requires that the CRPS be CRPS type II. Petitioner acknowledges that Varenna 2012 does not expressly disclose treating CRPS type II, but contends that "it would have been obvious to a POSA to administer neridronic acid for the treatment of pain associated with CRPS type II wherein bone fracture is a predisposing or triggering event." Pet. 77. Citing Schwarzer, Petitioner contends that it was known that "there are no clinical differences between CRPS type I and type II; expect for the nerve damage," and therefore "would **[*42]** have understood that the treatment options available for CRPS could be used in either type of CRPS." *Id.* at 77-78. In particular, Petitioner directs our attention to Schwarzer and contends that

> Schwarzer notes that two types of CRPS are recognized, CRPS type I without nerve injury, and CRPS type II which is associated with major nerve injury. Ex. 1020 at 249; Ex. 1003 P280. However, the authors drop this distinction soon after making it: in describing the treatment options, clinical symptoms, diagnostic criteria, main characteristics, incidence, and prognosis of the disease, Schwarzer refers to CRPS generally, encompassing both CRPS I and CRPS II. Ex. 1003 P282; *see generally* Ex. 1020.

Id.

Patent Owner presents no additional arguments regarding the obviousness challenge to claim 30, except for the previously-discussed arguments addressed to claim 1. *See generally* PO Resp. and PO Sur-Reply.

Having considered the parties' positions and evidence of record, summarized above, we find the preponderance of evidence of record to support Petitioner's position that a person of ordinary skill in the art would have understood that the treatment options available for CRPS could be used in either type I or type II of **[*43]** CRPS. Accordingly, for the reasons discussed above, Petitioner has shown by a preponderance of the evidence that claim 30 of the '999 patent would have been obvious over the combination of Varenna 2012, Schwarzer, Bruehl, Gatti, La Montagna, and Muratore.

3. The Ground Based on Lack of Enablement

We next address Petitioner's assertion that the '999 patent specification fails to enable the claimed invention. Pet. 25-30. We evaluate enablement by considering whether the patent disclosure, at the time of filing, [9] would have enabled a person of ordinary skill in art to make and use the subject matter of the claims. *In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)*. The touchstone of enablement is whether undue experimentation would have been required to practice the claimed invention. *Id.*

At the outset, we note that Petitioner has established that Varenna 2012 anticipates many of the challenged claims, including independent claim 1. *See supra*. That circumstance appears inconsistent with Petitioner's further view that the degree of detail and guidance provided in the specification is inadequate in view of the state of the prior art as revealed by the disclosure of Varenna 2012. Pet. 26-29. Significantly, on that point, Petitioner admits that "methods of treating pain associated with CRPS with **[*44]** neridronic acid--including pain associated with CRPS triggered by fracture--were known in the prior art." *Id.* at 30.

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[9] We follow Petitioner's convention of referring to the '999 patent specification, rather than any priority application, when discussing the ground based on lack of enablement. Pet. 26-28.

Having considered Varenna 2012 and Petitioner's arguments and evidence related to Varenna 2012, we find that the disclosure of Varenna 2012 would have informed an ordinary artisan, well before the critical date, exactly how to administer neridronic acid to humans having CRPS triggered by bone fracture with an expectation of mitigating pain associated with that condition. Ex. 1005, 534 (Abstract), 535 (study design), 536 (Table 1 and results and efficacy data), 538 (Table 2 and discussion of improvement in pain symptoms upon treatment with neridronate). That finding is fully consistent with views formed by the Examiner during patent prosecution. Ex. 1022, 454 ("[T]he dosage forms and the herein claimed routes of administration and the dosing regimens are all well-known according to the teachings of the cited prior art. The dosage of neridronic acid taught in the prior art encompasses the herein claimed dosage."). On that point, we observe that Varenna 2012--which is cited on the face of the '999 patent (Ex. 1001 (56))--was among the prior art references before the Examiner.

The **[*45]** information advanced in the Petition does not account adequately for the fact that Varenna 2012 establishes a level of ordinary skill in the art that makes reasonable the degree of detail set forth in the specification. Pet. 26-29. "The specification need not disclose what is well known in the art." *In re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991)*. On this record, the Petition does not advance information from which we reasonably can find that any experimentation, much less undue experimentation, would have been necessary to enable the claimed invention. Pet. 26-29. Here, we take account of both the disclosures set forth within the specification and the general knowledge of an ordinarily skilled artisan as demonstrated by Varenna 2012. *See, e.g.*, Ex. 1001, 2:59-60, 4:7-13, 7:38-8:38, 26:30-43, 33:26-57, 42:7-46:59, 51:24-52:61, 71:38-42, 72:12-15 (patent disclosures); Ex. 1005 (Varenna 2012). The state of the prior art informs our decision that the specification includes details and guidance that, under the particular facts and circumstances of this case, sufficiently enable the claims.

An enabling disclosure need not disclose any working examples or demonstrate that the claimed invention was actually reduced to practice at the time **[*46]** of filing. *Alcon Research Ltd. v. Barr Labs, Inc., 745 F.3d 1180, 1190 (Fed. Cir. 2014))*. Where there is no need for an actual reduction to practice, we are not persuaded that the failure to include a working example, specific to neridronic acid, supports a conclusion that undue experimentation would have been necessary to make and use the claimed invention. *See* Pet. 28-29 (arguing that the failure to include a working example directed to neridronic acid, in particular, supports a finding of lack of enablement).

In reaching our conclusions on the ground based on enablement, we take notice that "a considerable amount of [routine] experimentation" is permitted without rising to the level of undue experimentation under a correct enablement analysis. *PPG Indus. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)*. Petitioner does not address, much less explain adequately, how or why any required experimentation would have risen above the routine, given the state of the art as exemplified by the disclosure of Varenna 2012. Pet. 26-30.

In view of the above, we determine that Petitioner has failed to demonstrate that any challenged claim is unpatentable for lack of an enabling disclosure.

III. CONCLUSION

In summary, we make the following conclusions. [10]

			Claims	Claims Not
Claims	**35**	**Reference(s)/**	**Shown**	**Shown**

[10] 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. See 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)

	U.S.C. §	[*47] Basis	Unpatentable	Unpatentable
1-4, 9, 10, 12, 14, 16-18, 23-25, 27-29	102(a)	Varenna 2012	1-4, 9, 10, 12, 14, 16-18, 23-25, 27-29	
1-4, 9, 10, 12, 14, 16-18, 23-25, 27, 28	102(a)	Varenna 2016		1-4, 9, 10, 12, 14, 16-18, 23-25, 27, 28
1-4, 9, 10, 12, 14, c 16-18, 24-25, 27, 28	102(a)	Manara Varenna 2012, Varenna 2016, Manara,		1-4, 9, 10, 12, 14, 16-18, 24-25, 27,28
1-4, 9-20, 22-29	103(a)	Bruehl Gatti, La Montagna, Muratore	1-4, 9-20, 22-29	
5-8, 21	103(a)	Varenna 2012, Varenna 2016, Manara, Manicourt	5-8, 21	

Claims	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
30	103(a)	Varenna 2012, Varenna 2016 Manara, Schwarzer, Bruehl, Gatti, La Montagna, Muratore	30	
1-30 Overall Outcome	112(a)		1-30	1-30

IV. ORDER

Accordingly, it is

ORDERED that claims 1-30 of the '999 patent are unpatentable; 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*.

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

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