

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GRÜNENTHAL GMBH,
Petitioner,

v.

ANTECIP BIOVENTURES II LLC,
Patent Owner.

PGR2019-00003
Patent 9,867,839 B2

Before TONI R. SCHEINER, GRACE KARAFFA OBERMANN, and
SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

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 1–14 of U.S. Patent No. 9,867,839 B2 (Ex. 1001, “the ’839 patent”) are unpatentable. We also determine that Petitioner has failed to establish by a preponderance of the evidence that claims 15–30 of the ’839 patent are unpatentable.

A. Procedural Background

Grünenthal GMBH (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting post grant review of claims 1–30 of the ’839 patent. Antecip Bioventures II LLC (“Patent Owner”) did not file a preliminary response. Upon consideration of the information presented in the Petition, we instituted a post grant review of claims 1–30 of the ’839 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 9; “PO Resp.”), Petitioner filed a Reply (Paper 14; “Reply”), and Patent Owner filed a Sur-Reply (Paper 16; “Sur-Reply”).

The Petition is supported by the Declaration of Lawrence Poree, M.D., Ph.D. Ex. 1003.

Oral argument was conducted on February 4, 2020. A transcript is entered as Paper 21 (“Tr.”).

We address herein the arguments and evidence set forth in the Papers to the extent necessary to resolve the dispute between the parties with regard to each of the challenged claims.

B. The ’839 Patent (Ex. 1001)

The ’839 patent is titled “Osteoclast Inhibitors for Joint Conditions” (Ex. 1001, code (54)), and issued on January 16, 2018, from application number 15/438,513 (“the ’513 application”), filed February 21, 2017. According to the Specification of the ’839 patent, bisphosphonate compounds, such as neridronic acid and zoledronic acid, “are potent inhibitors of osteoclast activity, and are used clinically to treat bone-related conditions such as osteoporosis and Paget’s disease of bone; and cancer-related conditions including multiple myeloma, and bone metastases from solid tumors.” *Id.* at 1:46–50. In addition, according to the Specification, “neridronic acid and zoledronic acid, in an acid or a salt form, can be used to treat or alleviate pain or related conditions, such as joint conditions” (*id.*, Abstract), including osteoarthritis, rheumatoid arthritis, and complex regional pain syndrome (CRPS) (*id.* at 14:21–24).

“Commonly used measures of pain intensity include the visual analog scale (VAS) and the numerical rating scale (NRS).” *Id.* at 8:61–62. “With the VAS approach, patients rate the severity of their pain by marking a point on a 10-cm (or 100 mm) VAS . . . [w]ith the NRS approach, patients rate the severity of their pain by verbally responding to a 10-pt NRS.” *Id.* at 8:62–67. With either approach, 0 equals no pain, and 10 equals the worst possible pain. *Id.* at 8:67–9:1. “Knee pain in a person with a VAS score of 5 cm . . .

or higher, or an NRS score of 5 or higher, may be referred to herein as moderate to severe knee pain.” *Id.* at 9:6–9.

Finally, the Specification teaches that “the daily oral dose of neridronate^[1] is about 10 mg to about 1,000 mg, about 50 mg to about 500 mg, about 100 mg to about 500 mg, or about 150 mg to about 300 mg,” and “the parenteral dose . . . is about 5 mg to about 500 mg, about 5 mg to about 200 mg, or about 10 mg to about 150 mg.” *Id.* at 30:17–22.

C. Illustrative Claims

Claims 1 and 15, the only independent claims, are illustrative:

1. A method of treating pain associated with a joint comprising: administering neridronic acid in an acid form or a salt form to a patient who has suffered for at least 3 months with 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the 0–10 numerical rating scale (NRS) or 5 cm or greater using the 10 cm visual analog scale (VAS).

15. A method of treating pain associated with a joint comprising: orally administering zoledronic acid in an acid form or a salt form to a patient having 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the 0–10 NRS or 5 cm or greater using the 10 cm VAS, wherein a total of about 400 mg to about 600 mg of zoledronic acid is administered in 2 or 3 individual doses within a period of about a month.

Ex. 1001, 105:38–44, 106:14–21.

D. Asserted Prior Art

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

¹ Dr. Poree explains that “‘neridronate’ is synonymous with neridronic acid.” Ex. 1003 ¶ 150 (citing Ex. 1001, 32:6).

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

Ex. 1006: M. Muratore et al., *Il neridronato nel trattamento dell’algodistrofia simpatico riflessa del’anca: confront in aperto con il clodronato*, 5 PROGRESSI IN RHEUMATOLOGIA, ABSTRACT BOOK VII CONGRESSO NAZIONALE COLLEGIO DEI REUMATOLOGI OSPEDALIERI 89 (2004) (certified English translation: Neridronate in the treatment of reflex sympathetic hip algodystrophy: open comparison with clodronate) (“Muratore”).

Ex. 1007: D. Gatti et al., *Neridronic acid for the treatment of bone metabolic diseases*, 5 EXPERT OPIN. DRUG METAB. TOXICOL. 1305–11 (2009) (“Gatti 2009”).

Ex. 1009: G.S.E. Dowd et al., *Complex regional pain syndrome with special emphasis on the knee*, 89-B JOURNAL OF BONE AND JOINT SURGERY 285–290 (2007) (“Dowd”).

Ex. 1010: M. Walsh, WO 2007/092338 A2, published August 16, 2007 (“Walsh”).

Ex. 1011: D. Thompson et al., WO 2005/107751 A1, published November 17, 2005 (“Thompson”).

Ex. 1012: Fox et al., US 2004/0063670 A1, published April 1, 2004 (“Fox”).

Ex. 1013: M. Rossini et al., *Intra-articular clodronate for the treatment of knee osteoarthritis: dose ranging study vs hyaluronic acid*, 48 RHEUMATOLOGY 773–78 (2009) (“Rossini”).

Ex. 1014: M. Varenna, *Efficacy Study of Neridronate to treat Painful Osteoarthritis of the Knee With Bone Marrow Lesions* (2013) available at <https://clinicaltrials.gov/ct2/show/record/NCT01803360?view=record> (“Varenna Protocol”).

Ex. 1015: A. de Castro et al., *Zoledronic acid to treat complex regional pain syndrome type I in adult*, 12 REV DOR. SÃO PAULO 71–73 (2011) (“de Castro”).

Ex. 1016: J. Zaspel et al., *Treating CRPS I in the early stage – cortisone (methyl prednisone) versus bisphosphonate (zoledronic acid)*, GERMAN CONGRESS FOR ORTHOPEDICS AND TRAUMA SURGERY (2007) (“Zaspel”).

Ex. 1017: M. Hanna et al., WO 2011/097269, published August 11, 2011 (“Hanna”).

The Petition is supported by the Declaration of Lawrence Poree, M.D., Ph.D. Ex. 1003. We find that Dr. Poree is qualified to opine about the perspective of a person of ordinary skill in the art at the time of the invention. See Ex. 1004 (Dr. Poree’s curriculum vitae).

E. Asserted Grounds of Unpatentability

We instituted review of claims 1–30 of the ’839 patent as follows.
Paper 7.

Claims	35 U.S.C. § ²	Reference(s)/Basis
1–14	112(a)	Written Description
1–14	112(a)	Enablement
1–14	103	Varennna 2012, Muratore, Gatti 2009, Dowd
1–9, 13, 14	103	Varennna Protocol, Rossini

² The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 285–88 (2011), amended 35 U.S.C. §§ 102 and 103. Because the ’839 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. § ²	Reference(s)/Basis
1–9, 13, 14	103	Walsh, Thompson, Fox, Gatti 2009, Rossini
15–30	103	De Castro, Zaspel, Dowd, Hanna

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 at the time of the invention. Petitioner argues that a person of ordinary skill in the art 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 joint pain and/or other related types of pain, or in the study of joint pain and/or other related types of pain.” Pet. 13–14 (citing Ex. 1003 ¶¶ 18–21).

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 a joint using a medication, i.e. neridronic acid or zoledronic acid,” and as such, “a POSA would have an 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.*

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. Accordingly, we adopt Patent Owner's definition of a POSA for the purposes of this decision. That said, we discern no appreciable difference in the respective definitions of a POSA as that definition relates to the dispositive issues of this case, discussed below.

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”) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). We determine that the prior art here reflects an appropriate level of skill in the art and is consistent with the definition of a person of ordinary skill in the art, discussed above.

B. Claim Construction

For petitions filed before November 13, 2018, as is the situation here, we interpret claims in an unexpired patent using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.300(b) (2018).³ Under this standard, we interpret

³ Petitioner filed the Petition on October 16, 2018, prior to the effective date of the rule change that replaces the broadest reasonable interpretation standard with the federal court claim interpretation standard. *See Changes to the Claim Construction Standard for Interpreting Claims in Trial*

claim terms using “the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant’s specification.” *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997); see *In re Smith Int’l, Inc.*, 871 F.3d 1375, 1382–83 (Fed. Cir. 2017) (“[The] broadest reasonable interpretation . . . is an interpretation that corresponds with what and how the inventor describes his invention in the specification.”). “Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history.” *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Petitioner proposes constructions for two terms, listed in the chart below.

Term	Claims	Petitioner’s Proposed Construction
“A method of treating pain associated with a joint”	1–30	Requires that neridronic acid (claims 1–14) or zoledronic acid (claims 15–30) be administered to a patient having pain associated with a joint for the purpose of diagnosing, curing, mitigating, or preventing pain associated with a joint, or for activity that otherwise affects the structure or

Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019) (“This rule is effective on November 13, 2018 and applies to all IPR, PGR and CBM petitions filed on or after the effective date.”)).

		any function of the body in a patient with pain associated with a joint.
“pain associated with a joint”	1–30	Any pain related to a joint in any way.

Pet. 14 (chart identifying Petitioner’s proposed claim constructions); *see also, id.* at 15 (citing Ex. 1003 ¶¶ 39–41) (“given its broadest reasonable interpretation, ‘pain associated with a joint’ means ‘any pain related to a joint in any way.’”).

Patent Owner responds by first noting that claims 1 and 15 require “a patient who has suffered for at least 3 months with 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the 0–10 [numerical rating scale (NRS)] or 5 cm or greater using the 10 cm [visual analog scale (VAS)].” Ex. 1001, 105:38–44, 106:14–21; PO Resp. 2–3.

Patent Owner further contends that

the specification clearly states that for “patients with clinical knee osteoarthritis,” the decrease in VAS pain intensity was far greater for patients having a VAS score of 5 cm or greater as compared to patients having a VAS less than 5 cm. (Ex. 1001, col. 53, ll. 48-49; col. 54, ll. 25-46.) The specification further states “pain reduction was greater in patients with OARSI Grade 0 joint space narrowing, and greatest in patients with both baseline VAS $\geq$ 50 mm and OARSI Grade 0 joint space narrowing.” (Ex. 1001, col. 54, ll. 44-48 (emphasis added).)

Sur-Reply 1. Thus, according to Patent Owner, the plain language of the claims when read in light of the Specification would indicate to a person of ordinary skill in the art that the pain intensity limitation is in connection to joint pain. *Id.*; PO Resp. 2–3.

Furthermore, Patent Owner points out that Petitioner’s expert, Dr. Poree, testified that he understood the claims to refer to joint pain intensity.

PO Resp. 2–3; Sur-Reply 1. Specifically, Patent Owner directs our attention to the following testimony of Dr. Poree:

[Claim 1] covers (a) administration of neridronic acid for the purpose of treating any type of pain related to a joint in any way, as “treating” is broadly defined in the ’839 patent, (b) to a patient who has suffered from such pain that is greater than 5 cm on the VAS, (3) for at least 3 months.

Ex. 1003 ¶ 83 (emphasis omitted); PO Resp. 2–3; Sur-Reply 1.

In its Reply, Petitioner contends that

By the plain language of the claims, the patient need not have joint-associated pain with intensity of 5 or greater; he or she need only have joint-associated pain and pain with intensity of 5 or greater. Patent Owner does not point to any evidence in the intrinsic record that would compel a deviation from the plain reading of the claims. Patent Owner could have worded the claims to read “a patient who has suffered for at least 3 months with pain associated with a joint having intensity of 5 or greater,” but it did not. Instead, it wrote claims with two separate, clearly delineated requirements, which squarely contradicts Patent Owner’s proposed construction.

Reply 5 (emphases omitted).

Having considered the parties’ positions and evidence of record, summarized above, we agree with Patent Owner the challenged claims are directed to “treating pain associated with a joint” and that the plain reading of the claims, as well as the intrinsic evidence, support a conclusion that the term “pain intensity” is properly interpreted to refer to the intensity of joint pain. *See e.g.* Ex. 1001, Abstract (“neridronic acid and zoledronic acid . . . can be used to treat or alleviate pain or related conditions, such as joint conditions”). To the extent further 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. Printed Publication

1. Summary of Law

In a proceeding before the Board, 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 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 *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.’”).

2. *Parties' Arguments*

In the present case, Patent Owner argues that Petitioner cites to no evidence to support its contention that any of the relied upon eight non-patent references were publically accessible before the effective filing date of the invention and therefore prior art to the '839 patent. PO Resp. 3–9. Patent Owner contends that “Petitioner did nothing more than point to the date on the face of each document as proof of its printed publication status” and that “[t]he law requires considerably more than that.” *Id.* at 8. Patent Owner further contends that

It is likely that Petitioner will respond by essentially arguing that its non-patent references are from reputable publishers, or trustworthy sources, or that POSAs would recognize them as such. Indeed, Petitioner has already made such an argument with regard to Varenna Protocol. (Pet. at 39; Ex. 1003, ¶¶ 212–215.) But that only begs the question of why Petitioner failed to make even this minimal (and inadequate) effort for the other seven non-patent references. For each one, Petitioner offered no expert testimony and nothing that could qualify as argument or evidence to support a finding of printed publication status.

Id. at 9 (citing Pet. 26 (Ex. 1009), 27 (Ex. 1014), 29 (Ex. 1006), 30 (Ex. 1007), 59–60 (Ex. 1013), 68 (Ex. 1015), and 69 (Ex. 1016)); *see* Sur-Reply 4–8 (“Petitioner has not presented any evidence of the public accessibility of the eight non-patent references it has advanced as ‘printed publication’ prior art.”).

In its Reply, Petitioner, with regard to Verrena, Muratore, Gatti 2009, Dowd, Rossini, and deCastro, contends that “[i]t is evident from the face of six of the non-patent references [(i.e. Ex. 1005, Ex. 1006, Ex. 1007, Ex. 1009, Ex. 1013, and Ex. 1015)] that they are articles published in periodical

journals by an identified and reputable publisher prior to March 16, 2013.”

Reply 1.

With regard to Zaspel, Petitioner contends that

The seventh reference, Zaspel (Ex. 1016), is a meeting abstract from the German Congress for Orthopedics and Trauma Surgery published by German Medical Science GMS Publishing House, which is also plainly prior art. It bears a publication date of October 9, 2007 and a copyright date of 2007.

Id. at 2.

With regard to Varenna Protocol, Petitioner contends that

The eighth reference, the Varenna Protocol (Ex. 1014), falls into a different category because it is not a published journal article or meeting abstract, but rather is a record of a clinical trial from the website clinicaltrials.gov. For this reason, Petitioner provided additional proofs and expert testimony concerning this reference’s publication date.

Reply 2 (citing Pet. 39; Ex. 1003 ¶¶ 212–215; Ex. 1001, 5); *see* Ex. 1003 ¶ 214 (Dr. Poree testifying that “[a] POSA would have considered the posting dates cited at clinicaltrials.gov to be trustworthy and authoritative, and would have understood that the Varenna Protocol was published online on March 4, 2013 and last updated on March 14, 2013.”).

Petitioner further contends that

Patent Owner did not timely object to any of the cited non-patent references within ten business days of the institution of trial as required by 37 C.F.R. § 42.64(b)(1). Patent Owner therefore waived any evidentiary objections to the non-patent references, including their printed publication and copyright dates. Thus, those dates are properly before the Board; and absent any evidence to the contrary, they must be accepted as true and are sufficient evidence to show that these references qualify as prior art as the Board correctly found at the institution phase.

Reply 3–4.

3. Discussion

In post grant review proceedings, documents are admitted into evidence subject to an opposing party asserting objections to the evidence and moving to exclude the evidence. 37 C.F.R. § 42.64. Where, as here, a ground of unpatentability is based upon a reference that is alleged to be prior art as a printed publication, there may be issues regarding both the admissibility of that evidence and the sufficiency of that evidence. Generally, admissibility is addressed in a motion to exclude, and sufficiency is addressed within a party's papers. *See, e.g., Standard Innovation Corp. v. LELO, Inc.*, IPR2014-00148, Paper 42 (PTAB Apr. 23, 2015); *Valeo North America, Inc., et al. v. Magna Electronics, Inc.*, IPR2014-01208, Paper 49 (PTAB Dec. 21, 2015).

In this case, Patent Owner does not challenge the admissibility of evidence, which would have required Patent Owner to serve objections within the required ten business days of institution of trial and to file a motion to exclude. 37 C.F.R. §§ 42.64(b)(1), 42.64(c). Consequently, we only consider Patent Owner's challenge to the sufficiency of the evidence in its Patent Owner Response.

Regarding Patent Owner's challenge to the sufficiency of the evidence, we have considered the parties' positions and evidence of record, summarized above, and find Petitioner has made a sufficient showing that each of these references qualify as a prior art printed publication. Regarding Varenna 2012, Muratore, Gatti 2009, Dowd, Rossini, deCastro, and Zaspel, each of these references bears several hallmarks suggesting that each was published as part of a regularly distributed medical journal. For example, Varenna 2012 appears to have been published and made available to the

interested scientific community via the journal *Rheumatology* in 2012, prior to the priority date of the '839 patent. Reply 7–11; Ex. 1005 (indicia on the face of the document); Ex. 1044 (Patent Owner Response in PGR2017-00022). Varena 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 November 2012”); a link to the website of the journal (“www.rheumatology.oxfordjournals.org”); the publisher of the journal (“© 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 Varena 2012 could make inquiries (“Correspondence to: Silvano Adami, Rheumatology Unit, Policlinico GB Rossi, Piazzale Scuro, 37121 Verona, Italy”). Likewise, each of Muratore, Gatti 2009, Dowd, Rossini, de Castro, and Zaspel provides similar indicia of publication. Ex. 1005; Ex. 1006; Ex. 1007; Ex. 1009; Ex. 1013; Ex. 1015; Ex. 1016.

We are persuaded that the information pertaining to the publication on the face of each of Muratore, Gatti 2009, Dowd, Rossini, de Castro, and Zaspel is sufficient to establish each document qualifies 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*, IPR2018-01039, Paper 29

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.”).

Varenn Protocol differs from the other cited references in that it is a printout from a website not associated with a regularly distributed publication. Rather, Varenn Protocol is a printout from the website <https://www.clinicaltrials.gov>. Varenn Protocol, however, contains similar indicia of publication, in particular a “First Posted” date and a “Last Update Posted” date, indicating that the study record disclosed in Varenn Protocol was first available on clinicaltrials.gov on March 4, 2013, and that the information contained in the study record has not changed since March 14, 2013. Ex. 1014, 1; Pet. 39; Ex. 1003 ¶¶ 212–213.

Other indicia indicate that the website is associated with the U.S. National Library of Medicine at the National Institutes of Health (NIH). Ex. 1014, 1. In this regard, Dr. Poree testifies that clinicaltrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials, and one of ordinary skill in the art would have considered the posting dates cited at clinicaltrials.gov to be trustworthy and authoritative. Ex. 1003 ¶ 214.

Having considered such evidence, we determine that the totality of the evidence—the indicia of publication on the face of the document and undisputed testimony of Dr. Poree—supports a finding that Varenn Protocol was publically available as of March 4, 2013, the “First Posted” date on the face of the document. We further credit the testimony of Dr. Poree and are not persuaded by Patent Owner’s bare attorney argument to the contrary. *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) (attorney argument cannot take the place of evidence lacking in the record).

In view of the above, we determine that Varena Protocol qualifies as a prior art printed publication to the '839 patent.

D. The Asserted Grounds of Unpatentability

1. Written Description Support

Petitioner asserts that claims 1–14 lack written description support because “the '839 patent specification nowhere describes . . . administering neridronic acid to a patient having pain associated with a joint measuring ≥ 5 cm on the VAS for at least 3 months, as recited in claim 1.” (Pet. 22 (citing Ex. 1003 ¶ 63)). Petitioner acknowledges that “the '839 patent specification generally discusses administration of bisphosphonates to a patient that has ‘suffered from [an] inflammatory condition for at least 1 month, at least 2 months, at least 3 months, at least 6 months, or at least 1 year,’” but contends that “disease duration is not the same as pain duration.” *Id.* at 23 (citing Ex. 1001, 8:19–25). “Consequently,” Petitioner contends that the '839 patent’s disclosure “would not demonstrate to a POSA that the inventor was in possession of and actually invented methods of treating patients having pain associated with a joint measuring ≥ 5 cm on the VAS for particular periods of time, such as “‘at least 3 months.’” *Id.* (citing Ex. 1003 ¶¶ 66–68).

It is well settled that “original claims constitute their own description.” *In re Koller*, 613 F.2d 819, 823 (CCPA 1980); *see also In re Gardiner*, 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.”).

Claim 1, as originally filed, is as follows:

A method of treating pain associated with a joint comprising: administering neridronic acid in an acid or a salt form to a patient that has suffered for at least 3 months with 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the 0–10 numerical rating scale (NRS) or 5 cm or greater using the 10 cm visual analog scale (VAS).

Ex. 1002, 14 (file history of the '839 patent). Original claim 1 is equivalent in scope and virtually identical in language to the subject matter of challenged claim 1. Accordingly, we determine that claim 1 constitutes its own description.

On this record, we determine that Petitioner has failed to establish that claims 1–14 are unpatentable for lack of written description support.

2. *Enablement*

Petitioner contends that claims 1–14⁴ lack enablement because the Specification does not teach one of ordinary skill in the art how to administer neridronic acid to a patient who has suffered for at least 3 months with complex regional pain syndrome (CRPS). Pet. 46. Petitioner notes that “[t]he '839 specification does not contain any examples of methods of treatment involving neridronic acid, let alone examples of the use of neridronic acid to treat pain associated with CRPS wherein the patient has been suffering for 3 months from CRPS and a specific pain intensity.” *Id.* at

⁴ Petitioner notes that claims 10, 11, and 12 depend from claims 1, 2, and 3, respectively, and each specifies that the patient to be treated is suffering from complex regional pain syndrome (CRPS). Pet. 46–47. Petitioner contends that claims 1–9, 13, and 14 also lack enablement because they encompass treatment of CRPS.

48 (citing Ex. 1003 ¶¶ 72–73). Petitioner further notes that the Specification “broadly posits that ‘any suitable amount’ of a bisphosphonate may be used,” and “[t]he only disclosure specific to neridronate dosing in the specification states only that the daily oral dose may range anywhere from about 10 mg to about 1,000 mg and that the parenteral dose may range anywhere from about 5 mg to about 500 mg.” *Id.* (citing Ex. 1001, 32:4–35; Ex. 1003 ¶ 74). According to Petitioner, “[t]hat broad dosage range is not tied to any particular disease or duration of treatment, and the specification mentions various different conditions that may be treated.” *Id.* at 48–49 (citing Ex. 1001, 30:17–22; Ex. 1003 ¶¶ 75–76).

Citing *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), Petitioner contends that “the ’839 patent claims are unpatentable for lack of enablement” because “a significant amount of experimentation would be required to practice the invention.” *Id.* at 48.

“[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). “That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is ‘undue.’” *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). Some experimentation, even a considerable amount, is not “undue” if, for example, the Specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *Wands*, 858 F.2d at 737.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art The test is not merely

quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Forman, 230 USPQ 546, 547 (BPAI 1986). “The key word is ‘undue,’ not ‘experimentation.’” *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).

Even accepting that significant experimentation would be required to determine the appropriate dose of neridronic acid for a given patient, the information advanced in the Petition is insufficient to establish that the experimentation would have been anything other than straightforward, routine, and empirical, for one of skill in the art.

Moreover, the information advanced in the Petition does not account adequately for the general knowledge of the ordinarily skilled artisan as demonstrated by Varena 2012 (Ex. 1005, discussed in detail below). Based on the information presented, we find that the disclosure of Varena 2012 would have informed an ordinary artisan, before the critical date, exactly how to administer neridronic acid to humans suffering from CRPS with a reasonable expectation of mitigating pain associated with that condition. *See* Ex. 1005, 534 (Abstract), 535 (Study design), 536 (Results and Efficacy in double-blind phase), 538 (Table 2 and discussion of improvement in pain symptoms upon treatment with neridronate).

Having considered the parties positions and evidence of record, summarized above, we determine that Petitioner has failed to establish that claims 1–14 are unpatentable for lack of an enabling disclosure.

3. *Obviousness of Claims 1–14 over Varennna 2012 and Dowd, or alternatively over Muratore, Gatti 2009, and Dowd*

Claims 1–14 are directed, in relevant part, to a method of treating pain associated with a joint comprising administering neridronic acid in acid or salt form to a patient who has suffered pain of a specified intensity for at least 3 months. Claim 6 depends from claim 1 and specifies that the joint is a knee. Claim 10 also depends from claim 1 and specifies that that the patient is suffering from complex regional pain syndrome.

Petitioner argues that the subject matter of claims 1–14 would have been obvious because “it was well known in the prior art that neridronic acid could be administered to treat CRPS pain, a type of pain that is often associated with a joint” (Pet. 24 (citing Ex. 1003 ¶¶ 83–84)), particularly the knee (*id.* at 26 (citing Ex. 1009, 286)).

a. *Summary of Asserted Prior Art*

(i) *Varennna 2012 (Ex. 1005)*

According to Varennna 2012, complex regional pain syndrome type I (CRPS-I) “is a severely disabling pain syndrome.” Ex. 1005, 534. Varennna 2012 discloses the results of a randomized, double-blind, placebo-controlled human clinical study in which neridronic acid or placebo was administered to eighty-two patients with pain associated with CRPS-I of the hands or feet. *Id.* at 534, 535. Eligibility criteria for the study included disease duration “no longer than 4 months” and “spontaneous pain intensity in the affected limb of at least 50 mm on a visual analogue scale (VAS) ranging from 0 (no pain) to 100 mm (maximal pain).” *Id.* at 535. Patients in the treatment arm of the study received four intravenous infusions of 100 mg neridronic acid over ten days. *Id.* Treatment outcomes were assessed by, among other

things, “pain evoked by passive motion (ankle for foot involvement and wrist and finger joints for hand involvement).” *Id.*

Varennia 2012 concludes that the clinical study “has shown significant, clinically relevant and persistent benefit to patients with acute CRPS-I following an [intravenous] neridronate course, providing . . . conclusive evidence that the use of bisphosphonates, at appropriate doses, is the treatment of choice for CRPS-I.” *Id.* at 541.

(ii) *Muratore (Ex. 1006)*

Muratore teaches that reflex sympathetic algodystrophy⁵ is a syndrome characterized by, among other things, the presence of localized pain and severe functional limitation. Ex. 1006, 89. Eighteen patients, all suffering from femoral head algodystrophy with average duration of the disease of 4.1 ± 2.0 months, received either intravenous neridronate every 4 days, 4 times, or intravenous clodronate daily for 12 days. *Id.*

Muratore reports that both drugs were “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.” *Id.*

(iii) *Gatti 2009 (Ex. 1007)*

Gatti 2009 teaches that bisphosphonates, particularly neridronic acid, “are increasingly used for the treatment of reflex sympathetic dystrophy

⁵ According to Dr. Poree, “‘reflex sympathetic algodystrophy’ and ‘algodystrophy’ are synonyms for CRPS.” Ex. 1003 ¶ 31 (citing Ex. 1023, 713 (Bruehl paper on CRPS); Ex. 1005, 534, 540).

syndrome or algodystrophy,” and “the most effective dose is 100 mg diluted in 250 ml of saline solution given intravenously over 4 days.” Ex. 1007, 1305, 1308. According to Gatti 2009, “[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. “The efficacy was assessed by visual analogue scale for spontaneous pain and tenderness and by an arbitrary score (from 0 = normal to 4 = worst finding) of motion.” *Id.*

In addition, Gatti 2009 teaches that neridronic acid “has three peculiarities of some clinical value.” *Id.* at 1309. For example, “a unique advantage” of neridronic acid is that it can be administered intramuscularly, to “patients who cannot take oral bisphosphonates” or when “access to hospital services for [intravenous] infusions is either cumbersome or too expensive.” *Id.*

(iv) *Dowd (Ex. 1009)*

Dowd teaches that complex regional pain syndrome involves “an exaggerated response to injury of a limb, manifested by intense prolonged pain.” Ex. 1009, 285. Dowd teaches that “[t]he definite aetiology of complex regional pain sy[n]drome is unclear and many theories have been postulated.” *Id.*

According to Dowd, CRPS commonly affects the knee. *Id.* Dowd teaches that, “[w]hen the knee is affected, the patellofemoral joint is always involved.” *Id.* at 289. Dowd also teaches that “upper limbs are generally more amenable to treatment than the lower and children fare better than adults, with physiotherapy being quite effective in the former.” *Id.* (internal references omitted).

Dowd teaches that pharmacological agents used to treat knee pain include bisphosphonates. *Id.* at 288. In particular, Dowd discloses that

[Pharmacological agents] are used to modify the sympathetic and nonsympathetic symptoms and include the use of simple analgesics, NSAIDs, steroids, narcotics, anti-neuropathic drugs such as gabapentin, calcium metabolism modulators such as bisphosphonates and calcitonin, propranolol and nifedipine. Control of pain is essential for successful treatment and a combination of drugs, such as a tricyclic antidepressant, gabapentin and a strong opiate may be needed to achieve this.

Id. at 288 (internal references omitted).

According to Dowd, “[m]ore research is required to improve the understanding of this unpleasant condition.” *Id.* at 289.

b. Parties’ Arguments

Petitioner contends that a person of ordinary skill in the art “would plainly recognize that Varenna 2012 discloses that neridronic acid treats CRPS pain, including pain . . . associated with a joint.” Pet. 28 (citing Ex. 1003 ¶¶ 94–98; Ex. 1005, 535–538, 541). Moreover, Petitioner contends, “the VAS and pain duration ranges taught by Varenna 2012 overlap the ≥ 5 cm on the VAS for at least 3 months ranges recited in [the] claims.” *Id.* (citing Ex. 1003 ¶¶ 91–93). Inasmuch as Dowd “teaches that CRPS can affect the knee and cause knee pain, a type of pain associated with a joint” (*id.* at 31 (citing Ex. 1003 ¶ 89)), Petitioner contends a person of ordinary skill in the art “would have been motivated to combine the teachings of Varenna 2012 and Dowd because both references concern . . . the use of bisphosphonates to treat CRPS.” Pet. 31–32 (citing Ex. 1003 ¶ 110).

In any case, “[t]o the extent [Varenna 2012 or Muratore and Gatti 2009] do not independently disclose treatment of joint pain,” Petitioner

contends one of ordinary skill in the art “would have been motivated to apply the teachings of Varenna 2012 or Muratore and Gatti 2009, to the teachings of Dowd, and administer neridronic acid to a patient suffering from knee pain, where that knee pain is caused by CRPS.” *Id.* at 31 (citing Ex. 1003 ¶ 110).

Petitioner concludes that it would have been obvious for one of ordinary skill in the art “to administer neridronic acid, as disclosed in Varenna 2012 or Muratore and Gatti 2009, for the treatment of CRPS pain affecting the knee, as taught by Dowd.” Pet. 31 (citing Ex. 1003 ¶¶ 89, 108, 112).

In its Response, Patent Owner contends that “Petitioner has not shown that the combination of references teach or suggest ‘pain associated with a joint’ that has ‘a pain intensity of 5 or greater measured using the 0–10 numerical rating scale (NRS) or 5 cm or greater using the 10 cm visual analog scale (VAS).” Specifically, Patent Owner contends that

Varenna does not identify any VAS score for “pain associated with a joint.” Petitioner alleges that “[i]nclusion criteria for the [Varenna] study included... ‘spontaneous pain intensity in the affected limb of at least 50 mm on a visual analog scale (VAS) ranging from 0 (no pain) to 100 mm (maximal pain).’ (Pet. at 27, see also Ex. 1003, ¶ 93.)”

In fact, Varenna used a different pain scale in referring to “pain evoked by passive motion (ankle for foot involvement and wrist and finger joints for hand involvement).” (Ex. 1003, ¶ 96.) Under that different pain scale, Petitioner alleges that Varenna “found that ‘pain evoked by passive motion significantly improved’...falling ‘from 2.32 to 0.78 in the neridronate group and from 2.18 to 1.70 in the placebo group...[t]hus, Varenna discloses that neridronic acid treats CRPS pain, in particular pain associated with joints such as ankles, wrists, and fingers.” (Ex. 1003, ¶¶ 96–97 (emphasis added).) But Petitioner has failed to

explain how the values 2.32 to 0.78 and 2.18 to 1.70 for “pain associated with joints” teach or suggest “pain associated with a joint” that has “a pain intensity of 5 or greater measured using the 0–10 numerical rating scale (NRS) or 5 cm or greater using the 10 cm visual analog scale (VAS).”

PO Resp. 22–23 (emphasis omitted). Thus, according to Patent Owner, “neither Petitioner nor its expert provide any explanation as to why the VAS scores identified in Varena are the level of pain associated with a joint that the patients experienced.” *Id.* at 22.

Petitioner replies with the following:

First, Patent Owner’s arguments are based upon an erroneous claim construction. Claim 1, for example, requires “a patient who has suffered for at least 3 months with 1) pain associated with a joint and 2) a pain intensity of 5 or greater . . .” (emphasis added). By the plain language of the claims, the patient need not have joint-associated pain *with* intensity of 5 or greater; he or she need only have joint-associated pain *and* pain with intensity of 5 or greater.

. . .

Second, even if joint-associated pain having an intensity of 5 or greater were required, the claims would still be obvious over the prior art. Varena 2012’s disclosure of successful treatment of joint pain in patients reporting pain intensity of 5 or greater in the affected limb at a minimum suggests that neridronic acid can be used to treat joint-associated pain having intensity of 5 or greater. Ex. 1005 at 536, 538, 541.

Reply 5–6 (citing Ex. 1003 ¶¶ 87–89, 91–98).

In its Sur-Reply, Patent Owner argues as follows:

Petitioner’s expert identified two different pain scales used by Varena (Ex. 1005). The first is the VAS for pain in the “affected limb.” (Ex. 1003, ¶ 93.) The second is a scale where the patients had initial “pain evoked by passive motion (ankle for foot involvement and wrist and finger joints for hand involvement)” of 2.32 in neridronic acid group and 2.18 in the

placebo group. (*Id.*, ¶ 96.) It was Petitioner’s expert who connected the “pain evoked by passive motion” to joint pain (*id.*, ¶ 97), *but failed to explain how values of 2.32 and 2.18 in the “pain evoked by passive motion” correspond to pain associated with a joint with a VAS score of 5 cm or greater.* As a result, Petitioner failed to show what values of 2.32 and 2.18 for “pain evoked by passive motion” have to do with a VAS score of 5 cm or greater for pain associated with a joint.

Sur-Reply 10 (emphasis in original omitted; emphasis added).

With regard to Gatti 2009 and Muratore, Patent Owner contends Petitioner fails to explain how those references teach or suggest “pain associated with a joint” that has “a pain intensity of 5 or greater measured using the 0–10 numerical rating scale (NRS) or 5 cm or greater using the 10 cm visual analog scale (VAS).” PO Resp. 23. Patent Owner further directs our attention to the following testimony of Dr. Poree:

Although Gatti [2009] and Muratore do not expressly disclose the VAS scores of the patient population, a POSA would have known that CRPS is characterized and defined by severe and continuing pain, and would have expected that the patients treated included patients with VAS scores ≥ 5 cm.

Id. at 23–24 (citing Ex. 1003, ¶ 106) (emphasis omitted).

Patent Owner further contends that “Petitioner has not identified any information in Dowd related to the VAS or NRS intensity for pain associated with a joint.” *Id.* at 24.

c. Discussion

Challenged claims 1–14 of the ’839 patent are directed to treating a patient suffering for more than 3 months from joint-associated pain at an intensity of 5 or greater as measured using the NRS or VAS scale. The challenged claims do not recite an efficacy requirement, rather the claims define a patient population. For example, independent claim 1 is directed to

treating “a patient who has suffered for at least 3 months with 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the [NRS or VAS].” Ex. 1001, 105:38–44.

For the patient population element of the claims, Petitioner relies on the disclosure of Varenna 2012, or in the alternative, Muratore or Gatti 2009. Pet. 28 (“Varenna 2012 describes a randomized, double-blind, placebo-controlled human clinical study in which neridronic acid was administered to treat pain associated with CRPS.”), 30 (“Gatti 2009 and Muratore also firmly establish that neridronic acid can be used to treat CRPS pain and reduce VAS scores in patients with CRPS.”) (citing Ex. 1006, 89; Ex. 1007, 1308; Ex. 1003 ¶ 105). Having considered the parties positions and evidence of record, we determine for the reasons set forth below, that Varenna 2012 discloses the patient population of claim 1, whereas neither Muratore nor Gatti 2009 disclose sufficient information with regard to the pain intensity suffered by the respectively disclosed patient groups to support a similar finding.⁶

Varenna 2012 discloses the treatment of CRPS-I with neridronate in a randomized, double-blind, placebo-controlled study. Ex. 1005, 1. Patent Owner argues that Varenna 2012 does not expressly disclose that the

⁶ In contrast to Varenna 2012, Muratore and Gatti 2009 disclose the use of pain intensity scales as a measure of efficacy, and not to define patient populations. Ex. 1007, 1308; Ex. 1003 ¶ 105. Both Muratore and Gatti 2009 fail to disclose sufficient information with regard to the pain intensity to define the patient population according to the claims, which is necessary to reach that element of the claims. Our decision with regard to this ground therefore relies solely on Varenna 2012, alone or in combination with Dowd.

patients of the study suffered from pain associated from a joint. Rather, according to Patent Owner, the inclusion criteria of the Varenna 2012 study referred to pain intensity of a limb, not a joint. PO Resp. 21. Patent Owner acknowledges that Varenna 2012 measured joint pain as one outcome of the study, but contends that the joint pain was measured using a scale distinct from the NRS or VAS. *Id.* at 22–23.

We find Petitioner has the better position. The preponderance of evidence of record supports a finding that CRPS-I is a disease that may involve “pain associated with a joint” as set forth in the claims. *See e.g.* Ex. 1003 ¶ 32 (“A POSA also would have known that CRPS can affect the joints such as the knee.”). In the study of Varenna 2012, the patients were assessed for improvement of “pain evoked by passive motion (ankle for foot involvement and wrist and finger joints for hand involvement)” Ex. 1003 ¶ 96 (citing Ex. 1005, 537–538). Based on that information, and corresponding testimony of Dr. Poree, we determine that the patients disclosed in Varenna 2012 are CPRS-I patients suffering from “pain associated with a joint” as set forth in the claims.

Furthermore, Varenna 2012 expressly states that the inclusion criteria for the study included disease duration “no longer than 4 months” and “spontaneous pain intensity in the affected limb of at least 50 mm on a visual analogue scale (VAS) ranging from 0 (no pain) to 100 mm (maximal pain).” Ex. 1005, 535. Dr. Poree testified that those disclosed pain intensity ranges “overlap the ≥ 5 cm on the VAS for at least 3 months ranges recited in claims 1 and 10.” Ex. 1003 ¶ 93. Based on that information, we determine that the preponderance of evidence of record supports a finding that Varenna

2012 teaches administering neridronic acid to treat pain associated with a joint to the patient population recited in claims.

We acknowledge Patent Owner's argument that Varena 2012 discloses the clinical assessment of pain evoked by passive motion of joints (ankle, wrist, and fingers) using a scale distinct from the NRS or VAS. This fact is undisputed. *See* Ex. 1003 ¶ 96 (Dr. Poree discussing the results of Varena 2012 reported using an alternative pain intensity scale); Reply 7. As discussed above, however, the claims do not recite the use of NRS or VAS to assess clinical efficacy. Rather, the claims recite the use of NRS or VAS to define a patient population. In this regard, Varena 2012 used the VAS scale to set inclusion criteria for patients to be included in the study, and that patient population overlaps the patient population set forth in the claims. Ex. 1003 ¶ 93. Thus, taken together, we determine that the study of Varena 2012 assessed the disclosed CRPS-I patient population for improvements in joint pain following the administration of neridronic acid, and therefore teaches the method set forth in independent claim 1 and dependent claim 10 (reciting CRPS pain associated with a joint). Accordingly, we determine that Varena 2012, either alone or in combination with Dowd, teach the method set forth in independent claim 1 and dependent claim 10.

We also determine that the subject matter of dependent claims 2–9 and 11–14 would have been obvious over Varena 2012, either alone or in combination with Dowd. Claims 2 and 3 depend from claim 1 and recite narrower ranges of pain intensity: ≥ 8 cm and ≥ 9 cm on the VAS, respectively. Varena 2012 states that the patients had pain ≥ 50 mm on a 100 mm VAS. Ex. 1005, 535. Where a claimed range overlaps or lies

inside ranges disclosed by the prior art, a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 267-68 (C.C.P.A. 1976).

Accordingly, we determine that it would have been obvious to administer neridronic acid to patients with VAS scores ≥ 8 cm and ≥ 9 cm based on Vareenna 2012's inclusion criteria of ≥ 5 cm. Consequently, we determine that Vareenna 2012, either alone or in combination with Dowd, teach the method set forth in dependent claims 2–9 and 11–14.

Claims 11 and 12 depend from claims 2 and 3, respectively, and specify that the patient is suffering from CRPS. Thus, for all of the reasons discussed above with respect to claims 1–3, we determine that the subject matter of claims 11 and 12 would have been obvious over Vareenna 2012, alone or in combination with Dowd.

Claim 4 recites “[t]he method of claim 1, wherein the neridronic acid is administered parenterally.” Vareenna 2012 discloses intravenous administration of neridronic acid, which is a type of parenteral administration. Ex 1005, 535. Consequently, for all of the reasons discussed above with respect to claims 1 and 10, we determine that the subject matter of claim 4 would have been obvious over Vareenna 2012, alone or in combination with Dowd.

Claims 5 and 13 add the limitation of administering neridronic acid at an interval of 2, 3, or 4 days. Vareenna 2012 states that its treatment “was administered every third day four times” (Ex. 1005, 535), or, in other words, at an interval of 2 days (i.e. 2 days in between doses) (Ex. 1003 ¶ 124). Consequently, for all of the reasons discussed above with respect to claims 1 and 10, we determine that the subject matter of claims 5 and 13 would have been obvious over Vareenna 2012, alone or in combination with Dowd.

Claims 6–9 depend from claim 1 and contain an additional limitation of “wherein the joint is” a knee, elbow, wrist, or ankle, respectively. As discussed above, Vareena 2012 discloses the clinical assessment of patients that included the assessment of pain from the ankle, wrist and finger joints. Ex. 1005, 535. Based on this information, we agree with Petitioner that a person of ordinary skill in the art would have reasonably expected that neridronic acid could be used to treat CRPS of various joints, including knees, elbows, wrists, and ankles, especially in view of Dowd. Ex. 1009, 285 (disclosing that CRPS commonly affects the knee). Accordingly, we determine that the subject matter of claims 6–9 would have been obvious over Vareena 2012, alone or in combination with Dowd.

Claim 14 recites “[t]he method of claim 13 wherein each parenteral dose is about 10 mg to about 150 mg.” Vareena 2012 discloses administration of 100 mg neridronic acid parenterally, which falls within the range of claim 14. Ex. 1005, 535. Consequently, for all of the reasons discussed above with respect to claims 1 and 10, we determine that the subject matter of claim 14 would have been obvious over Vareena 2012, alone or in combination with Dowd.

In conclusion, we are persuaded by Petitioner’s arguments, as they are supported by the cited evidence, notwithstanding Patent Owner’s arguments, addressed above. Accordingly, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–14 of the

'839 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Vareenna 2012, alone or in combination with Dowd.⁷

4. Obviousness of Claims 1–9, 13, and 14 over Walsh, Thompson, and/or Fox, in combination with Gatti 2009, and Rossini

Petitioner contends that claim 1 is unpatentable because “it would have been obvious that neridronic acid could be administered to treat arthritis, a type of pain associated with a joint” (Pet. 49–50 (citing Ex. 1003 ¶¶ 143–145)), “based on Walsh, Thompson, and/or Fox alone or in combination” (*id.* at 55 (citing Ex. 1003 ¶ 164)), with additional motivation to select neridronic acid provided by Gatti 2009 and Rossini (*id.* at 57 (citing Ex. 1007, 1309), 59–60 (citing Ex. 1013, 773–774)). In addition, Petitioner contends, “based on results of multiple arthritis clinical trials involving other bisphosphonates, it would have been obvious . . . that neridronic acid could be used to treat arthritis pain in patients . . . having [pain] intensity of ≥ 5 on the VAS for at least three months.” *Id.* at 50 (citing Ex. 1003 ¶ 181).

a. Summary of Asserted Prior Art

(i) Walsh (Ex. 1010)

Walsh discloses pharmaceutical compositions comprising a mixture of methotrexate (an antifolate compound) and at least one bisphosphonate, as

⁷ In view of this determination, we do not reach Petitioner’s challenge to claims 1–9, 13, and 14 as obvious over the combination of Vareenna Protocol and Rossini. Because the obviousness ground over the combination of Vareenna 2012, alone or in combination with Dowd is dispositive as to claims 1–9, 13, and 14, we need not reach the obviousness ground over the combination of Vareenna Protocol and Rossini. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner “is entitled to a final written decision addressing all of the claims it has challenged”).

well as “the use of these compositions for the treatment of arthritis, including osteoarthritis and rheumatoid arthritis.” Ex. 1010 ¶ 1. Walsh discloses 10 suitable bisphosphonates, including alendronate, clodronate, zolendronate, and neridronate. *Id.* ¶ 11.

Example 1 of Walsh describes a proposed double blind, placebo-controlled, randomized study to evaluate the efficacy and safety of methotrexate combined with alendronate. *Id.* at 14 (Example 1). Eligibility criteria include “disease duration of at least 6 months.” *Id.* “Treatment efficacy is determined by various measurements, including patient reports of joint stiffness [and] joint pain.” *Id.* ¶ 54.

(ii) *Thompson (Ex. 1011)*

Thompson discloses a “method for treating pain associated with hip dysplasia . . . in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.” Ex. 1011, 2:17–19. Thompson teaches that neridronic acid is one of approximately 15 bisphosphonates suitable for that purpose. *Id.* at 4:9, 28.

(iii) *Fox (Ex. 1012)*

Fox teaches that bisphosphonates, including neridronic acid and zoledronic acid, “may be used for direct treatment of pain in diseases and conditions” such as osteoarthritis and rheumatoid arthritis. Ex. 1012 ¶¶ 5, 10, 18.

(iv) *Rossini (Ex. 1013)*

Rossini discloses a multicenter, randomized, partially double blind Phase 2 study to determine the most appropriate dose of intra-articular (IA) clodronate—a bisphosphonate—for relieving pain and improving the

function of an osteoarthritic knee. Eligibility criteria included clinically confirmed osteoarthritis of the knee, symptomatic for at least 3 months, and pain greater than or equal to 40 in a VAS of 0–100. Ex. 1013, 774.

b. Parties' Arguments

Briefly, Petitioner contends:

Walsh, Thompson, and Fox disclose administration of neridronic acid to treat arthritis pain, and Gatti 2009 provides additional motivation to select neridronic acid for treatment of arthritis pain. These references do not expressly disclose the treatment of patients who have suffered with pain ≥ 5 cm on the VAS for at least three months, as recited in claim 1. Nevertheless, it would have been obvious to a [person of ordinary skill in the art] that neridronic acid could be used to treat arthritis pain in such a patient population, based in part on clinical studies conducted using other bisphosphonates.

Pet. 59. In particular, Petitioner contends one of ordinary skill in the art would have been motivated to look to other clinical studies—e.g., Rossini—“regarding administration of other bisphosphonates for arthritis pain to obtain information about specific patient populations that could be treated with neridronic acid.” *Id.* at 59–60 (citing Ex. 1003 ¶¶ 172–175; Ex. 1013, 773–775). Regarding Rossini, Dr. Poree testifies as follows:

173. Rossini, for example, was a Phase 2 randomized, partially blind clinical trial comparing intra-articular clodronate, a “bisphosphonate with anti-inflammatory effects in experimental arthritis,” against hyaluronic acid in patients with primary knee osteoarthritis. Exhibit 1013, Rossini at 773.

174. Patients had to have “starting spontaneous pain ≥ 40 on a visual analogue score (VAS) of 0–100.” Exhibit 1013, Rossini at 774. The mean VAS score for patients receiving a 2 mg clodronate dose was 67.4mm $\pm$ 14.9, indicating that patients with VAS scores of ≥ 67.4 mm were treated. Exhibit 1013, Rossini at 775.

175. Clodronate demonstrated significant and clinically meaningful progressive improvements in pain and function at all doses administered. Exhibit 1013, Rossini at 775.

176. Rossini teaches that the patients were symptomatic for at least three months prior to treatment. Exhibit 1013, Rossini at 775.

177. Thus, Rossini indicates that clodronate treats arthritis pain in patients with VAS scores ≥ 50 mm for at least three months. A POSA would have known, and the '839 patent confirms, that ≥ 50 mm on a 100 mm VAS is equivalent to ≥ 5 cm on a 10 cm VAS scale. Exhibit 1001, '839 patent, 8:61-9:9.

Ex. 1003 ¶¶ 173–177.

Patent Owner in response contends that “[c]laims 1–9 and 13–14 are not obvious because there is no apparent reason to combine the neridronic acid in Walsh, Thompson, Fox, or Gatti [2009] with the patient population in Rossini.” PO Resp. 32. Patent Owner further contends as follows:

Petitioner alleges that “Walsh claim 4 depends from claim 1 and lists neridronic acid as one of only 10 bisphosphonates that may be selected.” (Pet. at 53.) Thompson has even lower odds because Petitioner alleges that “Claim 5 lists neridronic acid as one of only 14 bisphosphonates for use in the method of claim 4.” (Pet. at 54.) But Petitioner has not explained why a POSA would even make such a selection when none of the bisphosphonates in Walsh and Thompson have actually been shown to be effective in treating pain associated with a joint, and several of them have failed in animal or human tests. (Fox, Ex. 1012, ¶¶ 102–103; Rossini, 16 Ex. 1013 at 777.)

Id. at 32–33 (emphasis omitted).

Patent Owner further contends as follows:

between Fox and Rossini, three bisphosphonates failed to show any promise for treating pain associated with a joint. A third bisphosphonate, clodronate, failed in Fox’s experiment and gave

uncertain results in Rossini. Walsh, Thompson, and Gatti [2009] do not report any experimental results relevant to pain associated with a joint. (Ex. 1010; Ex. 1011; Ex. 1007.) Thus, at best, the combination of Walsh, Thompson, Fox, Gatti [2009], and Rossini have a success rate for bisphosphonates for pain associated with a joint that is one in four, and it is possible that all four bisphosphonates have failed.

Id. at 35.

In its Reply, Petitioner contends that studies disclosed in Walsh, Fox, and Rossini show that certain bisphosphonates were effective in treating certain types of pain. Reply 12. In particular, Petitioner contends as follows:

Walsh . . . teaches that in a study of patients with rheumatoid arthritis, a type of joint-associated pain, “[p]atients administered the combination of alendronate and methotrexate show significantly greater improvement than do patients administered placebo or methotrexate alone.” Ex. 1010 at Example 1. . . . Fox teaches that while pamidronate and clodronate were “ineffective in reversing inflammatory mechanical hyperalgesia,” they both “produced slight reductions of paw withdrawal thresholds at the highest doses tested.” Ex. 1012 ¶ [0103]. A reduction in paw withdrawal threshold is a measure of efficacy endorsed by and used in the ’839 patent examples and figures. *See, e.g.*, Ex. 1001 at Examples 2-3. . . .

And, for its part, Rossini expressly teaches that “[intravenous] injection of either [hyaluronic acid] or different doses of clodronate in symptomatic [knee osteoarthritis] is associated with significant and clinically meaningful progressive improvement in pain and function extending for at least 2 weeks after the last injection.” Ex. 1013 at 775.

Id. at 13.

In its Sur-Reply, Patent Owner contends that “Walsh does not actually show that alendronate was effective because nothing in Walsh suggests that

this clinical trial was actually conducted. (Ex. 1010, Example 1.) The description of Example 1 is prophetic, not journalistic.” Sur-Reply 14–15. Regarding the results disclosed in Fox, Patent Owner contends “a reduction of paw withdrawal threshold obviously indicates increased pain, meaning that they made the condition slightly worse. This further confirms that the drugs were not effective.” *Id.* at 15.

c. Discussion

The obviousness analysis requires that “the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success,” even “[i]f all elements of the claims are found in a combination of prior art references.” *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The “motivation to combine” and “reasonable expectation of success” factors are subsidiary requirements for obviousness subsumed within the Graham factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). The “prior art fails to provide the requisite ‘reasonable expectation’ of success where it teaches merely pursuit of a ‘general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.’” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).

The information presented by Petitioner in this ground identifies each element of the challenged claims in the prior art, however, we agree with Patent Owner that the Petition lacks sufficient information to support a

determination that a person of ordinary skill in the art would have had a reasonable expectation of success in treating the pain associated with a joint in the specific patient population recited in the claims. PO Resp. 35–37; Sur-Reply 18. At best, the Petition directs us to general guidance in the prior art with regard to the use of bisphosphonates in treating pain, but fails to point us to specific guidance directing a person of ordinary skill in the art to a method of treating pain associated with a joint comprising administering neridronic acid to a patient who has suffered pain of the claimed pain intensity for at least 3 months. Pet. 59–61. For example, while Rossini discloses that the bisphosphonate clodronate can be administered to treat arthritis pain in patients with VAS scores ≥ 50 mm for at least three months (Ex. 1013, 773–774), the record lacks sufficient evidence to support a conclusion that a person of ordinary skill in the art would have reasonably expected neridronic acid to perform the same as clodronate. Ex. 1010, Example 1; Ex. 1012 ¶¶ 102–103; Ex. 1013, 777; Sur-Reply 14–15.

Dr. Poree’s testimony does not help in that regard. The statements in Dr. Poree’s declaration mirror those provided in the Petition, and do not point to any evidence in the record to support a conclusion that a person of ordinary skill in the art would have considered neridronic acid to be a known substitute for clodronate. Ex. 1003 ¶ 173.

Accordingly, the Petition does not establish the requisite reasonable expectation of success for combining the disclosures of Rossini with Gatti 2009 and one or more of Walsh, Thompson, and Fox as argued by Petitioner. Thus, we determine that Petitioner has failed to demonstrate by a preponderance of evidence that challenged claims 1–9, 13, and 14 would

have been obvious over the combination of Walsh, Thompson, Fox, Gatti 2009, and Rossini.

5. Obviousness of Claims 15–30 over de Castro, Zaspel, Dowd, and Hanna

Claims 15–30 are directed, in relevant part, to a method of treating pain associated with a joint comprising orally administering zoledronic acid in acid or salt form, at a specified dosage, to a patient suffering pain of a specified intensity. Claim 24 depends from claim 15, and specifies that the patient is suffering from CRPS. Petitioner contends it would have been obvious to use oral zoledronic acid to treat CRPS pain associated with a joint in the patient populations specified in the claims. Pet. 67.

a. Summary of Asserted Prior Art

(i) De Castro (Ex. 1015)

De Castro describes a “study aimed at reporting the use of zoledronic acid in [a] CRPS type I patient refractory to traditional therapy.” Ex. 1015, 71. Parenteral zoledronic acid (5 mg) was administered to a hospitalized patient with a 16-year history of neuropathic pain, “with intensity 10 in the worst moments, according to [the] verbal numerical scale.” *Id.* at 72. “No zoledronic acid adverse effect was identified and [the] patient was discharged after total regression of edema and pain . . . [with] no CRPS type I recurrence in the six months following the administration of zoledronic acid.” *Id.*

De Castro defines CRPS as follows:

Complex regional pain syndrome (CRPS) is a regional pain condition associated to sensory changes caused by a noxious event, be it fracture, surgery or other type of injury. CRPS diagnosis is clinical, based on the presence of specific signs and

symptoms; the presence of initial injury may be disregarded; signs and symptoms should be divided in different groups; patients should have at least two of the following symptoms: sensory (hyperesthesia), vasomotor (change in temperature, skin color or both), sudomotor / water balance (edema, sweating or both), and motor (decreased mobility, weakness, shivering, functional limb amputation) or all of them; and patients should present at least two of the following signs: vasomotor, sudomotor / water balance and motor. So, CRPS is a neuropathic and disabling pain syndrome made up of motor, autonomic and sensory changes.

Id. at 71. De Castro does not expressly associate joint pain with CRPS.

(ii) *Zaspel (Ex. 1016)*

Zaspel discloses that “[t]he treatment of CRPS I, like the underlying pathophysiology, remains an incompletely researched field to this day.”

Ex. 1016, 1. Zaspel describes a clinical study in which “twenty-four patients who suffered from a clinically manifested CRPS I for less than three months” received cortisone or “a one-time short infusion of 5 mg zolendronate.” *Id.* at 2. “The severity of the pain was decisively and significantly improved” in the patients treated with zolendronate “when compared to cortisone over the entire [six month] observational period . . . result[ing] in a 70% reduction in the VAS.” *Id.*

Zaspel concludes that bisphosphonates appear to show promise for the permanent improvement in pain, but that “[i]t remains to be seen whether this tendency is confirmed in the presence of larger case numbers and longer observational periods.” *Id.*

(iii) *Hanna (Ex. 1017)*

Hanna teaches that “[o]rally administered drugs are becoming more preferred in various therapeutic areas,” and discloses techniques for

“creat[ing] oral dosage forms of drugs with poor aqueous solubility and/or poor permeability.” Ex. 1017, 4. “One such example is zoledronic acid which is only approved for intravenous administration due to its low oral bioavailability, resulting from poor permeability.” *Id.* Hanna discloses zoledronic acid forms and compositions with enhanced oral bioavailability. In particular, compared with the free acid, “oral bioavailability of greater than 8% has been achieved with zoledronic acid” by complexing it with DL-lysine, and “[t]he data predicts an oral bioavailability well over this with increasing amounts of amino acid.” *Id.* at 24, 25, 33, 77 (Leg 37), 79.

Hanna teaches that oral dosage forms of bisphosphonic acids will generally contain about 1 mg to about 500 mg of the active ingredient, and can be administered at various frequencies, for example, daily, twice weekly, every ten days, every two weeks, etc. *Id.* at 54.

b. Parties’ Arguments

Petitioner contends, “[t]o the extent that Zaspel and de Castro do not expressly teach treatment of CRPS pain associated with a joint as required by claims [15 and 24], it would have been obvious . . . to use zoledronic acid to treat CRPS pain associated with a joint,” given that Dowd “teaches that CRPS can affect the knee and is a cause of knee pain.” Pet. 70 (citing Ex. 1003 ¶¶ 266–267). In addition, Petitioner contends that all three references describe the use of bisphosphonates to treat CRPS. *Id.* at 71 (citing Ex. 1003 ¶¶ 268–269).

Petitioner acknowledges that one of ordinary skill in the art “would have known that bisphosphonates like zoledronic acid were associated with low oral bioavailability,” but contends that one “would have been motivated to consult other art concerning administration of bisphosphonates like

zoledronic acid to select a route of administration.” *Id.* at 71–72 (citing Ex. 1003 ¶¶ 270–271). Petitioner contends that Hanna discusses the advantages of administering zoledronic acid orally, and teaches methods of enhancing the oral bioavailability of zoledronic acid. *Id.* at 73 (citing Ex. 1017, 3, 5, 25, 34, 47, 77). In particular, Petitioner contends, “Hanna describes and teaches . . . how to prepare molecular complexes of zoledronic acid with amino acids such as lysine” with “greatly improve[d] oral bioavailability.” *Id.* In addition, Petitioner contends that Hanna’s dosage range and frequency of administration overlap those of claims 15 and 24. *Id.* (citing Ex. 1017, 54).

Given the advantages of oral administration and the improved oral bioavailability of zoledronic acid reported in Hanna, Petitioner concludes that it would have been obvious “to orally administer dosage forms containing zoledronic acid complexes like those disclosed in Hanna for the treatment of CRPS pain associated with a joint in the claimed patient population, as taught by de Castro, Zaspel, and Dowd.” *Id.* at 74 (citing Ex. 1003 ¶ 278).

Patent Owner contends that “[c]laims 15–30 are not obvious because Petitioner has not shown that a POSA would have had an apparent reason to combine “orally administering zoledronic acid” and “treating pain associated with a joint.” PO Resp. 11.

In its Reply, Petitioner argues that the Board’s prior findings in PGR2017-00022 preclude Patent Owner from contesting the obviousness challenge of claims 15–30 in this case. Reply, 17–18 (citing *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00022, Paper 50 at 90 (PTAB Nov. 14, 2018)).

c. Discussion

(i) Obviousness of Claims 15–30

Challenged claims 15–30 of the '839 patent are directed to treating a patient suffering from joint-associated pain at an intensity of 5 or greater as measured using the NRS or VAS scale. The challenged claims do not recite an efficacy requirement, rather the claims define a patient population. For example, independent claim 15 is directed to administering zoledronic acid “to a patient having 1) pain associated with a joint and 2) a pain intensity of 5 or greater measured using the 0–10 NRS or 5 cm or greater using the 10 cm VAS.” Ex. 1001, 105:38–44.

For the patient population element of the claims, Petitioner relies on the combination of de Castro, Zaspel and Dowd. Pet. 68–71. De Castro reports the treatment of a 31-year-old female “with history of neuropathic pain for 16 years.” Ex. 1015, 72. De Castro does not expressly disclose that the patient suffered from a pain intensity of 5 or greater measured using the 0–10 NRS or 5 cm or greater using the 10 cm VAS; rather, de Castro discloses that the patient reported pain that was “spontaneous, very severe with intensity 10 in the worst moments, according to verbal numerical scale.” *Id.* Petitioner contends that “based on de Castro’s treatment of a patient having pain of 10 on a 1–10 scale for well over three months, a POSA also would have known that zoledronic acid could be used to treat CRPS pain in patients experiencing pain ≥ 5 cm on the VAS for at least three months, as recited in claims 15 and 24.” Pet. 70 (citing Ex. 1003 ¶ 265). On this point, Dr. Poree testifies as follows:

A POSA also would have known that zoledronic acid could be used to treat CRPS pain in patients experiencing pain ≥ 5 cm on the VAS for at least three months, as recited in claims 15 and 24,

based on de Castro's disclosure of successful treatment of a patient having pain of 10 on a 1–10 scale for well over three months. Exhibit 1015, de Castro, at 72–73.

Ex. 1003 ¶ 72–73. We credit Dr. Poree's un rebutted testimony and determine that a person of ordinary skill in the art would have understood that the patient disclosed in de Castro experience pain at an intensity encompassed by the claims. De Castro, however, does not expressly disclose that the patient suffered from pain associated with a joint.

Neither does Zaspel. Zaspel discloses the treatment of 24 patients who suffered from CRPS-I for less than three months. Ex. 1016, 1.

According to Zaspel,

The patients treated with bisphosphonate zoledronic acid generally showed improvement in the dystrophic symptoms. The severity of the pain was decisively and significantly improved ($p < 0.001$) in the same group.

Id. at 2. Zaspel does not expressly disclose that the patient suffered from a pain intensity of 5 or greater measured using the 0–10 NRS or 5 cm or greater using the 10 cm VAS. Zaspel does not expressly disclose that the patient suffered from pain associated with a joint.

Dowd, however, discloses pain associated with a joint, but does not expressly disclose any patient suffering from a pain intensity of 5 or greater measured using the 0–10 NRS or 5 cm or greater using the 10 cm VAS. Petitioner relies on Dowd for its teaching that “CRPS can affect the knee and is a cause of knee pain” and that “bisphosphonates can be used to treat CRPS affecting the knee.” Pet. 70 (citing Ex. 1003 ¶ 267). On this point, Dr. Poree testifies as follows:

As discussed above, Dowd teaches that CRPS of the knee is a cause of knee pain, and that bisphosphonates can be used to treat

it, and Zaspel and de Castro teach that zoledronic acid is effective for the treatment of CRPS.

Ex. 1003 ¶ 267.

Having considered the parties positions and evidence of record, summarized above, we do not agree that the rationale and evidence of record are sufficient to establish that “[t]he POSA would have reasonably expected that zoledronic acid could be successfully used to treat CRPS of the knee, as discussed by Dowd.” Pet. 70. The prior art teaches that CRPS has many symptoms that generally involve injury to a limb. Ex. 1015, 71 (“decreased mobility, weakness, shivering, functional limb amputation”). However, it is unclear on this record whether such injury, or associated pain, necessarily involves a joint. Dowd discloses that under certain circumstances CRPS may develop as a result of a knee injury, in which case “the patellofemoral joint is always involved.” *Id.* at 289. Dowd also lists several medications that have been used to treat CRPS, of which bisphosphonates, in general,⁸ are disclosed. However, Dowd fails to disclose how much pain CRPS knee patients experience relative to the other “various presentations, postulated pathophysiology and anatomical distribution” of the syndrome. Ex. 1009, 285. Furthermore, Dowd discloses that the syndrome is complex, not well understood, and that the degree of treatment success is attributed to various factors including precipitating disease factors, affected limb, age, and the time at which treatment began. *Id.* at 289; *see also* Ex. 1016, 1 (“The treatment of CRPS I, like the underlying pathophysiology, remains an

⁸ Dowd does not expressly disclose the use of zoledronic acid.

incompletely researched field to this day.). The evidence of record fails to link intensity of pain with any of those various factors.

Taken together, the prior art describes a disease population that is large and diverse, but fails to sufficiently guide a person of ordinary skill in the art to the treatment of the specific subpopulation of patients defined by the claims. Accordingly, we determine that Petitioner has failed to demonstrate by a preponderance of evidence that challenged claims 15–30 would have been obvious over the combination of de Castro, Zaspel, Dowd, and Hanna.

(ii) Issue Preclusion

Petitioner contends that the Board’s findings in PGR2017-00022 collaterally estop Patent Owner from asserting that the subject matter of claims 15–30 would have been nonobviousness in view of de Castro, Zaspel, Dowd, and Hanna. Reply 17. Collateral estoppel, also known as issue preclusion, precludes a party from relitigating an issue “when an issue of fact or law is actually litigated and determined by a valid and final judgment, and the determination is essential to the judgment,” in which case “the determination is conclusive in a subsequent action between the parties, whether on the same or a different claim.” Restatement (Second) of Judgments § 27 (1982). The Supreme Court

has long recognized that “the determination of a question directly involved in one action is conclusive as to that question in a second suit.” The idea is straightforward: Once a court has decided an issue, it is “forever settled as between the parties,” thereby “protect[ing]” against “the expense and vexation attending multiple lawsuits, conserv[ing] judicial resources, and foster[ing] reliance on judicial action by minimizing the possibility of inconsistent verdicts.” In short, “a losing litigant deserves no rematch after a defeat fairly suffered.”

B & B Hardware, Inc. v. Hargis Indus., Inc., 135 S. Ct. 1293, 1302–03 (2015) (internal citations omitted). The Federal Circuit has articulated the following test for determining the proper application of collateral estoppel:

- (1) a prior action presents [the] identical issue;
- (2) the prior action actually litigated and adjudged that issue;
- (3) the judgment in that prior action necessarily required determination of the identical issue; and
- (4) the prior action featured full representation of the estopped party.⁹

VirnetX Inc. v. Apple, Inc., 909 F.3d 1375, 1377 (Fed. Cir. 2018) (quoting *Stephen Slesinger, Inc. v. Disney Enters., Inc.*, 702 F.3d 640, 644 (Fed. Cir. 2012)).

The Federal Circuit has applied collateral estoppel in the context of *inter partes* reviews. *MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1376 (Fed. Cir. 2018) (“It is well established that collateral estoppel . . . applies in the administrative context.”). Moreover, application of collateral estoppel in *inter partes* reviews “is not limited ‘to patent claims that are identical. Rather, it is the identity of the issues that were litigated that determines whether collateral estoppel should apply.’” *Nestle USA, Inc. v. Steuben Foods, Inc.*, 884 F.3d 1350, 1352 (Fed. Cir. 2018) (quoting *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1342 (Fed. Cir. 2013)). Those principles apply with equal force in the context of our administrative

⁹ The fourth factor of the collateral estoppel test has sometimes been referred to as “(4) the party defending against preclusion had a full and fair opportunity to litigate the issues.” *Levi Strauss & Co. v. Abercrombie & Fitch Trading Co.*, 719 F.3d 1367, 1371 (Fed. Cir. 2013). We consider the analysis to be the same regardless of how that factor is articulated.

post grant review process. The collateral-estoppel effect of an administrative decision of unpatentability generally requires the invalidation of related claims that present identical issues of patentability. *MaxLinear, Inc.*, 880 F.3d at 1377. “If the differences between the unadjudicated patent claims and adjudicated patent claims do not materially alter the question of invalidity, collateral estoppel applies.” *Id.*; see also *Soverain Software LLC v. Victoria's Secret Direct Brand Mgmt., LLC*, 778 F.3d 1311, 1315 (Fed. Cir. 2015); *Bourns, Inc. v. United States*, 537 F.2d 486, 493 (Ct. Cl. 1976) (per curiam).

Having considered the question of obviousness at issue in PGR2017-00022, we find that the unpatentability analysis in this case is materially different so as to account for the differences between the scope of the challenged claims in the '839 patent and U.S. Patent 9,408,862 B2 (“the '862 patent”), the patent challenged in PGR2017-00022. The obviousness analysis in PGR2017-00022 does not address treatment of a patient population having the pain intensity recited in claims 15–30 because the claims of the '862 patent do not contain such a limitation. *Grünenthal*, PGR2017-00022, Paper 50, 69–69, 90. Accordingly, we determine that the differences between the claims of the '862 patent and challenged claims 15–30 of the '839 patent materially alter the question of patentability presented before us in this proceeding. Because the requirements of issue preclusion have not been met, the doctrine is inapplicable in this case.

III. CONCLUSION

In summary, we make the following conclusions.¹⁰

Claims	35 U.S.C. §	Reference(s) /Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–14	112(a)	Written Description		1–14
1–14	112(a)	Enablement		1–14
1–14	103	Varenna 2012, Muratore, Gatti 2009, Dowd	1–14	
1–9, 13, 14	103 ¹¹	Varenna Protocol, Rossini		
1–9, 13, 14	103	Walsh, Thompson, Fox, Gatti 2009, Rossini		1–9, 13, 14

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).

¹¹ As explained above in Section II.D.3, we do not reach Petitioner’s challenge to claims 1–9, 13, and 14 as obvious over the combination of Varenna Protocol and Rossini.

Claims	35 U.S.C. §	Reference(s) /Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
15–30	103	de Castro, Zaspel, Dowd, Hanna		15–30
Overall Outcome			1–14	15–30

IV. ORDER

Accordingly, it is

ORDERED that claims 1–14 of the '839 patent are unpatentable;

FURTHER ORDERED that claims 15–30 of the '839 patent are not shown to be 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.

PGR2019-00003
Patent 9,867,839 B2

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