Paper No. ___
Filed: August 21, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GRÜNENTHAL GMBH,

Petitioner

v.

ANTECIP BIOVENTURES II LLC,

Patent Owner.

Case PGR2018-00092
U.S. Patent No. 9,820,999

PETITION FOR POST GRANT REVIEW

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

EXHIBIT LIST

Exhibit (Ex.)	Description	Abbreviation
1001	U.S. Patent No. 9,820,999	'999 patent
1002	[Reserved]	
1003	Declaration of Lawrence Poree, M.D., Ph.D.	Poree Decl.
1004	Curriculum Vitae of Lawrence Poree, M.D., Ph.D.	
1005	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)	Varenna 2012
1006	S. Bruehl, *How common is complex regional pain syndrome-Type I*, PAIN 129:1-2 (2007)	Bruehl
1007	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)	Gatti
1008	G. La Montagna et al., *Successful neridronate therapy in transient osteoporosis of the hip*, CLIN. RHEUMATOL. 24:67-69 (Aug. 2004)	La Montagna

1009	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)	Manicourt
1010	M. Muratore et al., *Il neridronato nel trattamento dell'algodistrofia simpatica riflessa dell'anca: confronto in aperto con il clodronato*, PROGRESSI IN REUMATOLOGIA, ABSTRACT BOOK VII CONGRESSO NAZIONALE COLLEGIO DEI REUMATOLOGI OSPEDALIERI 5(Suppl. 1):89 (April 16-18, 2004)	Muratore
1011	J. Yanow et al., *Complex regional pain syndrome (CRPS/RSD) and neuropathic pain: Role of intravenous bisphosphonates as analgesics*, THE SCIENTIFIC WORLD JOURNAL 8:229-36 (Feb. 2008)	
1012	U.S. Patent No. 6,468,559, issued Oct. 22, 2002	'559 patent
1013	U.S. Patent No. 4,822,609, issued Apr. 18, 1989	'609 patent
1014	S. Adami et al., *Intravenous neridronate in adults with osteogenesis imperfecta*, J. BONE & MINERAL RES. 18(1):126-30 (2003)	Adami

1015	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 (2016)	Varenna 2016
1016	U.S. Provisional Patent App. No. 61/646,538	'538 application
1017	Merskey et al., *Pain terms: A current list with definitions and notes on usage*, in CLASSIFICATION OF CHRONIC PAIN 207-213 (Merskey & Bogduk eds. 1994)	
1018	Fosamax® (alendronate sodium) Tablets for Oral Use and Oral Solution Prescribing Information (Feb. 2012)	Fosamax® Label
1019	Boniva® (ibandronate sodium) Tablets Prescribing Information (Jan. 2011)	Boniva® Label
1020	Schwarzer & Maier, *Complex regional pain syndrome*, *in* GUIDE TO PAIN MANAGEMENT IN LOW-RESOURCE SETTINGS 249-254 (Kopf & Patel eds. 2010)	Schwarzer
1021	File History of U.S. Patent No. 9,707,245, Part 1 of 2, pages 1-350	'245 file history

1022	File History of U.S. Patent No. 9,707,245, Part 2 of 2, pages 351-629	’245 file history
1023	Abe et al., *Improvement of pain and regional osteoporotic changes in the foot and ankle by low-dose bisphosphonate therapy for complex regional pain syndrome type I: a case series*, J. MED. CASE REPORTS 5(349):1-6 (Aug. 2011)	Abe
1024	U.S. Patent Application No. 13/894,274	
1025	U.S. Patent Application No. 14/063,979	
1026	U.S. Patent Application No. 14/279,229	
1027	U.S. Patent Application No. 14/530,556	
1028	International Publication No. WO 2015/184003	
1029	U.S. Provisional Patent Application. No. 62/378,140	
1030	U.S. Patent Application No. 15/357,932	
1031	U.S. Provisional Patent Application No. 62/431,287	
1032	U.S. Patent Application No. 14/279,241	
1033	International Publication No. WO 2015/060924	
1034	U.S. Patent No. 9,707,245	’245 patent

1035	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 (2016), available at https://academic.oup.com/painmedicine/article/18/6/1131/2924769	
1036	Oxford University Press Info re: Downloads and Public accessibility	
1037	Manara et al., *SAT0524 Predictors of a Clinical Response to Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I,* ANNALS OF THE RHEUMATIC DISEASES, 73(Suppl. 2) (2014)	Manara
1038	Manara et al., *SAT0524 Predictors of a Clinical Response to Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I,* ANNALS OF THE RHEUMATIC DISEASES, 73(Suppl. 2) (2014), available at https://ard.bmj.com/content/73/Suppl_2/781.1	

1039	File History of U.S. Patent No. 9,820,999 Part 1 of 3, Pages 1-484	
1040	File History of U.S. Patent No. 9,820,999 Part 2 of 3, Pages 485-851	
1041	File History of U.S. Patent No. 9,820,999 Part 3 of 3, Pages 852-1060	
1042	Manara et al., *SAT0524 Predictors of a Clinical Response to Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I*, ANNALS OF THE RHEUMATIC DISEASES, 73(Suppl. 2) (2014) (CD-ROM)	

I. INTRODUCTION

All of the claims of U.S. Patent No. 9,820,999 ("the '999 patent") cover methods 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 claim 1. CRPS is a severely debilitating pain syndrome that sometimes develops after trauma such as a bone fracture, a sprain, surgery, etc. Ex. 1003 ¶18. Long before any of the '999 patent's purported priority applications were filed, it was well-known that bisphosphonate drugs, like neridronic acid, could be used to treat pain associated with CRPS. *Id.* ¶75. As such, Patent Owner directed the '999 patent claims to effective treatment of pain associated with CRPS specifically ***triggered by fracture***.

But the '999 patent inventor did not actually invent such methods. Neither the inventor, the Patent Owner, nor any of their affiliated companies is actually performing studies on or developing neridronic acid. Neridronic acid was developed and studied in Italy by real-party-in-interest Abiogen Pharma SpA, which has licensed the development and marketing rights for North America to Petitioner Grünenthal GmbH.

Patent Owner initially sought claims covering neridronic acid for treatment of CRPS in late 2016 by filing continuation and continuation-in-part applications to its patents covering ***zoledronic acid*** (another bisphosphonate) and amending their claims and titles to refer to neridronic acid. Yet those new claims directed to CRPS treatment with neridronic acid were rejected. Ex. 1022 at 451-56. During prosecution of the '999 patent's parent application, the patent examiner correctly noted treating CRPS pain with bisphosphonates was obvious and well-known in the art. *Id.* at 454. In response, Patent Owner amended its claims to require treatment of CRPS specifically triggered by fracture. *Id.* at 509-19.

Patent Owner and its attorneys likely got the idea to claim treatment of pain associated with CRPS triggered by fracture from data generated by an Italian group ultimately published as 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 (Sept. 2016) (Ex. 1015, "Varenna 2016"). Varenna 2016 discloses that CRPS patients were more likely to respond to neridronate treatment if their CRPS was triggered by fracture rather than other events. Patent Owner cited to Varenna 2016—not its own experiments or any information in the specification—as "unexpected results" of what it now claims as its own invention.

But the use of neridronic acid to treat pain associated with CRPS triggered by fracture was already known in the art. The data that Patent Owner used to purportedly support the '999 patent and its parent's claims came from a much earlier randomized, double-blind, placebo-controlled clinical trial published in 2012 as 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"). Varenna 2012 disclosed—before the '999 patent's earliest possible priority date—that neridronic acid effectively relieves pain associated with CRPS triggered by fracture.

Indeed, even before 2012 it was known that neridronic acid could be used to treat CRPS, and bone fractures were known as one of the most common triggering events. *See, e.g.*, Ex. 1007 at 1308; Ex. 1008; Ex. 1010. The Varenna 2016 data does not change the fact that by 2012 or earlier, a POSA would have reasonably expected neridronic acid to be effective to treat pain associated with CRPS triggered by fracture. Thus, the '999 patent claims are anticipated, or at least obvious over, Varenna 2012 alone or in combination with other prior art demonstrating neridronic acid's efficacy in treating CRPS. And Patent Owner's dependent claims to specific dosing regimens, oral administration, and treatment of CRPS type II do not add anything that is inventive over the prior art.

Unsurprisingly, because Patent Owner did not invent the claimed methods, the ’999 patent specification also fails to teach a POSA how to perform and use them. Patent Owner attempted to support these claims by adding some sentences regarding fractures to the specification for the first time in a 2016 provisional application. But the specification lacks any examples or experimental data demonstrating the use of neridronic acid to treat pain associated with CRPS, let alone CRPS triggered by fracture. And other than broad ranges of potential dosages, there is no disclosure of dosing regimens a POSA could use to treat CRPS triggered by fractures in humans using neridronic acid. For example, the specification is completely silent as to the dosing frequency and duration for such treatment. The specification is also devoid of any disclosures regarding how an ***effective*** reduction in pain can be achieved using neridronic acid, as required by all of the ’999 patent claims. As a result, all of the ’999 patent claims are also invalid for lack of enablement.

Furthermore, because the ’999 patent and its priority applications do not enable the claims, and because disclosures purportedly describing the treatment of CRPS caused by fracture do not appear until a 2016 provisional application, the very data that Patent Owner relied upon for “unexpected results” is actually anticipatory prior art. This data is disclosed in Varenna 2016 and in the earlier publication M. Manara et al., *SAT0524 Predictors of a Clinical Response to*

Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I, ANNALS OF THE RHEUMATIC DISEASES, 73(Suppl. 2) (2014) (Exs. 1037, 1038, 1042, "Manara"), both of which are anticipatory.

Thus, for the reasons discussed below, Petitioner respectfully requests that the board cancel all claims of the '999 patent as unpatentable under 35 U.S.C. §§ 112, 102, and/or 103.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-in-Interest (§ 42.8(b)(1))

The real parties-in-interest are Petitioner Grünenthal GmbH and Abiogen Pharma SpA. Abiogen Pharma SpA developed neridronic acid and has licensed the development and marketing rights for North America to Petitioner Grünenthal GmbH.

B. Related Matters (§ 42.8(b)(2))

Petitioner filed post grant review petitions against Patent Owner's U.S. Patent No. 9,283,239 ("the '239 patent") on December 14, 2016 (Case PGR2017-00008), U.S. Patent No. 9,408,862 ("the '862 patent") on May 8, 2017 (Case PGR2017-00022), U.S. Patent No. 9,539,268 ("the '268 patent") on October 10, 2017 (Case PGR2018-00001), and U.S. Patent No. 9,707,245 ("the '245 patent," Ex. 1034) on April 18, 2018 (Case PGR2018-00062).

The challenged '999 patent, the '245 patent, and the '239 patent are all part of the same patent family. Each purportedly claims priority to Provisional

Application No. 61/646,538 filed on May 14, 2012 and U.S. Patent Application No. 13/894,274, filed on May 14, 2013. In PGR2017-00008, post grant review was instituted against the '239 patent on July 7, 2017 and the Board issued a final written decision finding all challenged claims unpatentable for lack of written description on June 22, 2018. An institution decision is forthcoming in PGR2018-00062.

The '862 and '268 patents belong to a different patent family than the '999 patent, but share the same inventor and also cover methods of treating pain conditions with bisphosphonate drugs. Post grant review was instituted against the '862 patent in PGR2017-00022 on November 15, 2017 and the Board heard oral argument on July 24, 2018. Post grant review was instituted against the '268 patent in PGR2018-00001 on May 1, 2018.

To Petitioner's best knowledge, the '999 patent is not currently involved in any other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

C. Lead and Back-up Counsel (§ 42.8(b)(3))

Lead Counsel	Back-up Counsel
Daniel J. Minion Registration No. 53,329 FITZPATRICK, CELLA, HARPER & SCINTO 1290 Avenue of the Americas New York, NY 10104 Tel: 212-218-2538 Fax: 212-218-2200	Bruce C. Haas Registration No. 32,734 FITZPATRICK, CELLA, HARPER & SCINTO 1290 Avenue of the Americas New York, NY 10104 Tel: 212-218-2290 Fax: 212-218-2200

dminion@fchs.com	bhaas@fchs.com

D. Service Information (§ 42.8(b)(4))

Please direct all correspondence to lead and back-up counsel at the above addresses and to GrunenthalPGR@fchs.com. Petitioner consents to electronic service to GrunenthalPGR@fchs.com and at the e-mail addresses above.

III. PAYMENT OF FEES

Pursuant to 37 C.F.R. §§ 42.203(a) and 42.15(b), the required fees are submitted herewith. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 50-3939.

IV. TIME FOR FILING PETITION

The ’999 patent issued on November 21, 2017. This Petition was timely filed on August 21, 2018, which is no later than the date that is nine months after the date of the grant of the patent. 37 C.F.R. § 42.202.

V. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.204(a), Petitioner certifies that the ’999 patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR of the ’999 patent challenging the claims on the grounds identified in this Petition.

The ’999 patent is available for PGR pursuant to the America Invents Act (“AIA”), Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 293 (2011) because, as

explained below in Section X, at least one claim has an effective filing date on or after March 16, 2013.

VI. CHALLENGED CLAIMS AND RELIEF SOUGHT

Petitioner respectfully requests post grant review and cancellation of '999 patent claims 1-30 as unpatentable under 35 U.S.C. §§ 112, 102, and/or 103. It is more likely than not that claims 1-30 are unpatentable on the following grounds:

Ground	Claims	Statutory Basis	Prior Art References
1	1-30	35 U.S.C. § 112(a) Lack of Enablement	
2	1-4, 9-10, 12, 14, 16-18, 23-25, 27-29	35 U.S.C. § 102 Anticipation	Varenna 2012
3	1-4, 9-10, 12, 14, 16-18, 23-25, 27-28	35 U.S.C. § 102 Anticipation	Varenna 2016
4	1-4, 9-10, 12, 14, 16-18, 24-25, 27-28	35 U.S.C. § 102 Anticipation	Manara
5	1-4, 9-20, 22-29	35 U.S.C. § 103 Obviousness	Varenna 2012 Varenna 2016 Manara Bruehl Gatti La Montagna Muratore
6	5-8, 21	35 U.S.C. § 103 Obviousness	Varenna 2012 Varenna 2016 Manara Manicourt

Ground	Claims	Statutory Basis	Prior Art References
7	30	35 U.S.C. § 103 Obviousness	Varenna 2012 Varenna 2016 Manara Schwarzer Bruehl Gatti La Montagna Muratore

VII. THE '999 PATENT PROSECUTION HISTORY

A. Application No. 15/647,140

The '999 patent issued from Application No. 15/647,140 (Exs. 1039-1041, "the '140 application"), filed July 11, 2017. *See* Ex. 1041 at 970-76. The '140 application's original title was "Co-Administration of Steroids and Zoledronic Acid to Prevent and Treat Pain," but Patent Owner filed amended the title to "Neridronic Acid for Complex Regional Pain Syndrome." Ex. 1039 at 164-66. The specification also included new passages concerning fracture as a "precipitating" event for CRPS, which first appeared in Provisional Application No. 62/431,287 filed December 7, 2016 and were absent from earlier applications. *See, e.g.*, *id.* at 22, ¶[49]*;* Ex. 1031 at 20, ¶48. The application underwent little substantive prosecution. Patent Owner filed a terminal disclaimer in response to a double-patenting rejection and all claims were allowed. Ex. 1041 at 970-76.

B. Application No. 15/357,932

The '999 patent is a continuation-in-part of application No. 15/357,932 (Ex. 1030, "the '932 application"), filed November 21, 2016, which issued as the '245

patent on July 18, 2017. The original title of the '932 application also referred to zoledronic acid until Patent Owner amended it to read "Neridronic Acid for Treating Complex Regional Pain Syndrome." Ex. 1021 at 134-38. Original claim 1, from which all of the other original claims (2-30) depended, recited "A method of treating pain associated with complex regional pain syndrome (CRPS) comprising administering neridronic acid to a human being, wherein the neridronic acid is in a salt or an acid form." *Id.* at 107.

The Examiner rejected the original claims as obvious over J. Yanow et al., *Complex regional pain syndrome (CRPS/RSD) and neuropathic pain: Role of intravenous bisphosphonates as analgesics*, THE SCIENTIFIC WORLD JOURNAL, 8:229-36 (Feb. 2008) (Ex. 1011) in view of U.S. Patent No. 6,468,559 (Ex. 1012), U.S. Patent No. 4,822,609 (Ex. 1013), and S. Adami et al., *Intravenous neridronate in adults with osteogenesis imperfecta*, J. BONE & MINERAL RES., 18(1):126-30 (2003) (Ex. 1014). Ex. 1022 at 453-56. The Examiner noted that "[s]ince bisphosphonates are known to be useful in treating CRPS, employing any known bisphosphonates, including neridronic acid, in the method of treating CRPS would be reasonably expected to be effective. In addition, the dosage forms and the herein claimed routes of administration and the dosing regimen are all well-known according to the teachings of the cited prior art." *Id.* at 454. The Examiner pointed out that the '559 patent teaches oral compositions containing

bisphosphonates, including neridronic acid, and that the ’609 patent and Adami teach intravenous administration of neridronic acid. *Id.* The Examiner concluded that “[i]t would have been obvious to one of ordinary skill in the art to employ neridronic acid orally or intravenously, in the dosage herein claimed, for treating CRPS.” *Id.*

Patent Owner did not challenge the Examiner’s conclusions. Instead, Patent Owner simply added “to a human being with CRPS, wherein bone fracture was a predisposing event for CRPS” to original claim 1. *Id.* at 510, 512.

Because the passages regarding fracture as a precipitating event for CRPS in the ’140 application were not added to the patent family until December 7, 2016, Patent Owner pointed to paragraphs [49] and [74] and examples 3 and 9 of the ’932 application specification for support. *Id.* at 514. But paragraphs [49] and [74] do not mention fractures or any other predisposing events for CRPS. Paragraph [49] relates to the age of patients treated for inflammatory conditions. Ex. 1021 at 25. Paragraph [74] simply lists nitrogen-containing bisphosphonates that allegedly may be administered to treat CRPS, none of which are neridronic acid. *Id.* at 30. Example 9 is similarly irrelevant; it describes a method of synthesizing two compounds referred to as “Compound 1” and “Compound 2,” neither of which is neridronic acid or a neridronate salt. *Id.* at 82-84. And example 3 concerns not neridronic acid, but ***zoledronic acid***—the compound

originally referred to in the application's title. *Id.* at 70-72. Example 3 describes a particular rat model that purportedly "replicates" various triggering events for human CRPS.

In actual fact, the '932 application specification—like all of the applications in the '999 patent's family filed before December 7, 2016—nowhere describes the use of neridronic acid to treat CRPS triggered by bone fracture. Nonetheless, after amending all claims to require bone fracture as a predisposing event for CRPS, Patent Owner argued that the cited prior art did not teach or suggest the new limitation of amended claim 1. Ex. 1022 at 516.

Patent Owner also attempted to demonstrate unexpected results as objective evidence of nonobviousness. Patent Owner did not point to experimental results described in the specification, or even to any experiments that the inventor or Patent Owner actually performed. Patent Owner instead relied on data generated by an Italian group led by Dr. Massimo Varenna, which were ultimately published in Varenna 2016. *Id.* at 514-19; Ex. 1015. After adding a claim limitation based on the Varenna group's work, Patent Owner argued that "CRPS patients wherein bone fracture was a predisposing event for CRPS are substantially more likely to benefit from bisphosphonate treatment than other CRPS patients," and that "[t]his unexpected benefit for this patient subpopulation is an objective indicia of non-obviousness supporting the patentability of the instant claims." Ex. 1022 at 518.

Apparently persuaded that the Varenna group's data somehow showed that the inventor had invented something, the Examiner allowed the claims on May 24, 2017. *Id.* at 548. The Examiner stated that "the herein claimed method of treating ***pain in patients that have fracture as the predisposing factor*** is not taught or fairly suggested by the prior art. The pain treatment to responders with fracture as the predisposing factor respond [sic] was superior than those to responders with other pre-disposing factors." *Id.* at 548. Thus, the claims were only allowed because the prior art cited by the examiner supposedly did not teach the treatment of pain associated with CRPS triggered by fracture.

VIII. PERSON OF ORDINARY SKILL IN THE ART

Challenged claims 1-30 are directed to methods of treating pain associated with CRPS. CRPS is described in the art as a "severely disabling pain syndrome characterized by sensory and vasomotor disturbance, [edema] and functional impairment that in most cases develop[s] following a trauma or surgery." Ex. 1003 ¶22; Ex. 1005 at 534. CRPS is also described in the '999 patent as "a debilitating pain syndrome . . . characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor and sensory changes." Ex. 1001 col. 13, ll. 11-14. Consequently, claims 1-30 are directed to the field of treatment of pain associated with CRPS. Ex. 1003 ¶20. A person of ordinary skill in the art for the '999 patent ("POSA") would therefore have 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. *Id.* ¶20.

IX. CLAIM CONSTRUCTION

In a PGR, patent claims are given their broadest reasonable interpretation in light of the specification as interpreted by a POSA. 37 C.F.R. § 42.200(b). Where "the specification . . . reveal[s] a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess . . . the inventor's lexicography governs." *Phillips v. AWH Corp.,* 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*).

The claim terms below require construction and should be given the constructions proposed below. The remaining terms should be given their broadest reasonable interpretation in light of the specification.

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 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.

A. "A method of treating pain associated with complex regional pain syndrome (CRPS) comprising selecting a human being having CRPS"

Claim 1 of the '999 patent is directed to "[a] method of treating pain associated with [CRPS] comprising selecting a human being having CRPS." This term should be construed as a limiting preamble. A preamble limits the invention if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim. *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). Moreover, the Federal Circuit has construed method of treatment preambles as limiting where the claims contain similar limitations. *See, e.g., Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003).

The '999 patent specification states that "[t]he term 'treating' or 'treatment' broadly includes any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals." Ex. 1001 col. 7, ll. 38-42; Ex. 1003 ¶31. The claimed "treatment" is directed to a specific condition: pain associated with CRPS. Ex. 1003 ¶32. A POSA would interpret these limitations of challenged claims 1-30 as requiring

administration of neridronic acid to a human being with CRPS for the purpose of diagnosing, curing, mitigating, and/or preventing pain associated with CRPS or for having activity that otherwise affects the structure or any function of the body in a human being with CRPS. *Id.* ¶33. The "treatment" limitation on its own does not connote any particular level of efficacy in reducing pain. *Id.* ¶34.

B. "triggered by bone fracture"

The '999 patent specification does not define "triggered by bone fracture." Ex. 1003 ¶35. Statements in the '999 patent regarding bone fracture as a "precipitating event" for CRPS first appeared in Provisional Application No. 62/431,287 filed December 7, 2016. *See, e.g.*, Ex. 1001 col. 8, ll. 27-37; Ex. 1031 at 20, ¶48.

The PTAB should "consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review," such as an IPR or PGR proceeding. *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016) (quoting *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292 (Fed. Cir. 2015)). The prosecution history of other patents in the same patent family may also inform the proper construction of claim terms. *See Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999). During prosecution of the parent '245 patent, Patent Owner stated that a "predisposing event [is] also called precipitating event and triggering event." Ex. 1022 at 518; Ex. 1003 ¶36. A POSA

would have known that a "precipitating event" or "precipitating condition" is an event or factor that causes or contributes to occurrence or onset of a disease or disorder. Ex. 1003 ¶37. Thus, a POSA would have understood that the term "triggered by bone fracture," as used in the '999 patent claims, means that bone fracture is an event that caused or contributed to the occurrence or onset of CRPS, and is synonymous with bone fracture as a "precipitating event" or "predisposing event." *Id.* ¶38.

C. "wherein the treatment is effective in reducing pain"

The term "wherein the treatment is effective in reducing pain" is an additional limitation of challenged claims 1-30 that imposes an express efficacy requirement. Ex. 1003 ¶39. The preamble requires that neridronate be administered to a human being for the purpose of treating pain associated with CRPS; this limitation requires that such treatment actually produce an observable and/or measurable reduction in pain. *Id.* ¶40. Claim 1 provides that the *treatment* must be *effective*, showing that an additional efficacy requirement is imposed. *Id.* ¶41. But further evidence that this limitation is an independent efficacy requirement can be found by comparing the '999 patent claims to the claims of the parent '245 patent. The '245 patent claims have a similar preamble, but do not have this limitation. *See* Ex. 1034 claim 1. This, too, strongly suggests that

"wherein the treatment is effective in reducing pain" is an additional limitation beyond the meaning of the preamble.

X. THE '999 PATENT IS ELIGIBLE FOR PGR

The application that issued as the '999 patent was filed July 11, 2017. The '999 patent purportedly claims priority to only one application filed before March 16, 2013: Provisional Application No. 61/646,538, filed May 14, 2012. Ex. 1016 ("the '538 application"). All of the other alleged priority applications were filed after March 16, 2013. During prosecution, the examiner treated the '999 patent (and its parent '245 patent) as applications filed on or after March 16, 2013 and therefore subject to the first-to-file provisions of the AIA. Ex. 1039 at 171; Ex. 1022 at 453.

A patent that issues from an application filed after March 16, 2013, but that claims priority to an application filed before March 16, 2013, is available for PGR "if the patent contains . . . at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 11 (P.T.A.B. Dec. 22, 2015). To meet the written description requirement of 35 U.S.C. § 112, the earlier application must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject

matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). As such, the specification must describe the invention in a manner "understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* "[A] description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352 (citing *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)).

To meet the enablement requirement of 35 U.S.C. § 112, the earlier application(s) must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citing *In re Wands*, 858 F.2d 731, 735, 736-37 (Fed. Cir. 1988)). A specification that "provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention" does not fulfill the enablement requirement. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1198 (Fed. Cir. 1999).

Here, the '538 application, the only purported priority application filed before March 16, 2013, completely fails to describe and enable the methods of any of the '999 patent claims.

A. The ’538 Application Fails to Describe and Enable the “triggered by bone fracture” Limitation of Claim 1

Challenged claim 1 of the ’999 patent concerns a “method of treating pain associated with [CRPS] comprising selecting a human being having CRPS ***triggered by bone fracture***.” Challenged claims 2-30 all depend from claim 1 and therefore incorporate the “triggered by bone fracture” limitation.

The ’538 application simply does not provide any written description of this limitation. No triggering events for CRPS, let alone bone fractures specifically, are described or mentioned in the ’538 application. In fact, the terms “bone,” “fracture,” and “triggered” do not appear anywhere in the application. Ex. 1003 ¶45. To the contrary, statements regarding the use of neridronate to treat pain associated with CRPS wherein bone fracture was a “precipitating event” were not introduced to specifications in the ’999 patent family until December 7, 2016 when Patent Owner filed Provisional Application No. 62/431,287. *See, e.g.*, Ex. 1031 at 20, ¶48. There is nothing in the ’538 application from which a POSA could have concluded that the inventor was in possession of and actually invented a method of treating pain associated with CRPS triggered by bone fracture. A POSA would not have even understood that administering neridronic acid to treat CRPS specifically triggered by bone fracture was an aspect of the alleged invention. Ex. 1003 ¶46.

The ’538 application also does not enable the “triggered by bone fracture” limitation. As an initial matter, the ’538 application does not contain any examples

of using neridronic acid to treat CRPS pain, let alone pain associated with CRPS triggered by bone fracture. *Id.* ¶45. Because triggering events and fractures are not even mentioned with respect to neridronate treatment, the application also fails to teach a POSA how to use neridronic acid to treat pain associated with CRPS triggered by fracture. *Id.* ¶47. The '538 application is completely devoid of information concerning the route of administration (*e.g.*, intravenous or oral), and the amount, frequency, and duration of neridronic acid dosing that a POSA could use to treat pain associated with CRPS triggered by bone fracture. Thus, the '538 patent does not teach a POSA how to use and perform the methods of treatment claimed in claims 1-30. Ex. 1003 ¶¶48-49.

B. The '538 Application Also Does Not Describe and Enable the "effective in reducing pain" Limitation of Claim 1

The '538 application also does not describe or enable an effective reduction in pain resulting from the administration of neridronic acid to any type of patient. There are no examples showing reduction in pain upon administration of neridronic acid to patients having CRPS, let alone CRPS triggered by bone fracture specifically. Ex. 1003 ¶¶50-51. The '538 application is devoid of information concerning the route of administration (*e.g.*, intravenous or oral), and the amount, frequency, and duration of neridronic acid dosing that a POSA could use to effectively reduce pain associated with CRPS triggered by bone fracture. *Id.* ¶51. In fact, the '538 application does not even state that neridronate is effective in

reducing CRPS pain. *Id.* ¶50. It broadly states that neridronate can be used to "treat CRPS," but as discussed above, the term "treatment" does not connote any particular level of efficacy in reducing pain. *See* Section IX.A. The specification also states that CRPS is characterized by not just pain, but also other signs and symptoms such as edema, changes in skin blood flow, and abnormal sudomotor activity. Ex. 1016 at 4. Treatment of CRPS simply does not inherently connote an effective reduction in pain as required by the '999 patent claims. Ex. 1003 ¶52. Consequently, the '538 application fails to describe and enable the '999 patent claims, and the '999 patent cannot claim priority to it.

C. The '538 Application Also Fails to Describe the Additional Limitations of Several Dependent Claims

The '538 application also fails to provide written description support for four types of additional limitations of several dependent claims. First, claims 10-26 recite particular amounts, frequencies, and/or durations of dosing for treatment of CRPS triggered by fracture with neridronic acid. But, the '538 application, as discussed above, does not disclose or enable the treatment of pain associated with CRPS triggered by bone fracture as required by claim 1. Unsurprisingly, it also contains no information about the dosing amounts or regimens that should be used to treat pain associated with CRPS triggered by bone fracture. A POSA would not understand that the inventor was in possession of the doses and/or dosing regimens of claims 10-26 based on the '538 application. Ex. 1003 ¶53. As one example, the

parenteral dosage range of "about 100 mg to about 300 mg of the neridronic acid . . . administered within one month" that is recited in claim 13 does not appear in the '538 application at all, let alone specifically for treatment of CRPS triggered by fracture. *Id.* ¶54.

Second, the '538 application only lists potential daily doses of neridronic acid. It does not describe the ***total*** dose of neridronic acid that should be administered for any type of CRPS pain. Thus, it fails to demonstrate possession of the total dose of 100 to 600 mg and 100 to 300 mg limitations recited in claims 14 and 15, respectively. *Id.* ¶55. The '538 application also does not contain any information regarding the frequency or duration of neridronic acid dosing for treatment of any type of CRPS pain. Thus, it also fails to demonstrate possession of the dosing regimen limitations of claims 18, 20, 23, and 25-26. *Id.* ¶56.

Third, the '538 application does not contain any information regarding the age of patients treated with neridronic acid. In fact, it does not even mention patient ages at all. Thus, the '538 application does not demonstrate that the inventor was in possession of and actually invented a method of treating CRPS with neridronic acid wherein the human is "at least 18 years of age" or "at least 40 years of age," as required by claims 27 and 28 respectively. *Id.* ¶57.

Fourth, the '538 application does not contain any information regarding the baseline pain intensity score of patients treated with neridronic acid, and does not

even mention pain intensity scores on the Numeric Rating Scale. Thus, the '538 application does not demonstrate that the inventor was in possession of and actually invented a method of treating CRPS with neridronic acid "wherein the human being has a baseline pain intensity score of at least 4," as required by claim 29. *Id.* ¶58.

* * *

For all of the reasons discussed above, the '538 application does not describe or enable the '999 patent claims. Because the '538 application is the only purported priority application filed before March 16, 2013, at least one claim of the '999 patent plainly has an effective filing date after March 16, 2013. Consequently, it is subject to the first-to-file provisions of the AIA and is eligible for PGR.[1]

[1] However, as discussed below, neither the '999 patent specification nor any of the applications it claims priority to enables claims 1-30 either. And none of the priority applications filed before December 7, 2016 provides written description support for the claims.

XI. HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1-30 Are Unpatentable Under 35 U.S.C. § 112(a) for Lack of Enablement

Challenged claim 1 of the '999 patent recites "[a] method of treating [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 claim 1 (emphasis added). Challenged claims 2-30 depend from claim 1 and therefore incorporate all of its limitations. The '999 patent specification does not enable a POSA to practice the purported inventions of these claims at least because it does not teach a POSA how to administer neridronic acid to a human being to treat pain associated with CRPS specifically triggered by fracture. And it certainly does not enable a method wherein such treatment is actually effective in reducing pain. Challenged claims 1-30 are therefore unpatentable for lack of enablement.

To satisfy the enablement requirement of 35 U.S.C. § 112, the specification must teach a POSA how to make and use the full scope of the claimed invention without "undue experimentation." *Genentech, Inc.*, 108 F.3d at 1365. It is not enough for the specification to "provide[] a starting point from which one of skill in the art can perform further research in order to practice the claimed invention." *Nat'l Recovery Techs., Inc.*, 166 F.3d at 1198. Factors to be considered in determining whether undue experimentation is required include (1) the quantity of

experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. However, analysis of all the factors is not required; "[t]hey are illustrative, not mandatory. What is relevant depends on the facts" of the particular case. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

Here, an analysis of the "Wands" factors demonstrates that the '999 patent claims are unpatentable for lack of enablement. Indeed, the specification provides little to no detail as to how critical aspects of the claimed invention can be practiced, namely, (1) the treatment of a human being having CRPS triggered specifically by bone fracture and (2) the effective reduction of pain in such a human being. *See Genentech*, 108 F.3d at 1365-68; *see also Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1281-85 (Fed. Cir. 2007).

1. A significant amount of experimentation is required due to the lack of direction and guidance in the specification, and the absence of any working examples

The '999 patent 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 triggered by bone fracture. Ex. 1003 ¶62.

It also provides no information about the dosing amounts or regimens that could be used to treat CRPS triggered by fracture. *Id.* ¶63. The specification broadly posits that "any suitable amount of an osteoclast inhibitor, including a bisphosphonate . . . may be used," without specifying any particular diseases or disorders, or methods of treatment. Ex. 1001 col. 32, ll. 37-40; Ex. 1003 ¶64. The only disclosure specific to neridronate dosing in the specification states only that the daily oral dose of neridronate may range anywhere from 10 mg to about 1,000 mg and that the parenteral dose may range anywhere from about 5 mg to about 500 mg. That broad dosage range is not tied to any particular disease or duration of treatment, whereas the specification elsewhere mentions various different conditions that may be treated. *See, e.g.*, Ex. 1001 col. 31, ll. 40-45; Ex. 1003 ¶65.

The specification does not specify the total dose of neridronic acid that should be administered for CRPS of any kind. It certainly does not teach a POSA, for example, that the total doses of 100-600 mg and 100-300 mg recited in claims 14 and 15 could be used to treat pain associated with CRPS triggered by bone fracture. *Id.* ¶66. The specification also does not contain any information regarding the frequency or duration of dosing of neridronic acid for treatment of CRPS. *Id.* ¶67. Based on the specification, a POSA would not know the dosing regimen of neridronate to use to treat CRPS triggered by fracture. *Id.* ¶¶68-69. The POSA would have to engage in significant experimentation, such as

conducting dose-finding studies and other clinical studies, to determine the appropriate dosing regimen to use. *Id*.

Moreover, the specification does not teach a POSA how to administer neridronate to ***effectively*** reduce pain in patients having CRPS triggered by bone fracture. No examples or data demonstrating effective pain relief using neridronate are provided. In particular, there are no examples or data demonstrating effective pain relief using neridronate specifically in humans having CRPS triggered by fracture. *Id.* ¶70.

Patent Owner may point to Example 3 as enabling, but this is incorrect for at least three reasons. First, Example 3 concerns the use of ***zoledronic acid***, not neridronic acid. *Id.* ¶72. Second, the example is a rat model and therefore is inapplicable to and does not support the treatment of human beings. *Id.* ¶73; *see also* Ex. 1017 at 210. And third, Example 3 does not describe treatment of human CRPS specifically triggered by bone fracture. Ex. 1003 ¶74. Although Example 3 uses a rat tibia fracture model of CRPS, "[t]his animal model has been shown to ***replicate*** the inciting trauma (such as a fracture, a surgery, a crushing injury, a cutting injury, a scratch, or a puncture injury), natural history, signs, symptoms, and pathologic changes observed in human CRPS." *Id.*; Ex. 1001 col. 51, ll. 33-38 (emphasis added). Thus, it is merely designed to replicate various types of inciting

trauma in humans. Example 3 simply does not instruct a POSA how administer ***neridronic acid*** to treat ***human*** CRPS ***triggered by fracture***. Ex. 1003 ¶74.

None of the applications to which the '999 patent purportedly claims priority remedy the lack of disclosure in the '999 patent specification. As discussed above, the '538 application does not describe or enable claims 1-30. U.S. Patent Application Nos. 14/530,556 (Ex. 1027), 14/279,229 (Ex. 1026), 14/063,979 (Ex. 1025), 13/894,274 (Ex. 1024), 15/357,932 (Ex. 1030), and 14/279,241 (Ex. 1032), U.S. Provisional Application Nos. 62/431,287 (Ex. 1031) and 62/378,140 (Ex. 1029), and PCT/US2015/032739 (Ex. 1028) and PCT/US2014/050427 (Ex. 1033) are all part of a chain of continuation or continuation-in-part applications culminating in the application that issued as the '999 patent. They all contain either the same or less information than the '999 patent specification and do not disclose any additional information regarding the effective reduction of pain in human CRPS triggered by fracture using neridronic acid. They do not contain any additional information about how to treat CRPS with neridronate other than the limited information in the '999 patent specification. Provisional Application No. 62/378,140 (Ex. 1029) does not even mention neridronic acid at all. As a result, claims 1-30 of the '999 patent, all of which require a method of using neridronic acid to treat a human being with CRPS triggered by bone fracture are unpatentable for lack of enablement. Ex. 1003 ¶77.

2. The prior art and a POSA's knowledge do not make up for the '999 patent's deficient disclosure

To be sure, methods of treating pain associated with CRPS with neridronic acid—including pain associated with CRPS triggered by fracture—were known in the prior art as explained in detail below in Sections XI.B - XII.E. However, although the specification need not disclose what is well known in the art, "that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement." *Genentech Inc.*, 108 F.3d at 1366. "[W]hen there is no disclosure . . . of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Id.* The prior art knowledge that CRPS triggered by fracture can be treated with neridronic acid cannot substitute for the enabling disclosure that is completely lacking from the '999 patent specification. Ex. 1003 ¶¶75-76.

B. Ground 2: Claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29 Are Anticipated Under 35 U.S.C. § 102 by Varenna 2012

Under 35 U.S.C. § 102(a), "[a] person shall be entitled to a patent unless . . . the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention." A claim is anticipated "if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631(Fed. Cir. 1987). Purported evidence of objective indicia of nonobviousness, such as unexpected results, is irrelevant to the anticipation inquiry. *See In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973); *In re Malagari*, 499 F.2d 1297, 1302 (C.C.P.A. 1974).

Challenged claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29 are anticipated by 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"). Varenna 2012 describes a randomized, double-blind, placebo-controlled human clinical study in which neridronate was administered to treat pain associated with CRPS, including in patients whose CRPS was triggered by fracture. Ex. 1003 ¶80; Ex. 1005 at 534, 536. Varenna 2012 is one of dozens of references listed on the face of the '999 patent, but was not applied by the examiner during prosecution. As

discussed in detail below, Varenna 2012 discloses each and every limitation of challenged claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29 and therefore anticipates those claims. Ex. 1003 ¶81.

1. Varenna 2012 Is Prior Art

Varenna 2012 is prior art to the '999 patent because it is a printed publication that was published on November 30, 2012, before the May 14, 2013 filing date of U.S. Patent Application No. 13/894,274. As discussed above, the '538 application—the only purported priority application filed before Varenna 2012's publication date—fails to enable and provide written description support for challenged claims 1-30 because it lacks any disclosure whatsoever of bone fracture as a triggering event for CRPS. *See* Section X.[2]

[2] Although Rheumatology Volume 52 Issue 3 is dated March 2013, Varenna 2012 was first published on November 30, 2012. Ex. 1005 at 534. Still, even if March 2013 were the publication date, Varenna 2012 would still be prior art to the '999 patent because it would have been published before the May 14, 2013 filing date of U.S. Patent Application No. 13/894,274.

2. Claim 1

Claim 1 recites "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." Varenna 2012 discloses all of the elements of Claim 1. It describes a randomized, double-blind, placebo-controlled human clinical study in which neridronate was administered to treat pain associated with CRPS in patients with CRPS triggered by fracture. Ex. 1005 at 534, 536; Ex. 1003 ¶80. Varenna 2012 therefore anticipates claim 1. Ex. 1003 ¶81.

a. "A method of treating pain associated with [CRPS]"

As discussed above, this claim term should be construed as requiring 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 having any activity that otherwise affects the structure or any function of the body in a human being with CRPS. The objective of the study in Varenna 2012 was "to test the efficacy of the amino-bisphosphonate neridronate in patients with CRP[S]-I." Ex. 1005 at 534; Ex. 1003 ¶83. According to Varenna 2012, "clinically relevant and persistent benefits" were associated with the administration of neridronate in the study. Ex. 1005 at 534; Ex. 1003 ¶84. "These results provide

conclusive evidence that the use of bisphosphonates, at appropriate doses, is the treatment of choice for CRPS-I." Ex. 1005 at 534; Ex. 1003 ¶84. Varenna 2012 observed that a 50% decrease in visual analogue scale (VAS) pain score, the primary measure of efficacy in the study, was obtained in 30 neridronate-treated patients (73.2%) vs. 13 controls. Ex. 1005 at 535, 536-37; Ex. 1003 ¶85. Thus, Varenna 2012 plainly discloses a method of treating CRPS as recited in Claim 1. Ex. 1003 ¶82.

b. "comprising selecting a human being having CRPS triggered by bone fracture"

As discussed above, 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. Varenna 2012 states that 82 patients with CRPS-I were enrolled in the study. Ex. 1005 at 536; Ex. 1003 ¶88. Varenna 2012 notes that "[n]o specific test is currently available to diagnose CRPS-I and the recently updated Budapest Criteria are widely accepted to make a clinical diagnosis due to their sensitivity and specificity." Ex. 1005 at 534. "All patients included in the study fulfilled the Budapest criteria for research purposes." *Id.* at 535; Ex. 1003 ¶88. Thus, there can be no doubt that Varenna 2012 discloses administration of neridronic acid to human beings having CRPS as recited in claim 1. Ex. 1003 ¶87.

Varenna 2012 also 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 ¶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 ¶89. After the double-blind phase of 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 ¶90. The breakdown of precipitating events is shown in Table 1:

TABLE 1 Demographic and clinical characteristics of patients with CRPS-I treated with neridronate or placebo

Characteristic	Neridronate ($n = 41$)	Placebo ($n = 41$)	P value
Age, mean (S.D.), years	58.2 (12.7)	57.0 (10.3)	0.6
Gender, M/F, n	16/25	13/28	0.6
Disease duration, mean (S.D.), weeks	4.7 (4.1)	5.0 (4.6)	0.7
Precipitating event, n (%)			
Fracture	11 (26.8)	17 (41.4)	0.2
Trauma	10 (24.4)	7 (17.1)	0.5
Surgery	5 (12.2)	4 (9.8)	0.9
Unknown	15 (36.6)	13 (31.7)	0.8
Site, n (%)			
Upper limb	8 (19.5)	12 (29.3)	0.4
Lower limb	33 (80.5)	29 (70.7)	

"The age distribution, male-to-female ratio and prevalence of precipitating events in the study population was similar to that reported in the largest epidemiological survey carried out in the Netherlands, suggesting a lack of referral bias." Ex. 1005 at 538-39. Thus, Varenna 2012 discloses selecting and treating a human being having CRPS triggered by bone fracture as required by claim 1. Ex. 1003 ¶87.

c. "and administering neridronic acid or a pharmaceutically acceptable salt thereof to the human being"

Varenna 2012 states that the patients in the treatment arm of the clinical study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1005 at 535; Ex. 1003 ¶92. Patients initially in the placebo arm of the study also later received neridronate in an open-extension phase of the study. Ex. 1005 at 535; Ex. 1003 ¶93. The use of the term "neridronate" in Varenna 2012 would indicate to a POSA that a salt form of neridronic acid was used, as permitted by claim 1. Ex. 1003 ¶94. Thus, Varenna 2012 discloses administration of a salt or an acid form of neridronic acid as required by claim 1. *Id.* ¶91.

d. "wherein the treatment is effective in reducing pain"

As discussed above, this limitation requires that the treatment actually result in an observed and/or measured reduction in pain in a patient. Ex. 1003 ¶95. According to Varenna 2012, "clinically relevant and persistent benefits" were associated with the administration of neridronate in the study. Ex. 1005 at 534; Ex. 1003 ¶97. The authors observed that a 50% decrease in visual analogue scale (VAS) pain score, the primary measure of efficacy in the study, was obtained in 30 neridronate-treated patients (73.2%) vs. 13 controls. Ex. 1005 at 535, 536-37; Ex. 1003 ¶97. They concluded that "a course of i.v. neridronate ***reduces pain intensity***

and improves clinical signs and functional status in patients with CRPS-I at either the hand or foot." Ex. 1005 at 538 (emphasis added); Ex. 1003 ¶98.

Moreover, "[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)]." Ex. 1005 at 536; Ex. 1003 ¶99. In the multivariate regression analysis, baseline variables other than treatment assignment did not appear to influence outcome measures. Ex. 1005 at 538; Ex. 1003 ¶99. In other words, 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. Ex. 1003 ¶100. Thus, Varenna 2012 discloses that the use of neridronate to treat CRPS triggered by bone fracture was effective in reducing pain, as required by claim 1. *Id.* ¶96.

3. Claim 2

Claim 2 recites "The method of claim 1, wherein the CRPS is CRPS type I." Varenna 2012 discloses administration of neridronate to patients with CRPS type I, including those who had CRPS triggered by fracture. Ex. 1003 ¶102; Ex. 1005 at 534, 536. Thus, Varenna 2012 discloses the additional limitation of claim 2 and therefore also anticipates claim 2. Ex. 1003 ¶102.

4. Claim 3

Claim 3 recites "The method of claim 1, wherein the neridronic acid is in a salt form." Varenna 2012 indicates that the patients were administered "neridronate." Ex. 1005 at 535. This would indicate to a POSA that a salt form of neridronic acid was used, as required by claim 3. Ex. 1005 at 535; Ex. 1003 ¶104. Thus, Varenna 2012 discloses the additional limitation of claim 3 and therefore anticipates claim 3. Ex. 1003 ¶104.

5. Claims 4 and 9

Claim 4 recites "The method of claim 1, wherein the neridronic acid[3] is administered intravenously." Claim 9 recites "The method of claim 1, wherein the neridronic acid is administered parenterally." A POSA would have known—and the '999 patent confirms—that intravenous administration is a type of parenteral administration. Ex. 1003 ¶106; Ex. 1001 col. 31, ll. 21-26. Varenna 2012 discloses intravenous administration neridronic acid for treatment of CRPS. Ex. 1005 at 534, 535; Ex. 1003 ¶107. Thus, Varenna 2012 discloses the additional

[3] "Neridronic acid" as used in the claims is plainly defined as including any form of the compound, including "pharmaceutically acceptable [neridronate] salts." *See* Ex. 1001 col.17, ll. 58-65.

limitations of claims 4 and 9 and therefore anticipates those claims. Ex. 1003 ¶107.

6. Claim 10

Claim 10 recites "The method of claim 9, wherein a total of about 5 mg to about 500 mg of the neridronic acid is administered within one month." In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1005 at 535; Ex. 1003 ¶109. This amounts to 400 mg administered within one month, which is within the range recited in claim 10. Ex. 1003 ¶109. Thus, Varenna 2012 discloses the additional limitation of claim 10 and therefore anticipates claim 10. *Id.*

7. Claims 12, 16, and 17

Claim 12 recites "The method of claim 9, wherein each dose contains about 10 mg to about 150 mg of the neridronic acid." Claim 16 recites "The method of claim 4, wherein each dose contains about 10 mg to about 150 mg of the neridronic acid." Claim 17 recites "The method of claim 4, wherein each dose contains about 100 mg of the neridronic acid."

In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1005 at 535; Ex. 1003 ¶111. Each dose was 100 mg, which is squarely within the

ranges required by claims 12 and 16 and meets the "about 100 mg" limitation of claim 17. Ex. 1003 ¶112; Ex. 1005 at 535. Thus, Varenna 2012 discloses the additional limitations of claims 12, 16, and 17 and therefore anticipates those claims. Ex. 1003 ¶112.

8. Claim 14

Claim 14 recites "The method of claim 1, wherein a total of about 100 mg to about 600 mg of the neridronic acid is administered."

In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1003 ¶114; Ex. 1005 at 535. This amounts to a total of 400 mg administered within one month, which is within the range required by claim 14. Ex. 1003 ¶114. Thus, Varenna 2012 discloses the additional limitation of claim 14 and therefore anticipates claim 14. *Id.*

9. Claim 18

Claim 18 recites "The method of claim 17, wherein the neridronic acid is administered at least four times."

In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1003 ¶116; Ex. 1005 at 535. The four intravenous infusions satisfy the "at least

four times" limitation of claim 18. Ex. 1003 ¶116. Thus, Varenna 2012 discloses the additional limitation of claim 18 and therefore anticipates claim 18. *Id.*

10. Claim 23

Claim 23 recites "The method of claim 1, wherein the neridronic acid is administered about once daily to about once weekly."

In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1005 at 535; Ex. 1003 ¶118. Four administrations over 10 days is more frequently than "about once weekly" and less frequently than "about once daily," falling squarely within the range of frequencies required by claim 23. Ex. 1003 ¶119. Thus, Varenna 2012 discloses the additional limitation of claim 23 and therefore anticipates claim 23. *Id.*

11. Claim 24

Claim 24 recites, "The method of claim 1, wherein the neridronic acid is administered in a single or in divided doses."

It is unclear whether claim 24 imposes any additional limitation on claim 1. A medication is either administered as a single dose or is divided into several doses. Ex. 1003 ¶120. Nevertheless, Varenna 2012 discloses administration of 400 mg of neridronic acid divided into four 100 mg doses administered over 10 days. It thus discloses administration of neridronic acid in divided doses as

required by claim 24 and therefore anticipates claim 24. Ex. 1003 ¶121; Ex. 1005 at 535.

12. Claim 25

Claim 25 recites "The method of claim 17, wherein about four doses of about 100 mg of the neridronic acid are administered."

In Varenna 2012, the patients in the neridronate arm of the study received an intravenous infusion of 100 mg neridronate given four times over 10 days. Ex. 1003 ¶123; Ex. 1005 at 535. This is about four doses of 100 mg, as recited in claim 25, and therefore anticipates claim 25. Ex. 1003 ¶123.

13. Claims 27 and 28

Claim 27 recites "The method of claim 1, wherein the human being is at least 18 years of age," and claim 28 recites "The method of claim 27, wherein the human being is at least 40 years of age."

As required by claim 27, Varenna 2012 discloses that one of the inclusion criteria for patients in the study was "age of at least 18 years." Ex. 1005 at 535; Ex. 1003 ¶125. In addition, the average age of the patients in the neridronate arm of the study was 58.2 years, which means patients over 40 years of age were included as required by claim 28. Ex. 1005 at 536, Table 1; Ex. 1003 ¶126. Thus, Varenna 2012 discloses administration of neridronate to patients at least 18 and at

least 40 years old, respectively, and therefore anticipates claims 27 and 28. Ex. 1003 ¶127.

14. Claim 29

Claim 29 recites "The method of claim 27, wherein the human being has a baseline pain intensity score of at least 4 on the 0-10 Numeric Rating Scale."

In Varenna 2012, one of the inclusion criteria for patients in the study was "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)," meaning that the participants in the study had a VAS score of at least 50 mm. Ex. 1005 at 535; Ex. 1003 ¶129. As confirmed by the '999 patent, which cites to prior art:

> Commonly used measures of pain intensity include the visual analog scale (VAS) and the numerical rating scale (NRS). With the VAS approach, patients rate the severity of their pain by marking a point on a 10-cm (or 100 mm) VAS (0=no pain and 10=worst possible pain). With the NRS approach, patients rate the severity of their pain by verbally responding to a 10-point NRS (0=no pain and 10=worst possible pain). VAS and NRS scores have been shown to be strongly correlated (slope of regression line, 1.01), indicating that a score on the 10-cm VAS is equivalent to the same score on 10-point NRS (Bijur P E et al. *Acad Emerg Med* 2003; 10:390-392).

> For example, a VAS score of 5 cm (or 50 mm) is equivalent to an NRS score of 5.

Ex. 1001 col. 9, l. 64–col. 10, l. 9; Ex. 1003 ¶129. Thus, a POSA would know that the 50 mm VAS score inclusion criteria of Varenna 2012 is the same thing as a NRS score of 5, which means the patients in Varenna 2012 had a baseline pain intensity score of at least 4 on the NRS scale as required by claim 29. Ex. 1003 ¶130. Therefore, Varenna 2012 discloses the additional limitation of claim 29 and anticipates claim 29. *Id.* ¶¶130-31.

C. Ground 3: Claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-28 Are Anticipated Under 35 U.S.C. § 102 by Varenna 2016

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 (Sept. 2016) (Ex. 1015, "Varenna 2016") also describes each and every element of challenged claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-28, and therefore anticipates those claims.

1. Varenna 2016 Is Prior Art to the '999 Patent

Patent Owner presented Varenna 2016 to the examiner during prosecution of the parent '245 patent as evidence of supposed "unexpected results" supporting the non-obviousness of the '245 patent claims. Ex. 1022 at 516-18. The examiner also noted these alleged "unexpected results" in the notice of allowance for the '999 patent. Ex. 1041 at 975-76. But the examiner did not analyze the disclosures

of the applications to which the ’999 patent purportedly claims priority. If he had, he would have concluded that Varenna 2016 does not support the patentability of the ’999 patent, but rather is anticipatory prior art.

Although the issue of the journal it appears in is dated June 2017, Varenna 2016 was first published on September 20, 2016. Ex. 1003 ¶133. Varenna 2016 appears in a periodical journal published by Oxford University Press dated June 2017. The article was publicly available on the internet on September 20, 2016. *Id.* The Varenna 2016 article can be found on Oxford University Press’s website at the address: https://academic.oup.com/painmedicine/article/18/6/1131/2924769. Ex. 1035; Ex. 1003 ¶133. The website of Exhibit 1035 contains the Varenna 2016 article and indicates that it was “Published: 20 September 2016.” Oxford University Press is a respected, trustworthy, and reliable publisher of scholarly journals. Ex. 1003 ¶134. A POSA would have accepted and credited the representation on the website that the article was published on September 20, 2106 as true. *Id.* Moreover, information obtained from Oxford University Press conclusively shows that the Varenna article was actually accessed and downloaded by members of the public as early as September 20, 2016. *Id.* ¶135; Ex. 1036.

As discussed above, not even the specification of the ’999 patent itself enables challenged claims 1-30, and none of its purported priority applications remedy its deficient disclosure. *See* Section XI.A. But even if the Board disagrees

with Petitioner's enablement ground, the earliest date to which the '999 patent could possibly claim priority is the December 7, 2016 filing date of Provisional Application No. 62/431,287. In this provisional application, Patent Owner for the first time added statements to the specification regarding bone fracture as a precipitating or triggering event for CRPS. *See, e.g.*, Ex. 1039 at 22, ¶[49]; Ex. 1031 at 20, ¶48.

None of the applications filed prior to December 7, 2016 distinguishes between different "precipitating" or "triggering" events for CRPS, describes bone fracture as a precipitating or triggering event for CRPS, or describes treatment of CRPS triggered by bone fracture. Ex. 1003 ¶¶137-39. Thus, even if the Board finds that the '999 Patent is not unpatentable for lack of enablement, the earliest application that could possibly enable and describe challenged claims 1-30 is Provisional Application No. 62/431,287. Because Varenna 2016 was published before that application was filed, it is prior art to the '999 patent. *Id.* ¶139.

2. Claim 1

Challenged claim 1 recites "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." As discussed in the sections that follow, Varenna

2016 discloses all of the elements of Claim 1, and therefore anticipates claim 1. Ex. 1003 ¶140.

a. "A method of treating pain associated with complex regional pain syndrome (CRPS)"

As discussed above, this claim term should be construed as requiring 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 having any activity that otherwise affects the structure or any function of the body in a human being with CRPS. Treating CRPS with bisphosphonates like neridronic acid was already well-known at the time Varenna 2016 was published. Ex. 1003 ¶142. Indeed, the Varenna 2016 authors "retrospectively collected and analyzed the data of patients with CRPS-I treated with i.v. infusions of various bisphosphonates during the last five years at a tertiary rheumatology care center in order to evaluate if variables related to patient and/or disease and the type of drug employed can influence the treatment outcome." Ex. 1015 at 1132. Stated differently, they "performed a retrospective data analysis of patients with a diagnosis of CRPS-I referred to [their] unit in the last five years for treatment with bisphosphonate infusions." *Id*.

It is clear that the patients treated in Varenna 2016 had CRPS. The Budapest 2007 criteria are universally recognized as the standard for identifying and diagnosing CRPS in patients. Ex. 1003 ¶144. In Varenna 2016, "[a]t the day of

the first infusion and at the following clinical evaluation, scheduled 40 days after the last infusion (day 36–54), all symptoms and signs included in the Budapest 2007 criteria were checked." Ex. 1015 at 1133; Ex. 1003 ¶144. "All patients were treated with an i.v. infusion of a bisphosphonate." Ex. 1015 at 1133. Citing to the Varenna 2012 clinical study performed by the same group, the authors stated that "[f]rom September 2011 to December 2013, patients were treated with neridronate 100 mg every third day for four occasions." *Id*. The success of the neridronate treatment was judged, in part, based on whether "CRPS-I could no longer be diagnosed accordingly with the Budapest 2007 criteria." *Id.*; Ex. 1003 ¶144. Thus, Varenna 2016 plainly discloses treatment of CRPS with neridronic acid, as required by claim 1. Ex. 1003 ¶141.

b. "comprising selecting a human being having CRPS triggered by bone fracture"

As discussed above, 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. As discussed above, the patients treated in Varenna 2016 clearly had CRPS. Among the 194 patients evaluated in Varenna 2016, "[t]he most common precipitating event was a fracture, reported by 83 patients (42.8%)." Ex. 1015 at 1134; Ex. 1003 ¶148.

Moreover, fracture patients were more likely to respond to treatment than other types of CRPS patients. "By considering the predisposing event, the greatest percentage of responders was found in patients who developed a CRPS-I following a fracture (69 out of 83, 83.1%). This result was significantly greater in comparison with the responder percentage observed in patients in whom the disease was triggered by all other predisposing events ($P = 0.005$) and with the responder percentages observed in CRPS-I following a trauma without fracture ($P = 0.01$) or following surgery ($P = 0.008$)." Ex. 1015 at 1134; Ex. 1003 ¶149 Thus, Varenna 2016 discloses treatment of CRPS comprising selecting a human being having CRPS triggered by bone fracture. Ex. 1003 ¶146.

c. "and administering neridronic acid or a pharmaceutically acceptable salt thereof to the human being"

According to Varenna 2016, "[a]ll patients were treated with an i.v. infusion of a bisphosphonate." Ex. 1015 at 1133. Citing to the 2012 clinical study performed by the same group ("Varenna 2012," see Section XI.B. above), the authors stated that "[f]rom September 2011 to December 2013, patients were treated with neridronate 100 mg every third day for four occasions." *Id*. The use of the term "neridronate" in Varenna 2016 would indicate to a POSA that a salt form of neridronic acid was used, as permitted by claim 1. Ex. 1003 ¶152. Thus,

Varenna 2016 discloses administration of a salt or an acid form of neridronic acid as required by claim 1. *Id.* ¶152.

d. "wherein the treatment is effective in reducing pain"

As discussed above, this limitation requires that the treatment actually result in an observed and/or measured reduction in pain in a patient. In Varenna 2016, 75% of the patients receiving neridronate responded to treatment, and 83% of patients who developed CRPS following fracture responded to treatment. Ex. 1015 at 1134; Ex. 1003 ¶154. A patient was only classified as a "responder" to treatment "if all the following criteria were simultaneously met: 1) CRPS-I could no longer be diagnosed accordingly with the Budapest 2007 criteria for clinical purpose (three symptoms and two signs); 2) the EVS was rated ≥ 2; and 3) the patient had stopped taking analgesics or other drugs for controlling pain." Ex. 1015 at 1133; Ex. 1003 ¶155. Thus, the responders to neridronate treatment who had CRPS caused by fracture necessarily reported a reduction in pain, indicating that the treatment was effective in reducing pain. Ex. 1003 ¶155. Varenna 2016 therefore discloses this element. Ex. 1003 ¶153.

3. Claim 2

Claim 2 recites "The method of claim 1, wherein the CRPS is CRPS type I."

Varenna 2016 discloses administration of neridronate to patients with CRPS type I, including those who had CRPS triggered by fracture. *See, e.g.*, Ex. 1015 at 1132. Thus, Varenna 2016 anticipates claim 2. Ex. 1003 ¶157.

4. Claim 3

Claim 3 recites "The method of claim 1, wherein the neridronic acid is in a salt form."

Varenna 2016 indicates that patients were administered "neridronate." Ex. 1015 at 1133. This would indicate to a POSA that a salt form of neridronic acid was used, as required by claim 3. Ex. 1003 ¶159. Thus, Varenna 2016 discloses the additional limitation of claim 3 and therefore anticipates claim 3. *Id.*

5. Claims 4 and 9

Claim 4 recites "The method of claim 1, wherein the neridronic acid is administered intravenously." Claim 9 recites "The method of claim 1, wherein the neridronic acid is administered parenterally."

A POSA would have known—and the '999 patent confirms—that intravenous administration is a type of parenteral administration. Ex. 1001 col. 31, ll. 21-26; Ex. 1003 ¶161. Varenna 2016 discloses intravenous administration of neridronic acid for treatment of CRPS. Ex. 1015 at 1133; Ex. 1003 ¶161. Thus, Varenna 2016 discloses the additional limitations of claims 4 and 9 and therefore anticipates those claims. Ex. 1003 ¶161.

6. Claim 10

Claim 10 recites "The method of claim 9, wherein a total of about 5 mg to about 500 mg of the neridronic acid is administered within one month."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133; Ex. 1003 ¶163. This amounts to 400 mg administered within one month, which is within the range recited in claim 10. Ex. 1003 ¶163. Thus, Varenna 2016 discloses the additional limitation of claim 10 and therefore anticipates claim 10. *Id.*

7. Claims 12, 16, and 17

Claim 12 recites "The method of claim 9, wherein each dose contains about 10 mg to about 150 mg of the neridronic acid." Claim 16 recites "The method of claim 4, wherein each dose contains about 10 mg to about 150 mg of the neridronic acid." Claim 17 recites "The method of claim 4, wherein each dose contains about 100 mg of the neridronic acid."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133; Ex. 1003 ¶165. Each dose was 100 mg, which is squarely within the ranges required by claims 12 and 16 and meets the "about 100 mg" limitation of claim 17. Ex. 1003 ¶165. Thus, Varenna 2016 discloses the additional limitations of claims 12, 16, and 17 and therefore anticipates those claims. *Id.*

8. Claim 14

Claim 14 recites "The method of claim 1, wherein a total of about 100 mg to about 600 mg of the neridronic acid is administered."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133. This amounts to a total of 400 mg administered, which is within the range required by claim 14. Ex. 1003 ¶167. Thus, Varenna 2016 discloses the additional limitation of claim 14 and therefore anticipates claim 14. *Id.*

9. Claim 18

Claim 18 recites "The method of claim 17, wherein the neridronic acid is administered at least four times."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133. The four occasions satisfy the "at least four times" limitation of claim 18. Ex. 1003 ¶169. Thus, Varenna 2016 discloses the additional limitation of claim 18 and therefore anticipates claim 18. *Id.*

10. Claim 23

Claim 23 recites "The method of claim 1, wherein the neridronic acid is administered about once daily to about once weekly."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133. Every third day is more frequently than "about once weekly" and less frequently than "about once daily," falling

squarely within the range of frequencies required by claim 23. Ex. 1003 ¶171. Thus, Varenna 2016 discloses the additional limitation of claim 23 and therefore anticipates claim 23. *Id.*

11. Claim 24

Claim 24 recites, "The method of claim 1, wherein the neridronic acid is administered in a single or in divided doses."

It is unclear whether claim 24 imposes any additional limitation on claim 1. A medication is either administered as a single dose or is divided into several doses. Ex. 1003 ¶173. Nevertheless, Varenna 2016 discloses administration of 400 mg of neridronic acid divided into four 100 mg doses administered every third day. Ex. 1015 at 1133. It thus discloses administration of neridronic acid in divided doses as required by claim 24. Ex. 1003 ¶174.

12. Claim 25

Claim 25 recites "The method of claim 17, wherein about four doses of about 100 mg of the neridronic acid are administered."

In Varenna 2016, "patients were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133. This is about four doses of 100 mg, as recited in claim 25. Ex. 1003 ¶176.

13. Claims 27 and 28

Claim 27 recites "The method of claim 1, wherein the human being is at least 18 years of age," and claim 28 recites "The method of claim 27, wherein the human being is at least 40 years of age."

Varenna 2016 discloses that the mean age at onset of CRPS was 57.1 plus or minus 12.9 years. Ex. 1015 at 1133-34. This means that patients over 18 years of age and patients over 40 years of age were necessarily included in the Varenna 2016 study, as required by claims 27 and 28. Ex. 1003 ¶178.

D. Ground 4: Claims 1-4, 9-10, 12, 14, 16-18, 24-25, and 27-29 Are Anticipated Under 35 USC § 102 by Manara

Manara et al., *SAT0524 Predictors of a Clinical Response to Bisphosphonates Treatment in Patients with Complex Regional Pain Syndrome Type I*, ANNALS OF THE RHEUMATIC DISEASES, 73(Suppl. 2) (2014) (Exs. 1037, 1038, 1042, "Manara") is an abstract for a EULAR (European League Against Rheumatism) conference held on 11–14 June, 2014 in Paris, France. The abstract was published in June 2014 in Volume 73, Supplement 2 of the periodical journal "Annals of the Rheumatic Diseases." Exhibit 1037, Manara at 781; Exhibit 1042. The article was also available online starting on June 10, 2014 at https://ard.bmj.com/content/73/Suppl_2/781.1 and was downloaded by members of the public as early as June 2014. *See* Exhibit 1038.

The Annals of the Rheumatic Diseases journal is a respected, authoritative, and reliable scholarly publication. Ex. 1003 ¶180. The June 2014 publication date is accurate and indicates that Manara was actually publicly available online and in print as of June 2014. *Id.* A POSA would rely upon the publication date in the journal and accept it as true. *Id.*

As discussed above, the '999 patent can, at best, claim priority only to Provisional Application No. 62/431,287 filed December 7, 2016. Because Manara was published and publicly available as of June 2014, before the provisional application was filed, it is prior art to the '999 patent. *Id.* ¶181.

Like Varenna 2016, Manara discloses an analysis of clinical data showing that patients with CRPS triggered by fracture respond better to treatment with neridronate than patients with CRPS having other causes. As such, it discloses each and every element of claims 1-4, 9-10, 12, 14, 16-18, 24-25, and 27-29 of the '999 patent and therefore anticipates those claims.

1. Claim 1

a. "A method of treating pain associated with complex regional pain syndrome (CRPS)"

According to Manara, "Complex Regional Pain Syndrome type I (CRPS-I) is a painful condition which can lead to potential disability." Ex. 1037 at 781; Ex. 1003 ¶184. "The efficacy of Bisphosphonate[] treatment in this syndrome has been demonstrated in trials in which different types and dosages of

[bisphosphonates] were investigated." *Id.* One of the previous trials cited is the study described in Varenna 2012. *Id.*

In Manara, the "[a]im of the study was to identify variables predictive of a clinical response to [bisphosphonate] treatment in a large cohort of subjects with CRPS-I." Ex. 1037 at 781; Ex. 1003 ¶185. To that end, a "retrospective analysis of patients with CRPS-I referred to [their] Unit in the last 5 years for a treatment with intravenous [bisphosphonates] (Neridronate 100 mg for 4 infusions, Pamidronate 60 mg for 4 infusions or Clodronate 300 mg for 10 infusions) was performed." Ex. 1037 at 781; Ex. 1003 ¶186. The patients in the study were identified as having CRPS by clinical diagnosis of CRPS-I according to the generally accepted Budapest criteria. Ex. 1037 at 781; Ex. 1003 ¶187.

The "outcome measures" of the study were "pain values." "A clinical response to the treatment was defined as a reduction in pain on a Visuo-Analogic Scale (VAS) higher than 50% compared to baseline at 45-60 days from the beginning of the treatment." Ex. 1037 at 781; Ex. 1003 ¶188. Thus, Manara plainly discloses the treatment of pain associated with CRPS as required by claim 1. Ex. 1003 ¶¶183, 189.

b. "comprising selecting a human being having CRPS triggered by bone fracture"

Manara specifically discloses the treatment of human beings having CRPS triggered by bone fracture. As discussed above, a POSA would know that

"triggering events," predisposing events," and "precipitating events" are synonymous, which is confirmed by statements made by the Patent Owner in the '245 patent file history. *See* Section IX.B above.

In Manara, "fracture as predisposing event was more likely to be found in responders (53.7% vs 30.6%, p=0.006)." Ex. 1037 at 781; Ex. 1003 ¶191. "At multivariate analysis . . . fracture as predisposing event [OR (95%CI): 3 (1.20, 7.52)] were associated with increased odds of response to the treatment." Ex. 1037 at 781; Ex. 1003 ¶193. Among its conclusions, Manara states that "[s]ubjects with a previous fracture may represent a subset of patients with a higher chance to benefit from [bisphosphonate] treatment." Ex. 1037 at 781; Ex. 1003 ¶194. Thus, Manara clearly discloses methods of treating patients having CRPS triggered by fracture. Ex. 1003 ¶195.

c. "and administering neridronic acid or a pharmaceutically acceptable salt thereof to the human being"

According to Manara, "[a] retrospective analysis of patients with CRPS-I referred to [their] unit in the last 5 years for a treatment with intravenous [bisphosphonate] was performed." Some of the patients received "Neridronate 100 mg for 4 infusions . . . ." Ex. 1037 at 781; Ex. 1003 ¶197. As a result, Manara plainly discloses administration of neridronic acid or a pharmaceutically acceptable salt thereof to a human being. Ex. 1003 ¶196.

d. "wherein the treatment is effective in reducing pain"

Manara discloses this claim element because it discloses that the use of neridronate to treat CRPS triggered by bone fracture was effective in reducing pain. As discussed above, Manara states that patients with fracture as a predisposing event were more likely to respond to treatment. According to Manara, responders are those whose "reduction in pain on a Visuo-Analogic Scale (VAS) [was] higher than 50% compared to baseline at 45-60 days from the beginning of the treatment." Ex. 1037 at 781; Ex. 1003 ¶¶199-201. Because Manara reports that fracture patients responded to treatment, and defined a response as an observed reduction in pain, it discloses the effective reduction of pain upon use of neridronic acid to treat CRPS triggered by fracture, as required by claim 1. Ex. 1003 ¶¶198, 202.

2. Claim 2[4]

Manara discloses administration of neridronate to patients with CRPS type I, including those who had CRPS type I caused by fracture, as required by claim 2. Ex. 1037 at 781. Thus, Manara anticipates claim 2. Ex. 1003 ¶204.

[4] The limitations of each dependent claim are provided in Sections XI.B and XI.C.

3. Claim 3

Manara indicates that the patients were administered "neridronate." Ex. 1037 at 781. This would indicate to a POSA that a salt form of neridronic acid was used, as required by claim 3. Thus, Manara anticipates claim 3. Ex. 1003 ¶206.

4. Claims 4 and 9

A POSA would have known, as the'999 patent confirms, that intravenous administration is a type of parenteral administration as required by claims 4 and 9. Ex. 1001 col. 31, ll. 21-26; Ex. 1003 ¶208. Manara discloses intravenous administration of neridronic acid for treatment of CRPS. Exhibit 1037 at 78. Thus, Manara anticipates claims 4 and 9. Ex. 1003 ¶209.

5. Claim 10

In Manara, the patients received intravenous neridronate, 100 mg for 4 infusions. Exhibit 1037 at 781. This amounts to 400 mg administered within one month, which is within the dosage range recited in claim 10. Thus, Manara anticipates claim 10. Ex. 1003 ¶211.

6. Claims 12, 16, and 17

In Manara, the patients received intravenous neridronate, 100 mg for four infusions. Exhibit 1037 at 781; Ex. 1003 ¶213. Each dose was 100 mg, which is squarely within the ranges required by claims 12 and 16 and meets the "about 100 mg" element of claim 17. *Id*. Thus, Manara anticipates claims 12, 16, and 17. Ex. 1003 ¶214.

7. Claim 14

In Manara, the patients in the neridronate arm of the study received intravenous neridronate 100 mg for four infusions. Exhibit 1037 at 781. This amounts to a total of 400 mg administered within one month, which is within the range required by claim 14. Thus, Manara anticipates claim 14. Ex. 1003 ¶216.

8. Claim 18

In Manara, the patients received intravenous neridronate 100 mg for four infusions. Exhibit 1037 at 781. The four intravenous infusions satisfy the "at least four times" element of claim 18. Thus, Manara anticipates claim 18. Ex. 1003 ¶218.

9. Claim 24

A medication is necessarily administered either in a single dose or in multiple, or divided, doses. Ex. 1003 ¶219. Manara discloses administration of 400 mg of neridronic acid divided into four 100 mg doses, as required by claim 24. Exhibit 1037 at 781. It thus anticipates claim 24. Ex. 1003 ¶220.

10. Claim 25

In Manara, the patients received intravenous neridronate 100 mg for four infusions, which is about four doses as required by claim 25. Ex. 1037 at 781. It therefore anticipates claim 25. Ex. 1003 ¶222.

11. Claims 27 and 28

According to Manara, "[a] total of 172 patients were included in the study, with a mean (SD) age of 56.7 (13.8) years." Ex. 1037 at 781. Because the average age was 56.7 years, patients over 18 years of age and over 40 years of age must have been included as required by claims 27 and 28. An average over 56.7 could not be achieved without including patients over 40, for example. Ex. 1003 ¶224. Thus, Manara discloses administration of neridronate to patients at least 18 and at least 40 years old, respectively and anticipates claims 27 and 28. Ex. 1003 ¶225.

E. Ground 5: Claims 1-4, 9-20, and 22-29 Are Obvious Based on Varenna 2012, Varenna 2016, and/or Manara, Optionally Combined with Bruehl and One or More of Gatti, La Montagna, and/or Muratore

1. Claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29

Petitioner submits that Varenna 2012, Varenna 2016, and Manara each disclose all of the elements of challenged claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29. However, to the extent the Board finds that these references do not specifically disclose treatment of pain associated with CRPS triggered by fracture, it nevertheless would have been obvious to a POSA to administer neridronic acid for the treatment of pain associated with CRPS triggered by fracture based on Varenna 2012, Varenna 2016, and/or Manara.

Varenna 2012 shows 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. Of the 41 patients enrolled in the placebo arm, 17 had fracture as a precipitating event for CRPS (41.4%). *Id.*; Ex. 1003 ¶232. After the double-blind phase of the study concluded, the patients who 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. According to Varenna 2012, "[t]his randomized controlled study provides evidence that a course of i.v. neridronate reduces pain intensity and improves clinical signs and functional status in patients with CRPS-I at either the hand or foot." *Id.* at 538; Ex. 1003 ¶233. A statistical analysis showed 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. *Id.* at 536, 538; Ex. 1003 ¶234.

Based on Varenna 2012, a POSA would have been motivated to administer neridronic acid to a human being having CRPS for the purpose of treating CRPS triggered by fracture as required by challenged claims 1-4, 9-10, 12, 14, 16-18, 23-25, and 27-29. This is because, at a minimum, Varenna 2012 shows that neridronic can be used to treat CRPS, and fracture patients were included in the study and benefited from the treatment. Ex. 1003 ¶¶235-236. Based on the positive results of the Varenna 2012 clinical study, a POSA would have had a

reasonable expectation that neridronic acid could be successfully administered to treat pain associated with CRPS triggered by fracture. *Id*.

As discussed above, Manara and Varenna 2016 independently disclose all of the elements of claim 1 and various dependent claims. Combined with Varenna 2012, they would have further reinforced the POSA's expectation of success in effectively treating pain in CRPS triggered by fracture with neridronic acid. Like Varenna 2012, Manara and Varenna 2016 concern the treatment of CRPS with neridronic acid, so a POSA would have been motivated to combine their disclosures. Manara and Varenna 2016 teach a POSA not only that neridronic acid is effective in treating pain in CRPS triggered by fracture, but that patients with CPRS triggered by fracture are even more likely to respond to treatment than patients having CRPS with other causes. Ex. 1003 ¶238.

But even if Varenna 2012, Varenna 2016, and/or Manara were not enough to render these claims obvious, there is ample information in other prior art sources from which a POSA would have concluded that neridronic acid could successfully be used to treat pain associated with CRPS, in particular CRPS triggered by fracture. Ex. 1003 ¶239.

S. Bruehl, *How common is complex regional pain syndrome-Type I*, PAIN 129:1-2 (2007) (Ex. 1006, "Bruehl") is an editorial discussing the incidence of CRPS. Bruehl was published in 2007, and is therefore prior art to the '999 patent.

It teaches a POSA that bone fractures are one of the most common precipitating (*i.e.*, triggering or predisposing) events for CRPS. Ex. 1003 ¶¶240-41; Ex. 1006 at 1.

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") is a 2009 publication describing the use of neridronic acid in a variety of bone metabolic diseases, including algodystrophy, or CRPS.[5] Gatti was published in 2009, and is therefore prior art to the '999 patent. It was not before the examiner during the prosecution of the '999 patent. Gatti states that as of 2009, intravenous doses of bisphosphonates were "increasingly used for the treatment of reflex sympathetic dystrophy syndrome or algodystrophy," and describes unpublished results of a study where almost 80% of patients given 100 mg of neridronic acid intravenously over 4 days saw greater than 70% symptomatic improvement. Ex. 1007 at 1308. Gatti also notes that these positive results formed the basis for an ongoing, randomized double-blind clinical trial. *Id.*; Ex. 1003 ¶244.

[5] Among other names, CRPS is also referred to as algodystrophy or reflex sympathetic dystrophy syndrome. Ex. 1007 at 1308; Ex. 1003 ¶243.

M. Muratore et al., *Il neridronato nel trattamento dell'algodistrofia simpatica riflessa dell'anca: confronto in aperto con il clodronato*, PROGRESSI IN REUMATOLOGIA, ABSTRACT BOOK VII CONGRESSO NAZIONALE COLLEGIO DEI REUMATOLOGI OSPEDALIERI 5(Suppl. 1):89 (April 16-18, 2004) (Ex. 1010, "Muratore") discloses the results of a study comparing 100 mg intravenous neridronate every 4 days, 4 times with 300 mg/day intravenous clodronate for 12 days in patients with femoral head algodystrophy. Ex. 1010 at 89; Ex. 1003 ¶245. Muratore was published in 2004, and is therefore prior art to the '999 patent. It was not before the examiner during the prosecution of the '999 patent. Muratore concludes that although both drugs demonstrated efficacy in the treatment of reflex sympathetic algodystrophy, the speed of improvement of pain symptoms was significantly faster in the patients treated with neridronate as compared to those treated with clodronate. Ex. 1010 at 89; Ex. 1003 ¶246.

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") reports a case study of a patient with transient osteoporosis of the hip who was "successfully treated" with 25 mg/month neridronate sodium. Ex. 1008 at 67-68. La Montagna was published in 2004, and is therefore prior art to the '999 patent. La Montagna was not before the examiner in the prosecution of the '999 patent. After two months of treatment with neridronate sodium, the patient

"[became] asymptomatic and showed no physical disability." Ex. 1008 at 68; Ex. 1003 ¶247. La Montagna teaches that transient osteoporosis is associated with fragility fractures. Ex. 1008 at 67; Ex. 1003 ¶248.

Thus, Varenna 2012 discloses a clinical study showing that neridronic acid can be used to treat pain associated with CRPS, including pain associated with CRPS triggered by fracture. In addition to the teachings of Varenna 2012 discussed above, Gatti, Muratore, and La Montagna all provide further evidence that neridronic acid can be used to treat CRPS. At a minimum, Varenna 2012, Gatti, Muratore, and/or La Montagna firmly establish that neridronic acid can be used to treat pain associated with CRPS generally. Bruehl teaches a POSA that fractures are one of the most common triggering events for CRPS. Ex. 1003 ¶250; Ex. 1006 at 1.

A POSA would have been motivated to combine the disclosures of Varenna 2012 with Bruehl and Gatti, Muratore and/or La Montagna. As discussed above, Varenna 2012 teaches that neridronic acid can be used to treat patients with CRPS, regardless of triggering event. It also teaches the treatment of patients wherein fracture was a triggering event specifically. 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, which is associated with fracture, can be successfully treated with neridronic acid.

Ex. 1003 ¶¶249-252. These references share a common goal of treating patients with CRPS, and a POSA reading Varenna 2012 would look to Gatti, Muratore, and La Montagna as further examples of CRPS patients treated with neridronic acid. *Id.*

A POSA would have been motivated to combine Varenna 2012 with Bruehl as well. In describing the patients studied, Varenna 2012 states that the "prevalence of precipitating events in the study population was similar to that reported in the largest epidemiological survey carried out in the Netherlands." Ex. 1005 at 538-39. To the extent Varenna 2012 does not teach treating patients with CRPS triggered by fracture specifically, a POSA would have been motivated to combine Varenna 2012's findings with Bruehl, which provides more information on this same epidemiological survey. Ex. 1006 at 1. Bruehl teaches that multiple studies have found fractures to be among the most common triggering events for CRPS, and a POSA reading Varenna 2012 would have looked to Bruehl for further information on the incidence of CRPS. Ex. 1006 at 1; Ex. 1003 ¶250.

A POSA would have been motivated to combine Gatti, Muratore, La Montagna, and Bruehl with Varenna 2012 because all of these references concern the study and treatment of CRPS. *Bosch Auto. Serv. Sols., LLC v. Matal*, 878 F.3d 1027, 1036 (Fed. Cir. 2017) (finding motivation to combine where references dealt with the same type of devices and were from the same field of endeavor). In

particular, Varenna 2012, Gatti, Muratore, and La Montagna all concern the use of the same active agent—neridronic acid. In other words, because all of these references concern CRPS treatment, a POSA would consider the content of all of these references together and conclude that pain associated with CRPS triggered by fracture can be treated with neridronate. Ex. 1003 ¶251. Even if Varenna 2012 did not teach fracture as a triggering event specifically, the other references would have confirmed that CRPS pain generally can be treated with neridronic acid and that fracture is among the most common triggering events. *Id.* ¶252

Based on this combination, a POSA would have had a reasonable expectation of success that neridronic acid could be used to treat pain associated with CRPS triggered by fracture. This is because even if Varenna 2012 did not disclose the treatment of CRPS triggered by fracture (it does), the combined art at a minimum discloses that (a) neridronic acid can be used to treat CRPS pain generally; (b) fractures were known to be one of the most common causes of CRPS; and (c) nothing in the prior art would have suggested to a POSA that use of neridronic acid to treat pain associated with CRPS triggered by fracture would be unsuccessful, while pain associated with CRPS triggered by other events would be successful. Ex. 1003 ¶¶252-254. Consequently, a POSA would have reasonably expected that neridronic acid could successfully be used to treat pain associated

with CRPS triggered by fracture, one of the most common triggering events for CRPS. *Id.* ¶252.

2. Claims 11, 13, 15, 19-20, 22, and 26

Dependent claims 11, 13, 15, 19-20, 22, and 26 all relate to specific neridronic acid dosing amounts, frequencies, and/or durations for the treatment of pain associated with CRPS triggered by bone fracture. The different dosing regimen limitations are shown in the table below:

Claim	**Limitation**
11	The method of claim 9 [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 [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 of claim 4 [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 [salt form], 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.

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. Ex. 1003 ¶256. Still, 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. Ex. 1003 ¶257.

The 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. But the '999 patent confirms and acknowledges that "[t]he effective amount of zoledronic acid or another bisphosphonate will vary depending on various factors known to the treating physicians, such as the severity of the condition to be treated, route of administration, formulation and dosage forms, physical characteristics of the bisphosphonate compound used, and age, weight and response of the individual patients." Ex. 1001 col. 31, ll. 27-33; Ex. 1003 ¶258. 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 ¶259. For example, in La Montagna, a dose of only 25 mg per month for six months was effective for treating transient osteoporosis of the hip, a type of CRPS. Ex. 1008 at 67-68; Ex. 1003 ¶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 ¶260. Based upon this prior art, a POSA would have reasonably expected that the dosing regimens of dependent claims 11, 13, 15, 19-20, 22, and 26 could successfully treat CRPS triggered by fracture in individual patients depending on the particular severity of the condition, route of administration, formulation and dosage forms, physical characteristics of the bisphosphonate compound used, and age, weight and response of the individual patient. Ex. 1003 ¶258.

Generally, 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 such concentration, proportion, or degree is critical. *See, e.g.*, *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). Indeed, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). "[D]iscovery of an optimum value of a result effective variable

in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980).

In fact, courts have frequently found that routine determination of the appropriate dose of a known drug is not inventive. *See, e.g.*, *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (describing "routine procedures" used to determine appropriate dose of drugs and finding that "experimentation needed to arrive at the claimed dosages was nothing more than routine"); *Warner Chilcott Co. v. Teva Pharms. USA, Inc*., 594 F. App'x 630, 636 (Fed. Cir. 2014) (150 mg monthly dose of the bisphosphonate risedronate was obvious even though the highest single dose actually tested in the prior art was 50 mg).

The '999 patent specification lists dozens of different dosage ranges and states that any suitable amount of a bisphosphonate may be used. The listed dosage ranges are not connected to any examples or other experimental data demonstrating efficacy for treatment of any condition, let alone CRPS triggered by fracture specifically. The specification attaches no criticality to any particular dosing regimen for any condition, and certainly does not suggest any critical dosing regimen for treating pain associated with CRPS triggered by fracture. Thus, 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. Ex. 1003 ¶¶257-58.

F. Ground 6: Claims 5-8 and 21 Are Obvious Based on Varenna 2012, Varenna 2016 and/or Manara in combination with Manicourt

Claims 5-8 and 21 require oral administration of neridronic acid. As discussed in detail above, Varenna 2012, Varenna 2016, and Manara each disclose intravenous administration of neridronic acid for the treatment of CRPS triggered by bone fracture. Varenna 2012, Manara and Varenna 2016 do not, however, expressly disclose oral administration of neridronic acid. Ex. 1003 ¶¶261-63. Nevertheless, 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, Varenna 2016, and/or Manara with Manicourt. Ex. 1003 ¶264.

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") was published in November of 2004 and is therefore prior art to the '999 patent. Manicourt is listed among dozens of other publications on the face of the '999 patent, but the examiner did not apply it to the claims during prosecution.

Manicourt teaches that ***oral*** administration of the bisphosphonate alendronate is well tolerated and effective for the treatment of CRPS. Ex. 1003 ¶265. Manicourt describes a "double-blind randomized study to assess the efficacy of oral alendronate versus placebo in patients with posttraumatic CRPS." Ex. 1009 at 3691; Ex. 1003 ¶266. The patients in the study all exhibited various clinical characteristics of CRPS, including severe spontaneous pain, allodynia and hyperalgesia of the diseased area, and skin swelling and discoloration. *Id.*

In the study, 3 of 20 patients in the treatment group and 4 of 20 patients in the placebo group had "fracture" as an "inciting injury" for CRPS. Ex. 1009 at 3693, Table 1; Ex. 1003 ¶267. The treatment group received daily doses of tablets containing 40 mg alendronate sodium for 8 weeks. Ex. 1009 at 3691-92; Ex. 1003 ¶268. The authors concluded 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." Ex. 1009 at 3696; Ex. 1003 ¶¶269-70.

As discussed above, based on Varenna 2012, Varenna 2016, and/or Manara, a POSA would have known that neridronic acid is effective for treating pain associated with CRPS triggered by bone fracture. Ex. 1003 ¶271. 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® (alendronate sodium) Tablets and Oral Solution, and Boniva®

(ibandronate sodium) Tablets. Ex. 1018 at 1, 3; Ex. 1019 at 1-2; Ex. 1003 ¶272. Therefore, a POSA reading Varenna 2012, Varenna 2016, and/or Manara would have been motivated to look to other prior art examples of orally administered bisphosphonates, like Manicourt. Ex. 1003 ¶272. A POSA would have been motivated to combine the disclosures of Varenna 2012, Varenna 2016, and/or Manara 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.* ¶271. Manicourt teaches a POSA that a pharmaceutically acceptable oral formulation of alendronate, one which was "well tolerated" and "effective," was possible. Therefore a POSA would have been motivated to administer neridronic acid orally. *Id.* ¶272.

A POSA would have had a reasonable expectation of success in administering neridronic acid orally, based on the efficacy demonstrated in Varenna 2012, Varenna 2016, and/or Manara, and on Manicourt's disclosure that the oral alendronate was "well tolerated." *Id.* ¶273.

G. Ground 7: Claim 30 Is Obvious Based on Varenna 2012, Varenna 2016, and/or Manara in Combination with Schwarzer, and Optionally in further Combination with Bruehl and Gatti, La Montagna, and/or Muratore

Claim 30 depends from claim 1 and further requires that the CRPS be CRPS type II. As discussed above, Varenna 2012, Varenna 2016, and/or Manara each

discloses intravenous administration of neridronic acid for the treatment of CRPS triggered by bone fracture. The addition of Bruehl and Gatti, La Montagna, and/or Muratore further reinforce this conclusion and show that the '999 patent claims would have been obvious to a POSA. These references do not expressly disclose treating CRPS type II. Nevertheless, 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. Ex. 1003 ¶¶276-278.

Schwarzer & Maier, *Complex regional pain syndrome, in* GUIDE TO PAIN MANAGEMENT IN LOW-RESOURCE SETTINGS 249-254 (Kopf & Patel eds. 2010) (Ex. 1020) ("Schwarzer") is a book chapter published in 2010, and is therefore prior art to the '999 patent. It was not before the examiner during the prosecution of the '999 patent. Ex. 1003 ¶279.

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 ¶280. 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 ¶282; *see generally* Ex. 1020. Further, Schwarzer teaches that "[t]here are no clinical differences between CRPS type I and type II; except for the nerve

damage." *Id.* at 249; Ex. 1003 ¶281. A POSA would have understood that the treatment options available for CRPS could be used in either type of CRPS. Ex. 1003 ¶283.

As discussed in more detail above, a POSA would have been motivated to combine the disclosure of Varenna 2012 with Bruehl, Gatti, La Montagna, and/or Muratore because all concern the study and treatment of CRPS. *Bosch Auto. Serv. Sols., LLC*, 878 F.3d at 1036. A POSA would have also been motivated to combine the disclosure of Schwarzer with these references. As discussed above, Varenna 2012, Gatti, Muratore, and La Montagna teach that neridronic acid can be used to treat patients with CRPS, and Bruehl teaches a POSA about the incidence of CRPS. Schwarzer shares a common goal with all of these references of treating and studying patients with CRPS, and provides a concise compilation of the information known to a POSA at the time. A POSA reading Varenna 2012, Bruehl, Gatti, La Montagna, and/or Muratore would have been motivated to look to Schwarzer for further information on CRPS. Ex. 1003 ¶284. Based on Schwarzer's disclosure that there are no clinical differences between CRPS type I and type II, a POSA would have been motivated to administer neridronic acid for treatment of pain associated with CRPS type II triggered by fracture. Given the clinical similarity of the two types of CRPS, a POSA would have reasonably

expected that neridronate could be used to treat CRPS type II triggered by fracture. Ex. 1003 ¶284.

H. No Objective Indicia of Nonobviousness Support Patentability

Petitioner is not aware of any objective indicia of nonobviousness that could support the patentability of the alleged invention. As discussed in detail above, it was well-known and recognized in the prior art that bisphosphonates, in particular neridronic acid, could be used to treat pain associated with CRPS, including CRPS triggered by fracture. Therefore, patentability of the alleged invention cannot be supported by any long-felt but unresolved needs, failure of others, skepticism in the art, or teaching away.

1. Patent Owner's Reliance on the Varenna Group's Data Does Not Establish Unexpected Results

During prosecution of the '999 patent and the parent '245 patent, Patent Owner pointed to data disclosed in Varenna 2016 that showed that patients with CRPS triggered by fracture were somewhat more likely to respond to treatment with neridronate than patients with other precipitating events as evidence of "unexpected results." Ex. 1022 at 516-18. Patent Owner's arguments are misplaced.

First of all, Varenna 2016 is prior art that anticipates or renders obvious the '999 patent claims. That Varenna 2016 was known and part of the prior art demonstrates that Patent Owner cannot point to it as evidence of "unexpected

results" supporting the patentability of the '999 patent claims. Second, as discussed above, even before the publication of Varenna 2016 it was already well-known in the art that neridronic acid could be administered for treatment of pain associated with CRPS. Ex. 1003 ¶285. A POSA also would have known that neridronic acid could be used to treat CRPS triggered by fracture in particular, and that neridronic acid was effective in reducing pain in patients with CRPS triggered by fracture. Ex. 1003 ¶285; Ex. 1005. And another clinical study by Manicourt showed that another bisphosphonate, alendronate, could be orally administered to effectively treat pain associated with CRPS triggered by fracture. Ex. 1009; Ex. 1003 ¶285. Thus, before the publication of Varenna 2016 and as of the '999 patent's earliest possible priority date, a POSA would have, at a minimum, reasonably expected that neridronic acid could be administered to treat and effectively reduce pain associated with CRPS in patients with CRPS triggered by bone fracture, as required by all of the '999 patent claims. Ex. 1003 ¶286.

The Varenna group's data shows that "patients affected by CRPS-I with an early disease, a warm disease subtype, and fracture as a predisposing event ***could be more responsive*** to intravenous bisphosphonate treatment . . . ." Ex. 1015 at 1135 (emphasis added); Ex. 1003 ¶287. Yet, as expected based upon the prior art, patients with various triggering or predisposing events—including fractures—responded to bisphosphonate treatment in the study. Indeed, as shown in the table

below, in the group with the lowest responder-to-non-responder ratio (surgery as a predisposing event), 57.1% of the patients responded to treatment. In addition, 69% of patients with an "unknown" predisposing event responded to treatment.

Table 2 Comparisons of demographic and clinical variables between 194 patients with CRPS-I responding/not responding to bisphosphonate treatment

	Responders (N = 139)	Nonresponders (N = 55)	Responder, %
Characteristics			
Age, y, mean ± SD	57.3 ± 12.3	56.5 ± 14.3	
Sex, male/female, N	50/89	22/33	
Disease duration, mo, median (IQR)	3 (2–5)	5 (3–8)*	
Disease localization, lower limb/upper limb, N	83/56	36/19	
Subtype, warm/cold/NA, N	111/13/15	31/18/6*	
Predisposing event, N			
Fracture	69	14	83.1†
Trauma	27	16	62.8‡
Surgery	16	12	57.1§
Others	7	4	63.6
Unknown	20	9	69.0

*$P = 0.0001$ vs responders.
†$P = 0.005$ for fracture vs all other predisposing events.
‡$P = 0.01$ for fracture vs trauma.
§$P = 0.008$ for fracture vs surgery.
CRPS-I = complex regional pain syndrome type I; IQR = interquartile range; NA = not applicable (swinging form and not reported).

Ex. 1015 at 1135, Table 2.

Notably, Dr. Varenna's data does not suggest that efficacy or pain relief was greater in the responders with fractures than it was in responders with other types of predisposing events. Ex. 1003 ¶¶288-289. In fact, Varenna 2016 states that the data demonstrate that fracture patients are "more likely to respond to treatment with bisphosphonates," but "[t]he differences in effectiveness observed between the different regimens are small." Ex. 1015 at 1137; Ex. 1003 ¶289.

This is at most a "difference in degree," not a "difference in kind," and is insufficient to rebut the *prima facie* case of obviousness. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). The '999 patent

claims do not require any particular percentage of patients to respond to treatment; they merely require that neridronic acid be used to treat CRPS triggered by fracture and that the treatment be effective in reducing pain. Thus, the Varenna group's purported discovery that a higher percentage of fracture patients respond to treatment than patients with other predisposing events does not change the fact that a POSA would have reasonably expected that neridronic acid could be used to effectively treat pain associated with CRPS triggered by fracture. Ex. 1003 ¶288.

"A mere difference in degree" of an expected property—like the difference in degree of response to treatment shown in Varenna 2016—is insufficient to establish unexpected results that support patentability. *See In re Papesch*, 315 F.2d 381, 392 (C.C.P.A. 1963). Indeed, the Federal Circuit has on multiple occasions rejected arguments that a higher than expected degree of efficacy establishes unexpected results that defeat an obviousness case. *E.g.*, *Bristol-Myers Squibb Co.*, 752 F.3d at 977 (affirming district court's finding of no unexpected results where the *degree* of a compound's activity was unexpected, but activity itself was not unexpected in view of the known effectiveness of a structurally similar compound); *In re Merck*, 800 F.2d 1091, 1098-99 (Fed. Cir. 1986) (evidence that drug was more potent and had stronger effect than prior art insufficient to outweigh evidence of obviousness); *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("[E]vidence of superior efficacy [of the bisphosphonate

ibandronate] does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected.").

Here, as in the cases cited in the preceding paragraph, the Varenna data showing that fracture patients are somewhat more likely to respond to treatment than may have been expected does not undercut the showing above that a POSA would have reasonably expected neridronic acid to be effective in treating pain associated with CRPS triggered by fracture, as claimed. Thus, Patent Owner's reliance on the Varenna group's work does not establish unexpected results and cannot overcome Petitioner's evidence of obviousness.

2. The Alleged Unexpected Results Are Not Commensurate With the Scope of the Challenged Claims

The alleged "unexpected results" in Varenna 2016 are also not commensurate with the scope of the challenged claims. First, all of the patients treated with neridronic acid that were surveyed in the Varenna 2016 analysis were given intravenous neridronic acid. Ex. 1015 at 1133. Therefore, any alleged unexpected results demonstrated by Varenna 2016 are not commensurate in scope with claims 5-8, and 21, which all require oral administration of neridronic acid, and therefore cannot support their patentability.

Second, Varenna 2016 states that the patients "were treated with neridronate 100 mg every third day for four occasions." Ex. 1015 at 1133. This is not

commensurate in scope with claims 11, 13, 15, 19, 20, 22, and 26, which require different dosing regimens. Any unexpected results demonstrated by Varenna 2016 therefore cannot support these claims.

XII. GROUNDS ARE NOT REDUNDANT

The asserted grounds are meaningfully distinct from each other and PGR should be instituted on each distinct ground. "[A]lternative grounds may be presented if an actual need for presenting alternatives exists and is adequately explained in the petition." *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012-00003, Paper No. 11 at 3 (P.T.A.B. Nov. 26, 2012). Redundancy is avoided "if the Petitioner reasonably articulates why each ground has strength and weakness relative to the other." *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012-00003, Paper No. 8 at 12 (P.T.A.B. Oct. 25, 2012). Petitioner advances both anticipation and obviousness grounds based on Varenna 2012, Varenna 2016, and Manara. Petitioner's anticipation grounds are based on a single prior art reference and cannot be rebutted by arguments based on objective indicia, teaching away, or the like. Petitioner's obviousness grounds have the advantage of including additional information from a POSA's knowledge, or other prior art references regarding treatment of CRPS with neridronate, and do not require that all elements of the challenged claims be present in a single reference.

Thus, both types of grounds are necessary so Petitioner can take advantage of the distinct strengths of each.

XIII. CONCLUSION

Petitioner requests that post-grant review be instituted for claims 1-30 of the '999 patent and that those claims be cancelled as unpatentable based on the above grounds.

Dated: August 21, 2018

By: /Daniel J. Minion/
Daniel J. Minion
Reg. No. 53,329

CERTIFICATE OF COMPLIANCE WITH TYPE VOLUME LIMITATION

Pursuant to Rule 37 C.F.R. § 42.24(d), the undersigned hereby certifies that, based upon the word count of the word-processing system used to prepare this petition, the number of words in this petition is 18,616. Pursuant to 37 C.F.R. § 42.24(a), this word count does not include "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

Dated: August 21, 2018

By: /Daniel J. Minion/
Daniel J. Minion
Reg. No. 53,329

CERTIFICATE OF SERVICE

The undersigned hereby certifies that copies of the Petitioner's PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 9,820,999 were served on August 21, 2018 as follows:

VIA FEDEX AND ELECTRONIC MAIL

Brent A. Johnson
MASCHOFF BRENNAN
20 Pacifica, Suite 1130
Irvine, CA 92618
Telephone: 949-202-1900
Facsimile: 949-453-1104
BJohnson@mabr.com

VIA FEDEX

Antecip Bioventures II LLC
630 Fifth Avenue, Suite 2000
New York, NY 10111

Dated: August 21, 2018

By: /Daniel J. Minion/
Daniel J. Minion
Reg. No. 53,329