

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ASCENDIS PHARMA A/S,
Petitioner

v.

BIOMARIN PHARMACEUTICAL INC.,
Patent Owner

Case PGR2026-00013
U.S. Patent No. 12,233,106

**DECLARATION OF DR. MARY JENNIFER ABUZZAHAB, M.D.,
IN SUPPORT OF PETITION FOR POST-GRANT REVIEW OF
U.S. PATENT NO. 12,233,106**

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I, Dr. Mary Jennifer Abuzzahab, M.D., hereby declare as follows.

I. INTRODUCTION

1. I have been retained as an expert witness on behalf of Ascendis Pharma A/S for the above-captioned post-grant review (PGR). I am being compensated for my time in connection with this PGR at my standard consulting rate, which is \$700 per hour. My compensation on this proceeding is not impacted in any way by the outcome of the proceeding.

2. I understand that this Declaration accompanies a petition for PGR involving U.S. Patent No. 12,233,106 (“the ’106 patent”) (EX1001), which resulted from U.S. Patent Application No. 17/811,748 (“the ’748 application”), filed on July 11, 2022. I understand that the ’106 patent alleges a priority date of July 9, 2021. I refer to this date throughout this declaration.

3. In preparing this Declaration, I have reviewed the ’106 patent and each of the documents cited herein, in light of general knowledge in the art before July 9, 2021. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art (“POSA”) (as defined further below in Section V before July 9, 2021.

II. MY BACKGROUND AND QUALIFICATIONS

4. I am a pediatric endocrinologist at the McNeely Pediatric Diabetes

Center and Endocrine Clinic at Children's Minnesota, in St. Paul, Minnesota. I obtained an M.D. from Eastern Virginia Medical School in 1991, after which I completed my pediatric internship and residence at Nationwide Children's Hospital in Columbus, Ohio from 1991-1994, and then served as Chief Resident from 1994-1995. After my chief year, I practiced pediatric medicine at Yukon-Kuskokwim Delta Regional Hospital in Bethel, Alaska, from 1995-1997. I then completed a pediatric endocrine fellowship at Children's Hospital Medical Center in Cincinnati, Ohio, from 1997-2000. After fellowship, I began practice as a pediatric endocrinologist at Children's Minnesota, where I have practiced from 2000 to the present. I started the endocrinology research program at Children's Minnesota, and am currently the Endocrine and Diabetes Research Director. I am a Board-certified physician in both Pediatrics (1994-present) and Pediatric Endocrinology (2001-present).

5. I have been a Fellow of the American Academy of Pediatrics since 1991, a member of The Endocrine Society since 1999, a member of the Lawson Wilkins Pediatric Endocrine Society since 2003, and a member of the European Society of Paediatric Endocrinology since 2020. I have been in service for the professional staff of Children's MN in several capacities as Chair of the Health Information Management Committee at Children's Minnesota (2009-2015), as Associate Chief of Medicine at Children's Minnesota (2017-2020), and Chair of

the Credentials Committee at Children's Minnesota (2019-present). I have collaborated with other pediatric endocrinologists on the Minnesota Pediatric Obesity Consortium (2011-2021), and the PREP Endocrinology Editorial Board (2016-2021), and in various research activities as outlined below. I have also served on several Data Safety Monitoring Boards on an *ad hoc* basis from 2019 through 2025.

6. I have extensive professional experience and expertise in the field of pediatric growth disorders, including endocrine-related disorders and genetic bone disorders such as skeletal dysplasia. I have direct personal experience and expertise in studying and treating pediatric achondroplasia patients, including treatments with CNP variants. I am one of the limited number of physicians in the country who treat achondroplasia. I have treated 7 patients with achondroplasia with CNP variant therapy, and two patients with Thanatophoric Dysplasia with CNP variant therapy. Due to the rarity of disorders such as achondroplasia and thanatophoric dysplasia, I am currently the only endocrine provider, out of 12 Pediatric Endocrinologists, at Children's Minnesota who treats children with CNP analogs. I also treat a variety of patients with other skeletal dysplasias. This is a broad category that includes disorders such as osteogenesis imperfecta, hypochondroplasia, McCune-Albright, SHOX gene deletions, and rickets; I estimate that I care for at least 100 patients with a skeletal dysplasia annually.

7. I have published numerous peer-reviewed articles related to pediatric endocrinology, in particular, on the topics of pediatric obesity, hypothalamic obesity, diabetes, and growth disorders. The indications on which I have published include achondroplasia, Noonan Syndrome, growth hormone deficiency, ketoacidosis, hyperphagia, Prader-Willi syndrome, hypothalamic obesity, diabetes, and general non-syndromic obesity. My publications on these topics include: “Once-Weekly Navepegritide in Children With Achondroplasia: The APPROACH Randomized Clinical Trial,” *JAMA Pediatrics* **2025**; “Once-weekly TransCon CNP (navepegritide) in children with achondroplasia (ACcomplisH): a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial,” *Eclinicalmedicine* **2023**; “Genetic conditions of short stature: A review of three classic examples,” *Front. Endocrinol.* **2022**; “Switching to weekly Lonapegsomatropin from daily Somatropin in children with growth hormone deficiency: The fliGHt Trial,” *Horm Res Paediatr* **2022**; “Long-term effectiveness and safety of childhood growth hormone treatment in Noonan Syndrome,” *Horm Res Paediatr.* **2021**; “Impact on bone of an estrogen receptor-alpha gene loss of function mutation,” *J Clin Endocrinol Metab.* **2008**; the conference paper “IGF Resistance. The Role of the Type 1 IGF Receptor” in *Deciphering Growth (Research and Perspectives in Endocrine Interactions)* **2003**; and “Intrauterine Growth Retardation (IUGR) Study Group. IGF-I receptor mutations resulting in

intrauterine and postnatal growth retardation.” *N Engl J Med.* **2003**. My full *curriculum vitae* is submitted herewith as EX1004.

8. In addition to my over thirty years of practice as a physician, educational training, and research experience, I have kept abreast of the fields of pediatric endocrinology, pediatric growth disorders, and achondroplasia by reading scientific literature, maintaining my board certifications, conferring and collaborating with colleagues in the field, and attending and presenting lectures at scientific conferences.

III. SUMMARY OF GROUNDS

9. Below is a summary of the Grounds I discuss in this declaration.

Ground	35 U.S.C. Section (AIA)	Claims Challenged	Art Combination
I	§ 103 (obviousness)	1-10, 13-14	Högler and Savarirayan
II	§ 103 (obviousness)	11-12	Högler, Savarirayan, and Bullens
III	§ 103 (obviousness)	1-10, 13-14	Pauli and Savarirayan
IV	§ 103 (obviousness)	11-12	Pauli, Savarirayan, and Bullens
V	§ 102 (anticipation)	1-7, 9-14	Wendt-242
VI	§ 112 (lack of enablement)	1-14	N/A
VII	§ 112 (improper dependent claim)	8	N/A

IV. LIST OF DOCUMENTS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 12,233,106 to Day et al., issued February 25, 2025 (“the ’106 patent”)
1002	Prosecution History of U.S. Patent No. 12,233,106 (“the ’106 Patent File History”)
1003	<i>Intentionally Left Blank</i>
1004	<i>Curriculum Vitae</i> of Dr. Mary Jennifer Abuzzahab, M.D.
1005	Savarirayan, R., <i>et al.</i> , “C-type natriuretic peptide analogue therapy in children with achondroplasia,” <i>New England Journal of Medicine</i> 381(1):25-35 (2019)
1006	Pauli, R. M., “Achondroplasia: a comprehensive clinical review,” <i>Orphanet Journal of Rare Diseases</i> 14(1):1 (2019)
1007	Högler, W., and Ward, L. M., “New developments in the management of achondroplasia,” <i>Wiener Medizinische Wochenschrift</i> 170(5):104-111 (2020)
1008	U.S. Patent No. 9,907,834 to Bullens et al., issued March 6, 2018
1009	Wendt, D. J., <i>et al.</i> , “Neutral endopeptidase-resistant C-type natriuretic peptide variant represents a new therapeutic approach for treatment of fibroblast growth factor receptor 3–related dwarfism,” <i>The Journal of Pharmacology and Experimental Therapeutics</i> 353(1):132-149 (2015)
1010	Baujat, G., <i>et al.</i> , “Achondroplasia,” <i>Best Practice & Research Clinical Rheumatology</i> 22(1):3-19 (2008)
1011	Ornitz, D. M., and Marie, P. J., “FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease,” <i>Genes & Development</i> 16(12):1446-1465 (2002)

Exhibit No.	Description
1012	Ornitz, D. M., and Legeai-Mallet, L., “Achondroplasia: development, pathogenesis, and therapy,” <i>Developmental Dynamics</i> 246(4):291-309 (2017)
1013	Wallis, G. A., “Bone growth: coordinating chondrocyte differentiation,” <i>Current Biology</i> 6(12):1577-1580 (1996)
1014	Su, N., <i>et al.</i> , “FGF signaling: its role in bone development and human skeleton diseases,” <i>Frontiers in Bioscience</i> 13:2842-2865 (2008)
1015	Krakow, D., “Skeletal Dysplasias,” <i>Clinics in Perinatology</i> 42(2):301-319 (2015)
1016	Nguyen, J. C., <i>et al.</i> , “Imaging of pediatric growth plate disturbances,” <i>Radiographics</i> 37(6):1791-1812 (2017)
1017	Yamanaka, S., <i>et al.</i> , “Circulatory CNP rescues craniofacial hypoplasia in achondroplasia,” <i>Journal of Dental Research</i> 96(13):1526-1534 (2017)
1018	Rimoin, D. L., <i>et al.</i> , “The Skeletal Dysplasias: Clinical–Molecular Correlations,” <i>Annals of the New York Academy of Sciences</i> 1117(1):302-309 (2007)
1019	Krejci, Pavel, <i>et al.</i> , “Interaction of fibroblast growth factor and C-natriuretic peptide signaling in regulation of chondrocyte proliferation and extracellular matrix homeostasis,” <i>Journal of Cell Science</i> 118(21):5089-5100.
1020	Pejchalova, K., <i>et al.</i> , “C-natriuretic peptide: an important regulator of cartilage,” <i>Molecular Genetics and Metabolism</i> 92(3): 210-215 (2007)
1021	Wu, C., <i>et al.</i> , “Furin-mediated processing of Pro-C-type natriuretic peptide,” <i>Journal of Biological Chemistry</i> 278(28):25847-25852 (2003)

Exhibit No.	Description
1022	Meyer, M., <i>et al.</i> , “Chapter 58: Natriuretic peptides,” <i>Acute Heart Failure</i> 608-620 (2008)
1023	U.S. Patent No. 8,198,242 to Wendt et al., issued June 12, 2012
1024	<i>Intentionally Left Blank</i>
1025	Mortier, G. R., <i>et al.</i> , “Nosology and classification of genetic skeletal disorders: 2019 revision,” <i>American Journal of Medical Genetics Part A</i> 179(12):2393-2419 (2019)
1026	Breinholt, V. M., <i>et al.</i> , “TransCon CNP, a sustained-release C-type natriuretic peptide prodrug, a potentially safe and efficacious new therapeutic modality for the treatment of comorbidities associated with fibroblast growth factor receptor 3–related skeletal dysplasias,” <i>The Journal of Pharmacology and Experimental Therapeutics</i> 370(3):459-471 (2019)
1027	Merker, A., <i>et al.</i> , “Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort,” <i>American Journal of Medical Genetics Part A</i> 176(8):1723-1734 (2018)
1028	Reid, C. S., <i>et al.</i> , “Cervicomedullary compression in young patients with achondroplasia: value of comprehensive neurologic and respiratory evaluation,” <i>The Journal of Pediatrics</i> 110(4):522-530 (1987)
1029	Hecht, J. T., <i>et al.</i> , “Mortality in achondroplasia,” <i>American Journal of Human Genetics</i> 41(3):454-464 (1987)
1030	Simmons, K., <i>et al.</i> , “Mortality in babies with achondroplasia: revisited,” <i>Birth Defects Research Part A: Clinical and Molecular Teratology</i> 100(4):247-249 (2014)
1031	Bartels, Cynthia F., <i>et al.</i> , “Mutations in the transmembrane natriuretic peptide receptor NPR-B impair skeletal growth and cause acromesomelic dysplasia, type Maroteaux,” <i>The American Journal of Human Genetics</i> 75(1):27-34 (2004)

Exhibit No.	Description
1032	Chitty, L. S., <i>et al.</i> , “New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell-free fetal DNA in maternal plasma,” <i>Ultrasound in Obstetrics & Gynecology</i> 37(3):283-289 (2011)
1033	“General Clinical Pharmacology Consideration for Neonatal Studies for Drugs and Biological Products Guidance for Industry,” U.S. Department of Health and Human Services, July 2019
1034	<i>Intentionally Left Blank</i>
1035	Horton, W. A., <i>et al.</i> , “Achondroplasia,” <i>The Lancet</i> 370(9582):162-172 (2007)
1036	Bianchi, M. L., “Hypophosphatasia: an overview of the disease and its treatment,” <i>Osteoporosis International</i> 26(12):1743-2757 (2015)
1037	McInerney-Leo, A. M., <i>et al.</i> , “Short-rib polydactyly and Jeune syndromes are caused by mutations in WDR60,” <i>The American Journal of Human Genetics</i> 93(3):515-523 (2013)
1038	Yasoda, A., and Nakao, K., “Translational research of C-type natriuretic peptide (CNP) into skeletal dysplasias,” <i>Endocrine Journal</i> 57(8) 659-666 (2010)
1039	Prickett, T. C., and Espiner, E. A., “C-type natriuretic peptide (CNP) and postnatal linear growth,” In <i>Handbook of growth and growth monitoring in health and disease</i> (pp. 2789-2809). New York, NY: Springer New York (2011)
1040	Miura, K., <i>et al.</i> , “Overgrowth syndrome associated with a gain-of-function mutation of the natriuretic peptide receptor 2 (NPR2) gene,” <i>American Journal of Medical Genetics Part A</i> 164(1):156-163 (2013)

Exhibit No.	Description
1041	European Patent 0769554 B1 to Tanaka et al., issued March 5, 2008
1042	Naski, M. C., <i>et al.</i> , “Repression of hedgehog signaling and BMP4 expression in growth plate cartilage by fibroblast growth factor receptor 3,” <i>Development</i> 125(24):4977-4988 (1998)
1043	Bienaimé, J.-J., “38 th Annual J.P. Morgan Healthcare Conference,” BioMarin. PowerPoint Presentation. January 2020.
1044	Minina, E., <i>et al.</i> , “Interaction of FGF, Ihh/Pthlh, and BMP signaling integrates chondrocyte proliferation and hypertrophic differentiation,” <i>Developmental Cell</i> 3(3): 439-449 (2002)
1045	Oefner, C. <i>et al.</i> , “Structure of human neutral endopeptidase (Neprilysin) complexed with phosphoramidon,” <i>Journal of Molecular Biology</i> 296(2) 341-349 (2000)
1046	International Publication WO 2009/067639 (Wendt)
1047	Definition of “Mammal,” Merriam-Webster’s Collegiate Dictionary, 11 th Edition (2020).
1048	Definition of “Mammal,” Cambridge Advanced Learner’s Dictionary, 4 th Edition (2013).
1049	Watanabe, Y. <i>et al.</i> , “Comparison of the hydrolysis of the three types of natriuretic peptides by human kidney neutral endopeptidase 24.11,” <i>Biochemical and Molecular Medicine</i> 61(1):57-51 (1997)
1050	Mora, Camilo, <i>et al.</i> , “How many species are there on Earth and in the ocean?,” <i>PLoS Biology</i> 9(8):e1001127 (2011)
1051	Shim, K. S., “Pubertal growth and epiphyseal fusion,” <i>Annals of Pediatric Endocrinology & Metabolism</i> 20(1):8-12 (2015)
1052	Excerpt from Nelson, D. L., and Cox, M. M., “Lehninger Principles of Biochemistry,” W. H. Freeman (2013)

Exhibit No.	Description
1053	Long, S., <i>et al.</i> , “A novel method for the large-scale production of PG-CNP37, a C-type natriuretic peptide analogue,” <i>Journal of Biotechnology</i> 164(2); 196-201 (2012)
1054	Neumeyer, L., <i>et al.</i> , “Clinical charts for surveillance of growth and body proportion development in achondroplasia and examples of their use,” <i>American Journal of Medical Genetics Part A</i> 185(2):401-412 (2021)
1055	Hoover-Fong, J. E., <i>et al.</i> , “Achondroplasia Natural History Study (CLARITY): a multicenter retrospective cohort study of achondroplasia in the United States,” <i>Genetics in Medicine</i> 23(8):1498-1505 (2021)
1056	<i>Intentionally Left Blank</i>
1057	<i>Intentionally Left Blank</i>
1058	Burdan, F., <i>et al.</i> , “Morphology and physiology of the epiphyseal growth plate,” <i>Folia Histochemica Et Cytobiologica</i> 47:5-16 (2009)
1059	Anderson, B. J., and Holford, N. H. G., “Understanding dosing: children are small adults, neonates are immature children.” <i>Archives of Disease in Childhood</i> 98:737-744 (2013)
1060	<i>Intentionally Left Blank</i>
1061	Wiens, J. J., “Explaining large-scale patterns of vertebrate diversity,” <i>Biology Letters</i> 11: 20150506 (2015)
1062	Espiner, E. <i>et al.</i> “Plasma C-Type Natriuretic Peptide: Emerging Applications in Disorders of Skeletal Growth.” <i>Hormone Research in Paediatrics</i> 90: 345-357 (2019).
1063	Lorget, F., <i>et al.</i> “Evaluation of the Therapeutic Potential of a CNP Analog in a Fgfr3 Mouse Model Recapitulating Achondroplasia 2012.” <i>The American Journal of Human Genetics</i> 97: 1108-1114 (2012).

V. PERSON OF ORDINARY SKILL IN THE ART

10. I understand that patent law analyses are performed from the viewpoint of a person of ordinary skill in the art (“POSA”). I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA in relation to the subject matter of the claims of the ’106 patent would have possessed a strong understanding of treating pediatric skeletal dysplasias, including achondroplasia. A POSA would typically have a Ph.D. in a relevant field (e.g., endocrinology or pharmacology) with several years of experience studying and/or developing therapeutics for bone disorders or endocrine disorders or have an M.D. with experience in a relevant field (e.g., pediatric endocrinology, pediatric orthopedics, or genetic medicine) and several years of experience studying and/or treating bone disorders, such as skeletal dysplasia.

11. A POSA may be part of a multi-disciplinary team, drawing upon his or her own skills and taking advantage of certain specialized skills of others in the team, to solve a given problem. For example, such a team may be comprised of an M.D. specializing in treating pediatric patients with bone disorders, and a biochemist or geneticist specializing in studying genetic bone disorders such as skeletal dysplasias.

VI. STATE OF THE ART BEFORE JULY 9, 2021

12. I present below a summary of what the art would have conveyed to a POSA before July 9, 2021, regarding skeletal dysplasias such as achondroplasia, and treatments thereof.

A. The art taught that achondroplasia is one of several hundred skeletal dysplasias -genetic disorders that effect bones and cartilage.

13. Skeletal dysplasias “are a clinically and genetically heterogeneous group of disorders of bone and/or cartilage.” EX1018, Abstract. By 2021, the art showed that “461 different diseases that are classified into 42 groups [] affecting 437 different genes have been found.” EX1025, Abstract. The genes involved in skeletal dysplasias are “functionally diverse, involved in a broad range of cell biologic processes, and cause disease by a variety of mutational mechanisms.” EX1025, 2417. As such, a POSA would have understood that the term “skeletal dysplasia” encompasses a broad set of indications caused by a diverse set of mutations.

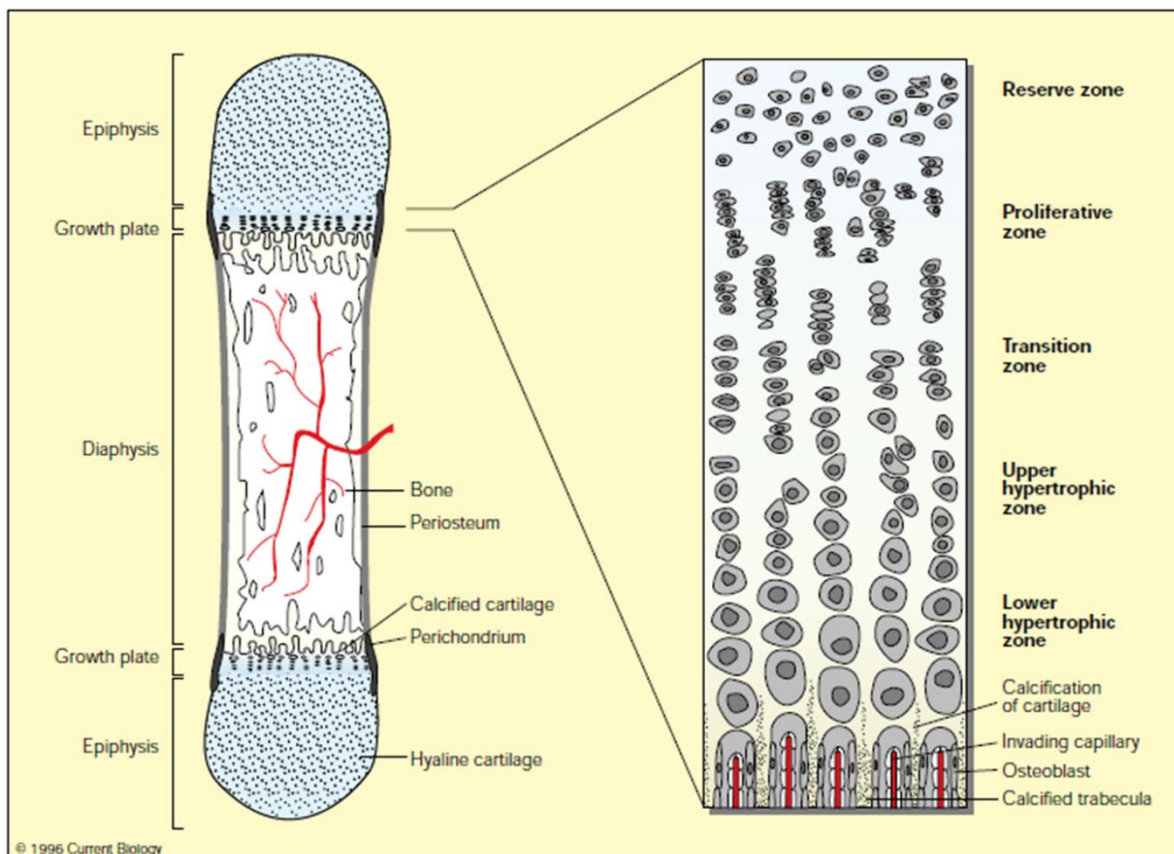
14. Achondroplasia is the most common skeletal dysplasia and the most common form of short limb dwarfism in human beings, affecting somewhere between 1-in-10,000 and 1-in-30,000 live births. EX1015, 8; EX1035, 162. Patients with achondroplasia suffer from characteristic short stature along with an array of complications primarily caused by abnormal growth in endochondral

bone, including long bones and some craniofacial bones. EX1035, 166.

Specifically, achondroplasia is a disease related to a defect in the formation of cartilage: the problem lies in the expansion of the cartilaginous growth plate (discussed below), a bone structure responsible for growth. This reduced growth capacity particularly affects the proximal long bones of the arms and legs, such as the humerus and the femur, leading to short-limb dwarfism. EX1035, 162. The short stature associated with achondroplasia results from disproportionate shortening of the limbs with respect to the torso and proximal segments, referred to as rhizomelia. EX1012, 291; EX1010, 3-5. Other common features of achondroplasia are narrowing of the foramen magnum (the hole in the base of the skull connecting the brain to the spinal cord), and narrowing of the backbone around the spinal cord, referred to as foramen magnum stenosis and spinal stenosis, respectively. EX1012, 291; EX1010, 3-5. As discussed below, these features can result in complications that increase morbidity and mortality.

15. Patients with achondroplasia have a defect in the process of “endochondral ossification,” which is responsible for generating long bone growth. EX1011, 1446; EX1042, 4977; EX1013, 1577; EX1044, 439; EX1014, 2842. One place where endochondral ossification occurs is in a structure called the “cartilaginous growth plate” (also referred to as an “epiphyseal plate” or simply “growth plate”), which can be found close to the ends of long bones. EX1011,

1446; EX1013, FIG. 1; EX1051, 8; EX1007, 109. Growth plates have several different regions characterized by chondrocytes in various stages of differentiation. EX1013, FIG. 1; EX1014, FIG. 2A. Ultimately, long bone growth “depends on an intricate balance between chondrocyte proliferation ... and chondrocyte death.” EX1016, Abstract. The figure below depicts the basic physiology of long bone formation. This figure shows the spatial relationship between the long bone and the growth plate, along with the different zones in a growth plate, and a POSA would have been familiar with this depiction of bone formation.



EX1013, FIG. 1.

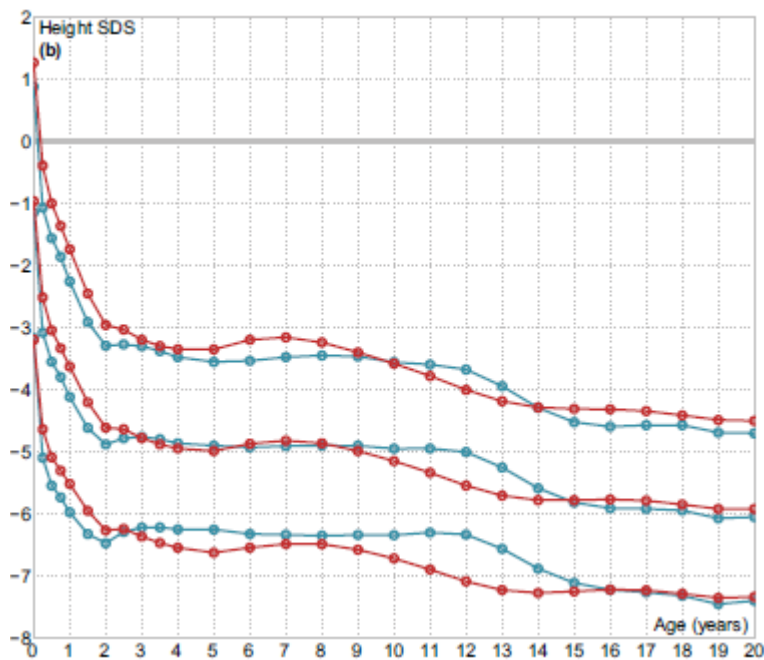
16. Growth plates are known to be open (visible)” on “virtually all images obtained in skeletally immature children.” EX1016, Abstract. Long bones continue to grow until “epiphyseal closure” when the growth plates close after puberty. EX1007, 109; EX1051, 8; EX1058, 5.

17. Achondroplasia results from a mutation in fibroblast growth factor receptor 3 (FGFR3) that “permanently activates the fibroblast growth factor receptor 3 (FGFR3) and its downstream mitogen-activated protein kinase (MAPK) signalling pathway” which inhibits chondrocyte proliferation and differentiation. EX1007, 104-105; EX1035, Abstract, Figure 3; EX1017, 1526; EX1005, 26. The consequence of this increased FGFR3 signaling in the growth plates of bones is to “dramatically inhibit[] both chondrocyte proliferation...and differentiation,” which results in slowing of bone growth. EX1042, 4984, FIG. 8.

B. The art taught that loss of height in achondroplasia patients occurs during the first two years of life.

18. As Merker disclosed in 2018, in achondroplasia patients, the “[l]oss in height position, that is, reduction in height standard deviation scores, occurred mainly during first 2 years of life.” EX1027, Abstract, 1725; EX1007, 105. Merker explained that a significant amount of height position is “lost” during the “first 2 years of life” of achondroplasia patients, resulting in “extensive loss in height position.” EX1027, Abstract, 1725, 1728. Merker further elaborated that “postnatal growth was relatively normal during the first months of life,” but “thereafter

growth velocity abruptly slowed down causing a major decrease in height position on the general population growth curve approaching -4.0 standard deviation score (SDS) before 1 year of age and -5.0 SDS at 2 years of age.” *Id.* The image below, from Merker, shows this loss of height position relative to children without achondroplasia (middle trace is average, traces above and below are $\pm$ two standard deviations, for both sexes).



EX1027, 1725.

19. According to Merker, “FGFR3 signaling might be more dominant during [infancy], or might play a different role than in later growth periods[,]” meaning that FGFR3 signaling may be particularly key to growth during this time period. EX1027, 1728. As such, a POSA would have understood that the first two years of life are an attractive age range for the treatment of short stature in

achondroplasia patients. Indeed, as taught by Högler, “short stature syndromes by definition necessitate intervention in the young[.]” EX1007, 109. Högler also explains that, given the known respiratory complications associated with achondroplasia very early in life (see discussion below in Section VI.E), “the timing of future interventions would need to be shortly after, or before, birth.” EX1007, 106. Thus, a POSA would have understood that early treatment of achondroplasia would have been crucial to address short stature and mitigate potentially fatal complications.

20. Indeed, loss of height in achondroplasia patients in the first two years of life was well known in the art. A meta-analysis of achondroplasia babies published prior to July 2021 revealed that “birth length of achondroplasia subjects overlaps that of average stature newborns,” but that “[s]hortly thereafter, the length curves rapidly diverge so that the 95th percentile line for achondroplasia falls below the 5th percentile line for average stature by 3 months of age in males and 4 months in females.” EX1055, 4. Hoover-Fong described this loss of height by disclosing that “linear growth deviates from average stature by 6 months of age.” EX1055, 6. Similarly, Neumeyer described that “[d]espite almost normal birth length and growth development during first postnatal months, length position in the normal population chart decreases fast to about –5 standard deviation scores (SDS) after the first year of life.” EX1054, 401. Neumeyer also discloses that

“[d]eviant body proportions in achondroplasia can be observed already during infancy.” EX1054, 402. As such, a POSA would have been well-aware of the loss of height that occurs within the first two years of life.

21. A POSA also would have understood that the “[s]hort stature, whilst not a disease in and of itself, can affect daily life and is often met by limited societal acceptance, and may impact quality of life in cases of extreme short stature.” EX1007, 105. In sum, a POSA would have understood that the field was highly active in developing treatments for short stature in achondroplasia and would have known that that treating short stature is beneficial to patients with achondroplasia. A POSA also would have known that such treatment would be particularly advantageous during the first two years of life, when the majority of negative deviation from the mean height is observed.

C. The art taught that children with achondroplasia had an increased risk of death in the first 2 years after birth due to a narrowed foramen magnum and its associated complications.

22. Before July 9, 2021, a POSA would have known that the base of the cranium (or skull) is cartilaginous and is therefore affected by FGFR3 mutations. Infants with achondroplasia have an increased risk of foramen magnum stenosis, which is a narrowing of the hole in the base of the skull, where the spinal cord connects to the brain. EX1006, 9. Foramen magnum stenosis and spinal stenosis are caused by “premature closure of synchondroses (cartilaginous joints).”

EX1007, 106. “The diminution of foraminal size [in foramen magnum stenosis] arises directly from the decreased growth of cartilaginous bone” and “abnormality of the synchondroses” at the base of the skull. EX1006, 9.

23. Foramen magnum stenosis was recognized in the field as a significant risk factor for sudden infant death in infants with achondroplasia. Specifically, it was known that “infants with achondroplasia [were] at increased risk for unexpected death” because the “foramen magnum is often abnormal in shape” for infants with achondroplasia, potentially leading to “apneic deaths aris[ing] from compression of vertebral arteries at or near the craniocervical junction.” EX1006, 9. Similarly, Yamanaka taught that “achondroplasia is ... characterized by ... foramen magnum stenosis, leading to serious neurologic complications and hydrocephalus.” EX1017, Abstract. Highlighting the significance of this symptom, Pauli also disclosed that “without careful assessment some infants with achondroplasia will die because of craniocervical junction issues.” EX1006, 9-10. Similarly, Yamanaka disclosed that, for achondroplasia patients, “[f]oramen magnum stenosis can cause hydrocephalus, potentially resulting in brainstem compression, apnea, or sudden death.” EX1017, 1526. As such, a POSA would have understood that foramen magnum stenosis increased the chance of sudden death in infants with achondroplasia.

24. Compression of the cervicomedullary cord, the area where the

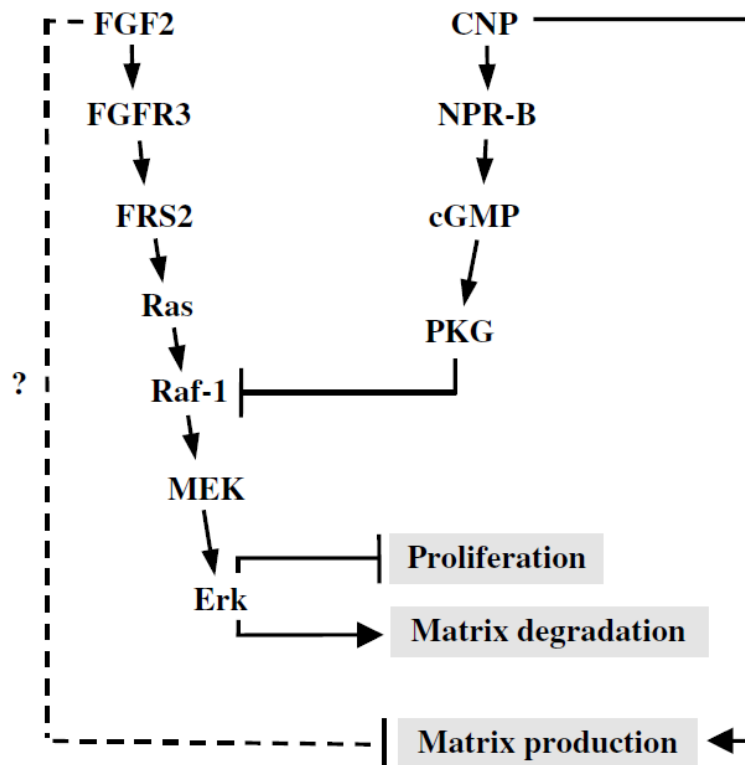
brainstem transitions into the spinal cord, was also identified as a co-morbidity of achondroplasia before 2021. It was known that cervicomedullary cord compression (stenosis) led to “respiratory compromise, apnea, and sudden infant death.”

EX1028, 522; EX1010, 10. For example, Baujat discloses that “Apnoea is [a] common [complication]” of achondroplasia in children,” due to this compression, which “may increase the risk of sudden unexpected death in infants [SIDS],” and that these complications “arise particularly during the first year of life.” EX1010, 8, 10. Because of these known complications, the art taught that “[i]t is critical that [the achondroplasia] diagnosis not be delayed since certain complications can only be prevented through assessment in early infancy.” EX1006, 4; *see also*, EX1006, 9 (“if preventive assessments are to be effective they must be completed early in infancy.”). As such, a POSA would have known that foramen magnum stenosis and cervicomedullary cord compression are causes of these potentially serious complications for young achondroplasia patients.

25. In summary, a POSA before 2021 would have known that infants with achondroplasia had higher rates of foramen magnum stenosis, respiratory compromise (including sleep apnea), cervicomedullary cord stenosis, and other craniocervical junction issues. And a POSA would have known that these issues resulted in a higher chance of sudden infant death, particularly in the first year of life.

D. The art taught that C-type natriuretic peptide (CNP) is a peptide hormone that promotes bone growth.

26. C-type natriuretic peptide (CNP) is a peptide hormone that binds to natriuretic peptide receptor B (NPR-B) and causes cells to produce intracellular cyclic guanosine monophosphate (cGMP). EX1019, 5091, FIG. 3. CNP was widely recognized as an “important regulator of cartilage homeostasis and endochondral bone growth.” EX1020, Abstract. Indeed, before 2009 it was reported that genetically engineered “knockout” mice lacking CNP expression (CNP-null mice) were “dwarfed, with long bones and vertebrae measuring only 50-80% of wild-type littermates.” EX1020, 212. Conversely, “when CNP is overexpressed in the mouse cartilage...the animals show general skeletal overgrowth.” EX1020, 212. Additionally, mice with loss-of-function mutations in NPR-B (the cognate receptor of CNP) “exhibit dwarfism with short limbs and tails.” EX1020, 212. In part, CNP promotes bone growth by inhibiting the signaling of FGFR3. EX1019, 5092. Figure 10 from Krejci, which summarizes the interaction between CNP and FGFR3 signaling, is produced below.



EX1019, FIG. 10.

27. Before 2021, it was known that CNP is synthesized as a “prepropeptide,” with further processing by proteolytic cleavage to yield least two physiologically active peptides, a full-length, 53-amino acid polypeptide (CNP-53) and its truncated C-terminal fragment, a 22-amino acid polypeptide peptide (CNP-22). EX1021, 25847; EX1022, 608-09. CNPs are generally identified by appending a number to the acronym “CNP” indicating the number of amino acids in the peptide. EX1041, ¶18; EX1026, Abstract, 459. Thus, CNP-53 refers to a naturally occurring human CNP peptide having 53 amino acids in a specific sequence, and CNP-22 refers to a truncated peptide containing the 22 C-terminal amino acids

found in CNP-53. EX1041, ¶18; EX1021, 25852, FIG. 8. Typically, intermediate numbers (*e.g.*, CNP-37) refer to the number of amino acids in the sequence of CNP-53, counting from the C-terminus. For example, the table below shows the sequences of CNP-53, CNP-22, and CNP-37. A POSA would know that, by convention, amino acid sequences are typically presented in text format with the N-terminus on the left, and the C-terminus on the right.

NAME	SEQUENCE
CNP-53	DLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI GSMSG LGC
CNP-37	QEHPNARKYKGANKKGLSKGCFGLKLDRI GSMSG LGC
CNP-22	GLSKGCFGLKLDRI GSMSG LGC

A POSA would have understood that different CNP variants had different pharmacokinetic characteristics, making some variants more viable therapeutic agents than others. For example, naturally occurring CNP-22 was known to have a half-life of only a few minutes. EX1062, 346. Longer CNPs were known to have longer half-lives. *Id.*

E. The art taught that vosoritide is a CNP variant with a longer half-life useful for treating achondroplasia in children.

28. Given the known genetic mutation causing constitutively active FGFR3 signaling in achondroplasia patients, and CNP's known role in inhibiting FGFR3 signaling, CNP was actively studied as a therapeutic agent for treating achondroplasia well before July 9, 2021. EX1017, Abstract; EX1005, 25;

EX1043¹, 23-27; EX1007, 108; EX1006, 41; EX1008, 25:36-3:39. However, unmodified CNP-22 was known to have a short half-life *in vivo*, limiting its clinical effectiveness. EX1009, Abstract; EX1026, Abstract, 459. As such, the art taught that modified, or “stabilized” variants of CNP had a longer *in vivo* half-life compared to unmodified CNP-22 and were thus more attractive as therapeutic agents for treating achondroplasia. EX1012, 302; EX1009, Abstract; EX1026, Abstract, 459. Stabilized variants commonly feature either CNP peptides longer than CNP-22, polyethylene glycol conjugated (PEGylated) CNP peptides, or both. EX1009, Table 1; EX1026, Table 4.

29. Before July 9, 2021, a stabilized form of CNP known as vosoritide was already in clinical trials for treating children with achondroplasia. EX1005, 25; EX1007, 108; EX1043, 21-27; EX1006, 41. Vosoritide is a recombinant CNP peptide analogue that was “developed to have a longer half-life than its endogenous form in order to prolong pharmacologic activity.” EX1005, 26. Lorget

¹ The JP Morgan presentation (EX1043) was downloaded from the website, https://static.seekingalpha.com/uploads/sa_presentations/350/50350/original.pdf (last accessed November 18, 2025). EX1043 is the type of document experts in the field would reasonably rely on when formulating opinions about ongoing clinical trials.

explained in 2012 that “BMN 111 [vosoritide] mimics CNP pharmacological activity and has an extended half-life as a result of neutral-endopeptidase (NEP) resistance that allows one-daily SC administration.” EX1063, 1108. Before July 9, 2021, POSAs knew that the amino acid sequence of vosoritide “consists of the 37 C-terminal amino acids of human CNP plus the amino acids glycine and proline added to the N-terminal portion of the peptide.” EX1026, 460; EX1053, Abstract, 196. As such, vosoritide was also known in the art as “Pro-Gly-CNP37” and “PG-CNP37.” EX1026, 460; EX1053, Abstract, 196; EX1008, 4:44-45, 4:52-53, 14:54-55. Vosoritide/Pro-Gly-CNP37 is also sometimes referred to as BMN-111. EX1006, 41; EX1007, 108. Högler refers to BMN111 as “CNP-39,” which a POSA would have understood to be the “CNP-37” plus the N-terminal proline and glycine (Pro-Gly)—i.e., Pro-Gly-CNP37/vosoritide. EX1007, 108.

30. A POSA would have known that vosoritide was an effective treatment for achondroplasia before July 9, 2021. For example, Wendt 2015 teaches that vosoritide binds to NPR-B, stimulates cGMP production, and enhances bone growth. EX1009, Table 1, 141. And Wendt-242 discloses that the CNP variants of its disclosure, including vosoritide, “stimulat[e] matrix production, proliferation, and differentiation of chondrocytes and increase[e] long bone growth,” making it “useful for treating mammals, including humans, suffering from a bone-related disorder, such as a skeletal dysplasia.” EX1023, 83:39-43. As such, a POSA would

have known that the art considered vosoritide to be a “potent stimulator of endochondral ossification,” one of the “possible therapeutic options” for achondroplasia. EX1012, 302; EX1005, 25; EX1006, 41.

31. Given its clinical utility for treating achondroplasia, it is no surprise that vosoritide was in clinical trials for treating children with achondroplasia well before July 9, 2021. As Savarirayan explained in 2019, a multinational, Phase 2 study of treating achondroplasia in children aged 5 to 15 with vosoritide was conducted from January 2014 through October 2017. EX1005, 26. Savarirayan disclosed that treating pediatric achondroplasia patients with vosoritide “resulted in a sustained increase in the annualized growth velocity for up to 42 months” at doses of 15.0 and 30.0 µg/kg of body weight. EX1005, 25. Savarirayan also disclosed that there was “an ongoing ... clinical trial (NCT03583697) of vosoritide in infants and younger children (age range, 0 to <60 months).” EX1005, 34. Indeed, according to BioMarin’s own 2020 presentation, this ongoing clinical trial “include[d] infants and toddlers ages 0-5 years *to provide maximum benefit*” for achondroplasia patients. EX1043, 26 (emphasis added). According to BioMarin’s 2020 presentation, the vosoritide dosing of achondroplasia patients aged 6 months to 2 years was 30 µg/kg, and the “safety and tolerability in infants and children” was generally consistent with the safety profile of the Phase II vosoritide clinical trial that resulted in drug approval. EX1043, 26. As such, a POSA would have

known that vosoritide showed success in the clinic, resulting in increased growth velocity of pediatric patients. And a POSA would have known that there were active efforts to treat infants and young children below the age of 5 years old with vosoritide.

VII. OVERVIEW OF THE '106 PATENT AND PROSECUTION HISTORY

A. Overview of the '106 Patent and Claims

32. The '106 patent issued on February 25, 2025, from U.S. Appl. No. 17/811,748 (“the '748 application”), filed July 11, 2022. The '748 application claims priority to provisional application Nos. 63/350,196 and 63/220,275, filed on June 8, 2022, and July 9, 2021, respectively. The '106 patent purports to disclose administering to patients having a skeletal dysplasia from the age of “about 0 month to about 2 years old” a CNP variant to treat the skeletal dysplasia. EX1001, 63:35-67:40. The CNP variants recited include truncated versions of wild-type CNP-53, referred to as CNP-52 through CNP-18, as well as PEGylated CNP variants, and modified CNP variants containing other deviations from the naturally occurring sequence. EX1001, 63:35-67:40. As evident from its disclosures throughout, the '106 patent specification is directed towards treating achondroplasia patients with the drug vosoritide (Pro-Gly-CNP37) in the achondroplasia patient population. EX1001, 63:35-67:40.

33. Independent claim 1 of the '106 patent recites a method of treating a

patient “from about 0 month to about 2 years old comprising administering to the subject a composition comprising” a CNP variant selected from a list of 65 different CNP variants. EX1001, 63:35-67:40. Claims 2-14 all depend either directly or indirectly from claim 1, and further narrow the independent claims with, *e.g.*, the dosing regimen, method of administration, dose concentration, patient population age, skeletal dysplasia to be treated, excipients, and CNP variant selected to be administered. EX1001, 67:40-69:10.

B. Prosecution History

34. I have reviewed the file history of the '106 patent. EX[1002. I understand from the file history that during prosecution, the Examiner issued a single Office Action on February 1, 2024, rejecting the pending claims as obvious over Bullens (US Patent No. 9,907,834, EX1008) and a PCT application publication, WO 2009/067639 (referred to herein as “the '639 publication,” EX1046). EX1002, 900-11. The Examiner found that Bullens disclosed the use of vosoritide to treat achondroplasia, and that the '639 publication taught that “CNP variants ... can be administered to treat ... achondroplasia,” and that “the ideal age range of achondroplasia patients will be from infant (<1 year of age) to pre-adolescent (< 13 years of age).” EX1002, 909.

35. During prosecution, the Examiner also rejected original dependent claims 12 and 14 as improper dependent claims for failure to limit the claims from

which they depend. EX1002, 904-05. The Examiner also rejected original dependent claim 15 for being unclear due to the claim's recitation of parenthetical expressions. EX1002, 905-06.

36. On August 1, 2024, BioMarin amended the claims and argued (i) that not all elements of the claims were disclosed or suggested in the prior art, (ii) that the art provides no reasonable expectation of success, and (iii) that the specification provides unexpected benefits of the claimed invention. EX1002, 935-36. BioMarin claimed that “although [the ’639 publication] generally discloses that younger children suffering from achondroplasia *could* benefit from treatment with CNP,” that treatment of this population had not been disclosed by the ’639 publication. EX1002, 936 (emphasis original). BioMarin also argued that a POSA would not have had a reasonable expectation of success in treating this population, and that unexpected results disclosed in the ’106 patent specification weigh against obviousness. EX1002, 936.

37. The Examiner then issued a notice of allowance on October 29, 2024, describing that “one of ordinary skill in the art would not have predicted the results in children from about 0 month old to about 2 years old of instant application.” EX1002, 966.

VIII. LEGAL BASIS FOR MY ANALYSIS

38. When considering the ’106 patent and stating my opinions, I am

relying on legal principles that have been explained to me by counsel.

A. Claim Construction

39. I understand that in a PGR, patent claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention, in view of the patent's specification and its prosecution history—unless the patent explicitly defines the claim term. I also understand that when a patent explicitly defines a claim term in the specification, the patent's definition controls.

40. I understand that claim 1 is the independent claim in the '106 patent, and that claims 2-14 are dependent claims depending directly or indirectly from claim 1. I understand that a dependent claim contains all limitations of the claim from which it depends. Thus, I understand that claims 2-14 require all the limitations of claim 1.

B. Obviousness

41. I understand that an obviousness analysis involves comparing a claim to the prior art to determine whether the claimed subject matter would have been obvious to a POSA in view of the prior art and general knowledge in the art. I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention. I further understand that to show obviousness the following factual inquiries must be performed: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the

prior art; (c) resolving the level of skill in the art; and (d) considering any known objective evidence of non-obviousness.

42. I also understand that, for a finding of obviousness, a POSA needs to have (i) a reason or motivation to modify or combine the prior art to arrive at the claimed subject matter and (ii) a reasonable expectation of doing so successfully.

43. I understand that the reason to combine prior-art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a POSA that does not need to be explicit in any reference.

44. I understand that a “reasonable expectation of success” is assessed in view of the prior art and general knowledge of the art from the viewpoint of a POSA, and it does not require an absolute certainty of success.

45. I also understand that the objective evidence of non-obviousness (also called objective indicia of non-obviousness) can include evidence of commercial success attributable to the claimed invention, evidence of industry praise for the claimed invention, evidence of a long-felt need in the art that was solved by the claimed subject matter, evidence that others copied the claimed subject matter, or

evidence that the claimed subject matter achieved an unexpected, superior result relative to the closest prior art. I understand that such evidence must have a nexus, or causal relationship, to the claimed subject matter beyond what was available in the prior art and must be commensurate in scope with the patent claim(s) at issue.

C. Anticipation

46. It is my understanding from counsel that a prior art reference anticipates a claim (e.g, the claim is not novel over the prior art reference) if it (i) discloses each and every element recited in the claim, arranged as claimed and (ii) enables a POSA to make and use the subject matter that anticipates the claim without having to undertake undue experimentation.

47. I understand that for the purposes of anticipation, the prior art reference only needs to enable a single embodiment that anticipates the claims at issue. I additionally understand that a reference can anticipate even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a POSA, reading the reference would at once envisage the claimed arrangement or combination.

D. Enablement

48. I understand that for enablement, a patent specification must describe the invention with sufficient detail such that a POSA can make and use the full scope of the claimed invention without undue experimentation as of the filing date.

I understand that the following factors can be weighed to determine whether undue experimentation would have been needed (the so-called *Wands* factors): (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

49. I understand that the determination that “undue experimentation” would have been needed to make and use the claimed invention is a conclusion reached by weighing the above-noted factors. I understand that whether some experimentation is necessary does not necessarily make such experimentation undue and that even a considerable amount of experimentation is not undue, if it is merely routine.

E. Indefiniteness

50. I understand that the written description provided by a patent specification must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter regarded as the invention. I understand that the claims must be discernable to a POSA based on the language of the claim, the specification, and the prosecution history, along with the POSA’s knowledge in the field.

IX. CLAIM CONSTRUCTION

51. In construing the claims of the '106 patent, I understand that claims must be construed according to the plain and ordinary meaning of given terms, as understood by one of ordinary skill in the art in light of the patent claims, specification, and prosecution history. It is my opinion that a POSA would have viewed the following terms as such:

A. “Subject”

52. Claims 1, 3, and 6-8 recite the term “subject.” Each of claims 2-14 of the '106 patent depend directly or indirectly from claim 1. The '106 patent broadly defines “subject” as follows:

As used herein, the term “subject” *encompasses mammals and non-mammals*. Examples of *mammals include*, but are not limited to, *any member of the mammalian class*: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of *non-mammals include, but are not limited to*, birds, fish, and the like. The term does not denote a particular age or gender.

EX1001, 18:55-65.

53. In light of this evidence, a POSA would have interpreted the term “subject” as any mammal or non-mammal. A POSA would then have interpreted “mammal” according to the plain and ordinary meaning of the term, *e.g.*, a warm-

blooded vertebrate that gives live birth and nourishes young with milk. The dictionary definition of “mammal,” such as the one provided from the Merriam-Webster dictionary, is consistent with this interpretation: “any of a class (Mammalia) of warm-blooded higher vertebrates [] that nourish their young with milk secreted from mammary glands, have the skin usually more or less covered with hair, and include humans.” EX1047.

54. Given this understanding of “mammal” subjects, a “non-mammal” subject of the ’106 patent would have been understood to be vertebrates that are not a mammal (e.g., birds, amphibians, fish, and reptiles). This construction is supported by other dictionaries. While the Merriam-Webster dictionary simply defines “nonmammalian” as “not of, relating to, or being a mammal,” the Cambridge dictionary describes “fish, birds, amphibians, and reptiles” as examples of “non-mammalian vertebrates.” EX1047; EX1048.

55. Thus, in light of the intrinsic and extrinsic evidence, a POSA would have interpreted the term “subject” to include mammals and non-mammals.

B. “Amount effective to treat”

56. Claim 1 recites the term “amount effective to treat.” Claims 2-14 depend directly or indirectly from claim 1. The ’106 patent defines an “effective amount” as a “dosage sufficient to produce a desired result on a health condition, pathology, or disease of a subject or for a diagnostic purpose” comprising “a

subjective or objective improvement in the recipient of the dosage.” EX1001,

17:28-32. And the ’106 patent also describes “treatment” as prophylactic (“decreasing the risk of developing pathology”), therapeutic (“diminishing or eliminating those signs of symptoms” of a given pathology), or diagnostic.

EX1001, 17:46-64. The ’106 patent states that “[i]n one embodiment, the treatment is an improvement in one or more symptoms of skeletal dysplasia,” including “increased long-bone growth” and “improved or increased growth velocity.”

EX1001, 4:19-24. I understand from my review of the file history that the term was not addressed during the ’106 patent’s examination. EX1002, 878-879, 934-938, 974. As such, a POSA would have understood the term “amount effective to treat” as a dosage sufficient to produce a desired result in a health condition, pathology, or disease of a subject or for a diagnostic purpose and comprising a subjective or objective improvement in the recipient of the dosage for prophylactic or therapeutic or diagnostic treatment.

X. CLAIMS 1-14 OF THE ’106 PATENT ARE UNPATENTABLE.

A. Ground I: Claims 1-10 and 13-14 of the ’106 patent would have been obvious over Högler and Savarirayan.

57. Claims 1-10 and 13-14 of the ’106 patent would have been obvious over Högler and Savarirayan. As I discuss below, Högler and Savarirayan disclose each and every element of claims 1-10 and 13-14. And, a POSA would have been motivated to modify Savarirayan in view of Högler to arrive at the claimed

methods, with a reasonable expectation of success. Thus, the combination of Högler and Savarirayan renders claims 1-10 and 13-14 of the '106 patent obvious.

1. Högler and Savarirayan render claim 1 obvious.

a. Högler and Savarirayan teach or suggest each and every element of claim 1.

58. For ease of reference, I have broken claim 1 into four elements:²

- [1.1] “A method of treating skeletal dysplasia...”
- [1.2] “in a subject about 0 month to about 2 years old...”
- [1.3] “comprising administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject...”
- [1.4] wherein the CNP variant is selected from the group consisting of SEQ ID NO: 1 (Pro-Gly-CNP37)...” [i.e., vosoritide]. EX1001, 63:36-67:40.

i. A method of treating skeletal dysplasia...

59. A POSA would have understood that Savarirayan discloses “A method of treating skeletal dysplasia...” (claim element [1.1]) because Savarirayan discloses “[*treatment*] (that) resulted in a sustained increase in the annualized

²A claim appendix, including the breakdown of the elements of claim 1, is included as Appendix A.

growth velocity for up to 42 months” in “children with *achondroplasia*,” and that “C-type natriuretic peptide–based therapy may enhance endochondral ossification and improve skeletal growth in children with achondroplasia.” EX1005, 25, 35 (emphasis added). As discussed above in Section VI.A, a POSA would have understood that achondroplasia is a type of skeletal dysplasia. See e.g., EX1007, 105 (“The term skeletal dysplasia refers to over 400 genetic conditions affecting bone size, shape and elongation” and “[a]chondroplasia ... is the most common form of disproportionate short stature.”); EX1005 26; Section VI.A. The ’106 patent also confirms this knowledge in the art, stating that “U.S. Pat. Nos. 8,198,242 . . . disclose[s] use of CNP variants to treat skeletal dysplasias, such as achondroplasia.” EX1001, 3:34-42.

ii. in a subject about 0 month to about 2 years old...

60. Högler teaches or suggests claim element [1.2], “a subject about 0 month to about 2 years old...[.]” EX1001, 63:36-37. Högler reviews “new developments in the management of achondroplasia” and teaches that achondroplasia is “associated with potentially serious medical complications such as foramen magnum and spinal stenosis, both of which cause increased morbidity and mortality.” EX1007, Title, 105. Högler teaches or suggests the claimed subject population in two ways. First, Högler teaches that “[achondroplasia]-specific growth curves have recently been established, which also demonstrate that the

main loss of height occurs in *the first 2 years of life.*” EX1007, 105 (emphasis added). A POSA would interpret this disclosure as identifying the achondroplasia patient population of 0-2 years old because Högler specifically identifies the “first 2 years of life.” EX1007, 105. Högler teaches that although short stature is “not a disease in and of itself, [it] can affect daily life and is often met by limited societal acceptance, and may impact quality of life in cases of extreme short stature.” EX1007, 105. Thus, Högler suggests a subject population of “about 0 month to about 2 years old,” as claimed in the ’106 patent.

61. Second, Högler also teaches that there is an “increased risk of *first-year* deaths in infants with achondroplasia” and that “[o]ne of the factors contributing to infant mortality is foramen magnum stenosis” which can cause “cervical cord compression leading to respiratory failure and sudden infant deaths,” EX1007, 105. Högler discloses that one such study reported a 6-fold increased risk of death. EX1007, 105.

62. Högler further teaches that “[g]iven the occurrence of complications from foramen magnum stenosis very early in life, the timing of future interventions would need to be *shortly after, or before, birth.*” EX1007, 106. Some of these potential complications include identifies “[n]arrowing of upper respiratory airways,” which results in “30-60% of all infants with achondroplasia” having sleep disorders. EX1007, 105-06.

63. As such, a POSA would interpret this disclosure identifying achondroplasia patients at elevated risk of foramen magnum stenosis as identifying the achondroplasia patient population of 0–1-year-old (infants). Thus, Högler teaches or suggests treating achondroplasia (a skeletal dysplasia) in infants (0-1 year old) and in the broader age group 0-2 years old to reduce the loss of height and mitigate the co-morbidities of achondroplasia such as foramen magnum stenosis, apnea, sleep disorders, and sudden death. A POSA also would have generally understood that the epiphyses remain open in 0-2 yr olds with achondroplasia, making them prime candidates for successful treatment. EX1016, Abstract; EX1051, 8.

64. I understand from counsel that, when a prior art range (such as 0 to 1 year old) is subsumed within a claimed range (here, about 0 month to about 2 years old), the prior art range is considered to disclose the given element. As such, Högler discloses claim element [1.2], because it discloses both the achondroplasia population of 0-1 year old, as well as the population of 0-2 years old. EX1007, 105.

65. Additionally, Savarirayan teaches claim element [1.2] because Savarirayan discloses an on-going clinical trial (NCT03583697) treating “*infants and younger children (age range, 0 to <60 months)*” with vosoritide. EX1005, 34. A POSA would have known infants to be 0 months to 1 year old children, which

fall within the claimed “about 0 month to about 2 years old” subject. EX1023,
140:6-8.

iii. administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject...

66. Savarirayan discloses “*administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject...*” (claim element [1.3]) because Savarirayan discloses “[i]n children with achondroplasia, once-daily ***subcutaneous administration of vosoritide*** ... resulted in a ***sustained increase in the annualized growth velocity*** for up to 42 months.” EX1005, 25 (emphasis added). Savarirayan also discloses that “[v]osoritide is a recombinant ***C-type natriuretic peptide*** analogue[.]” with which treatment resulted in “a sustained increase in the annualized growth velocity for up to 42 months” that “approximated the annualized growth velocity of average-height children of similar age” such that there was “[p]roportional growth between the upper-body and lower-body segments [], with no clinically relevant change in the body-segment ratio.” EX1005, Abstract, 25, 26, 34. Further, Högler discloses clinical studies (NCT02055157; NCT02724228) treating achondroplasia by administering 15 µg/kg of “CNP analogue vosoritide (BMN111)” in “children with achondroplasia (aged 5–14 years).” EX[Högler], 108. Högler discloses that the “first 6 months of

treatment demonstrate[d] a dose-dependent increase in the annualized growth velocity, and a sustained increase in annualized growth velocity of 1.5 cm/year” for up to 42 months. EX1007, 108. Because the treatment method of the clinical trials disclosed in Högler and Savarirayan improves annualized growth velocity, they teach administering vosoritide in an amount effective to treat achondroplasia and thus disclose claim element [1.3].

iv. wherein the CNP variant is selected from the group consisting of SEQ ID NO: 1 (Pro-Gly-CNP37)...

67. Finally, Savarirayan discloses a “*CNP variant ... selected from the group consisting of SEQ ID NO: 1 (Pro-Gly-CNP37)...*” (claim element [1.4]) because Savarirayan teaches administering *vosoritide*. EX1005, Abstract. As discussed in Section VI.C, a POSA would have known that vosoritide is also known as Pro-Gly-CNP37. EX1026, 459-460; EX1053, Abstract, 196; EX1063, 1108, Fig. S2. It was well-known that the sequence of vosoritide is Pro-Gly-CNP37—i.e., the same sequence claimed in claim 1 as SEQ ID NO: 1. EX1026, Abstract, 459; EX1053, Abstract; EX1063, 1108, Fig. S2. And Savarirayan discloses administering vosoritide as claimed: “[i]n children with achondroplasia, once-daily ***subcutaneous administration of vosoritide...***” EX1005, 25. Högler also teaches administering vosoritide to children with achondroplasia. EX1007, 108. Specifically, Högler teaches that “using BMN111 (vosoritide) in 35 children

with achondroplasia (aged 5-14 years) ... as a once daily subcutaneous injection and a dose of 15 mcg/kg” resulted in “a sustained increase in annualized growth velocity.” EX1007, 108.

68. I understand from counsel that, if even one species listed in a claimed group is taught or suggested by the prior art, then the entire group is deemed as taught in the art. Thus, even though claim 1 lists 65 different CNP variants as possibilities, because both Savarirayan and Högler teach administering vosoritide (SEQ ID NO: 1 in the claimed group), the art teaches claim element [1.4]. Högler and Savarirayan teach administering vosoritide in an amount effective to treat achondroplasia because the treatment method of the clinical trials taught in each reference improves annualized growth velocity meeting the '106 patent's description of “treating.” (see Section IX.B above). As such, Högler and Savarirayan teach claim element [1.4].

b. A POSA would have been motivated to combine the CNP treatment disclosed in Savarirayan with the patient population disclosed in Högler and Savarirayan to treat achondroplasia.

69. Based on the disclosures of Savarirayan and Högler, a POSA would have been motivated to treat achondroplasia in the patient population of about 0 months to about 2 years with vosoritide for two reasons. First, a POSA would have been motivated to treat achondroplasia in subjects about 0 months to about 2 years old with vosoritide to reduce short stature. Second, a POSA would have been

motivated to treat achondroplasia in subjects about 0 months to about 2 years old with vosoritide to reduce or eliminate complications associated with achondroplasia, such as foramen magnum stenosis. I discuss each rationale below.

i. A POSA would have been motivated to treat achondroplasia in subjects about 0 months to about 2 years old to reduce short stature.

70. Högler teaches: “Mean adult height in achondroplasia is 132cm in males and 124cm in females. New disease-specific growth curves have recently been established, which also demonstrate that the main loss of height occurs in the *first 2 years of life*.” EX1007, 105 (emphasis added); *see also*, EX1027, Abstract, 5-6; EX1054, 401-402; EX1055, 4, 6. A POSA would have been motivated to treat the short stature typical of achondroplasia within these first two years of life, when height is lost.

71. Loss of height in achondroplasia patients in the first two years of life was well known in the art. A meta-analysis of achondroplasia babies published prior to July 2021 revealed that “birth length of achondroplasia subjects overlaps that of average stature newborns,” but that “[s]hortly thereafter, the length curves rapidly diverge so that the 95th percentile line for achondroplasia falls below the 5th percentile line for average stature by 3 months of age in males and 4 months in females.” EX1055, 4. Hoover-Fong described this loss of height by disclosing that “linear growth deviates from average stature by 6 months of age.” EX1055., 6.

Similarly, Neumeyer described that “[d]espite almost normal birth length and growth development during first postnatal months, length position in the normal population chart decreases fast to about –5 standard deviation scores (SDS) after the first year of life.” EX1054, 401. Neumeyer also discloses that “deviant body proportions in achondroplasia can be observed already during infancy.” EX1054, 402. As such, a POSA would have been well-aware of the loss of height that occurs within the first two years of life and would have been motivated to treat a patient with achondroplasia during this time period.

72. Indeed, Högler explicitly suggests that “short stature syndromes by definition necessitate intervention in the young, prior to epiphyseal closure[.]” EX1007, 109. A POSA would have understood that achondroplasia is a short stature syndrome, as discussed in Section VI.A, and as taught by both Högler (“[a]chondroplasia is the most common form of disproportionate short stature”) and Savarirayan (“[a]chondroplasia is a genetic disorder ... resulting in disproportionate short stature”). EX1007, 104; EX1005, 25. This means that a POSA would have understood that the 0–2-year-old window was a key achondroplasia patient population age to treat short stature, as it is prior to epiphyseal closure.

73. While short stature is “not a disease in and of itself, [short stature] can affect daily life and is often met by limited societal acceptance, and may impact

quality of life in cases of extreme short stature.” EX1007, 105. Thus, a POSA would have been motivated to treat this short stature to avoid its impact on daily life and potential quality of life, including, and especially, during the first two years of life.

74. A POSA also would have known that vosoritide could be used to treat short stature, because Savarirayan teaches treatment of achondroplasia patients with vosoritide for short stature: “During the first 6 months of treatment, a dose-dependent *increase in the annualized growth velocity* was observed with vosoritide up to a dose of 15.0 µg per kilogram, and a *sustained increase in the annualized growth velocity* was observed at doses of 15.0 and 30.0 µg per kilogram for up to 42 months.” EX1005, 25 (emphasis added). Savarirayan also suggests vosoritide treatment by of children age 0-60 months by disclosing “[a]n ongoing phase 2, randomized, double-blind, placebo-controlled clinical trial (NCT03583697) of vosoritide in infants and younger children (age range, 0 to <60 months)[.]” EX1005, 34. Further, Höglér teaches that “BMN111 [vosoritide] treatment in the [achondroplasia] mouse model led to a significant recovery of bone growth.” EX1007, 108. This gives a POSA further motivation to treat short stature of children 0-2 years old with vosoritide.

75. A POSA would have understood that vosoritide was a suitable option to increase height velocity, height z-score, and linear bone growth. Thus, a POSA

would have been motivated to treat the patient population of about 0 months to 2 years old with vosoritide to alleviate the short stature phenotype associated with achondroplasia.

ii. A POSA would have been motivated to treat achondroplasia in subjects about 0 months to about 2 years old to reduce or eliminate foramen magnum stenosis.

76. A POSA also would have been motivated to combine Savarirayan and Högler to reduce or eliminate foramen magnum stenosis in children with achondroplasia. As discussed in Section VI.E, a POSA would have known that foramen magnum stenosis is a co-morbidity of achondroplasia. For example, a POSA would have generally known that “achondroplasia is ... characterized by ... foramen magnum stenosis”; “Craniofacial features of achondroplasia include ... foramen magnum stenosis[.]” EX1017, Abstract, 1526. The ’106 patent defines “treatment” as “prophylactic treatment or therapeutic treatment or therapeutic treatment.” EX1001, 17:46-50. The ’106 patent further defines therapeutic treatment, in part, as “treatment administered to a subject who exhibits signs or symptoms of a pathology for the purpose of diminishing or eliminating those signs or symptoms.” EX1001, 17:58-61. Thus, according to the ’106 patent, diminishing or eliminating foramen magnum stenosis would be consistent with “treating” achondroplasia.

77. A POSA would have been motivated to treat achondroplasia in the

patient population about 0 months to about -2 years old with vosoritide to reduce or eliminate complications associated with foramen magnum stenosis. Höglér teaches that foramen magnum stenosis “can cause cervical cord compression leading to respiratory failure and sudden infant deaths.” EX1007, 105; EX1029, Abstract; EX1030, 247. Because “complications from foramen magnum stenosis [occur] very early in life, the timing of future interventions would need to be shortly after, or before, birth.” EX1007, 106. A POSA also would have understood that these complications include “hydrocephalus, potentially resulting in brainstem compression, apnea, or sudden death.” EX1017, Abstract, 1526; *see also* EX1017, 1526 (“Craniofacial features of achondroplasia include ... foramen magnum stenosis[.]”). Höglér also teaches that “[a]chondroplasia is caused by a heterozygous, activating mutation in the fibroblast growth factor receptor-3 (FGFR3) gene” that activates its downstream MAPK signaling pathway and “inhibits chondrocyte differentiation and puts a break on growth plate function, in addition to causing serious medical complications such as foramen magnum and spinal stenosis and upper airway narrowing.” EX1007, Abstract, 105. This mutation “puts a continuous permanent break onto chondrocyte proliferation in all growth plates” with the “faster proliferating growth plates (femur, humerus) tend[ing] to be more affected than slower ones at other sites” to cause “reduced growth of legs and arms” (which manifests as short stature). EX1007, 105. The

role of this mutation was well known in the art. For example, Yamanaka teaches that the “developmental mechanisms of . . . foramen magnum stenosis in achondroplasia are related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes.” EX1017, 1526.

78. In short, a POSA would have understood that the foramen magnum stenosis can cause severe complications from achondroplasia, including “sudden infant death[.]” EX1007, 105. Höglér’s teachings are consistent with the general understanding in the art. For example, Yamanaka advises that “early administration [of CNP] may be an important determinant of clinical effectiveness[.]” strengthening the position that a POSA would want to treat an achondroplasia patient early in life. EX1017, 1533. A POSA thus would have been motivated to treat achondroplasia in the first year of life to reduce or eliminate foramen magnum stenosis, thereby lowering the risk of death in the first year of life due to complications such as cervicomedullary cord compression, sleep apnea, or other respiratory complications.

79. Further, Yamanaka discloses that “the foramen magnum stenosis observed in FGFR3^{ach} mice was significantly ameliorated in Fgfr3^{ach}/SAP-Nppc-Tg mice due to enhanced endochondral bone growth of the anterior intraoccipital synchondrosis. These results clearly demonstrate the therapeutic potential of *CNP for treatment* of midfacial hypoplasia and *foramen magnum stenosis in*

achondroplasia.” EX1017, Abstract (emphasis added). Here, a POSA would have understood that FGFR3^{ach} mice are a mouse model of achondroplasia , which display “dwarfism and short limb bones.” EX1017, 1528. This mouse model was also shown to exhibit a “significantly smaller” foramen magnum compared to wild-type mice. EX1017, 1532. However, by overexpressing CNP in these mouse models achondroplasia, “[t]he narrowed foramen magnum was rescued[.]” EX1017, 1532. Further, Högler teaches that CNP “antagonizes the FGFR3-induced activation of the MAPK signalling pathway in growth plate chondrocytes and thus counteract the effects of the FGFR3 mutation.” EX1007, 106. And Högler teaches “CNP analogue vosoritide (BMN111)” was successful in causing a “sustained increase in annualized growth velocity” in 5-14 year old children with achondroplasia. EX1007, 108. As such, a POSA would have understood that CNPs, such as the claimed CNP variants, were known to counteract FGFR3 activation. Similarly, Savarirayan teaches that CNP (vosoritide) treatment resulted in increased growth velocity that “approximated the annualized growth velocity of average-height children of similar age” with “no clinically relevant change in the body-segment ratio.” EX1005, Abstract, 25, 34.

80. In terms of which CNP treatment to use, a POSA would have known that vosoritide had already demonstrated success in treating achondroplasia in children. Pauli teaches that CNP is “the most advanced ... therapeutic option” for

the treatment of achondroplasia, teaching that “BMN-111 (i.e., vosoritide) reversed the achondroplasia phenotype in the mouse model of this disorder.” EX1006, 41. Pauli also describes the “greater stability” of vosoritide compared to CNP22, and notes that human trials for achondroplasia patients that are “infants and children” are ongoing. EX1006, 41. As such, a POSA would have been motivated to treat achondroplasia and foramen magnum stenosis in infants, as taught by Högler, with vosoritide, as taught by Savarirayan, to reduce the foramen magnum stenosis phenotype and reduce the chance of potentially fatal complications.

c. A POSA would have had a reasonable expectation of success in treating achondroplasia in subjects about 0 months to about 2 years old with vosoritide.

81. A POSA would have had a reasonable expectation of success in treating achondroplasia patients aged about 0 months to about 2 years old because the art taught that vosoritide counteracts the constitutively active FGFR3 signaling in achondroplasia. EX1007, 108; EX1005, 25-26. A POSA would have known that the FGFR3 mutation associated with achondroplasia slowed bone growth as early as *in utero*, meaning that a POSA would have reasonably expected vosoritide to effectively inhibit FGFR3 signaling in subjects about 0 months to about 2 years old. EX1012, 296 (“[t]he diagnosis of Ach[ondroplasia] is usually made at birth, but may be suspected based on late prenatal ultrasound images”); EX1010, 4 (“diagnosis of achondroplasia may be suspected in the third trimester by abnormal

ultrasound findings”). Further, the successful pediatric clinical trials of vosoritide for addressing short stature in achondroplasia patients would have provided additional expectation of success. EX1005, 25 (“[i]n children with achondroplasia, once-daily subcutaneous administration of vosoritide ... resulted in a sustained increase in the annualized growth velocity”); EX1007, 108 (disclosing once daily pediatric administration of vosoritide resulting in “sustained increase in annualized growth velocity”). In addition, Yamanaka showed that foramen magnum stenosis caused by achondroplasia was rescued when CNP was overexpressed. EX1017, Abstract, 1533.

82. Specifically, a POSA would have known that the short stature of achondroplasia is caused by a mutation in the FGFR3 gene, which “permanently activates the receptor” and “puts a continuous permanent break on chondrocyte proliferation in all growth plates.” EX1007, 105. Indeed, Högler teaches that “[a]chondroplasia is caused by a heterozygous, activating mutation in fibroblast growth factor receptor-3 (FGFR3) gene” that activates its downstream MAPK signaling pathway and “inhibits chondrocyte differentiation and puts a break on growth plate function, in addition to causing serious medical complications such as foramen magnum and spinal stenosis and upper airway narrowing.” EX1007, Abstract, 105. This mutation results in a phenotype of “reduced growth of legs and arms,” leading to short stature. EX1007, 105. Högler also teaches that FGFR3

activating mutation “puts a continuous permanent break onto chondrocyte proliferation in all growth plates” with the “faster proliferating growth plates (femur, humerus) tend[ing] to be more affected than slower ones at other sites” to cause “reduced growth of legs and arms” (which manifests as short stature).

EX1007, 105. As discussed above in Section C.A.1.b, the role of FGFR3 mutations and the MAPK pathway in triggering achondroplasia and its symptoms was well known in the art. EX1035, Abstract, Figure 2; EX1007, 105; EX1017, 1526; EX1005, 26. For example, Yamanaka teaches that the “developmental mechanisms of ... foramen magnum stenosis in achondroplasia are related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes.” EX1017, 1526.

83. Högler also describes efforts to treat achondroplasia, describing:

[S]trategies involving C-type natriuretic peptide (CNP), which, via its receptor NPR-B, antagonizes the FGFR3-induced activation of the MAPK signaling pathway in growth plate chondrocytes and thus counteract[s] the effects of the FGFR3 mutation.

EX1007, 106. Högler elaborates that treatment of an achondroplasia mouse model with vosoritide led to “a significant recovery of bone growth,” describing that the authors of this study “concluded that their results provided proof of concept that BMN 111 [vosoritide] might benefit individuals with achondroplasia and hypochondroplasia.” EX1007, 108. Högler also teaches that the use of vosoritide in

children with achondroplasia given as a once daily subcutaneous injection demonstrated an “increase in growth velocity” and a “sustained increase in annualized growth velocity of 1.5 cm/year.” EX1007, 108.

84. In light of these teachings, a POSA would have had a reasonable expectation of success that vosoritide would “counteract[] the effects of constitutively active FGFR3” in the age population about 0 months to about 2 years old, leading to increased annualized growth velocity and reduction of short stature. EX1005, 34. Further, a POSA would have known that FGFR3 mutations cause slowed bone growth as early as in-utero. “[P]resentation of *de novo* cases [of achondroplasia] often occurs in the third trimester when the fetus is scanned for some other reason and short limbs and other features, [] may be evident.” EX2032, 283. Yamanaka also teaches that “CNP reverses the effects of FGFR3 signaling, which suppresses the proliferation and differentiation of growth plate chondrocytes and ultimately endochondral bone growth by inhibiting the MAPK pathway.” EX1017, 1533. An FGFR3 mutation is the cause of achondroplasia, thus the slowed bone growth in achondroplasia patients is a result of FGFR3 signaling. EX1035, Abstract. A POSA would have known that the short stature of achondroplasia patients is caused by a FGFR3 mutation in which the receptor is constitutively activated, and that vosoritide inhibits the FGFR3 signaling pathway. EX1035, Abstract, Figure 2; EX1007, 105; EX1017, 1526; EX1005, 26. Thus, the

POSA would have expected vosoritide to inhibit FGFR3 signaling in in subjects about 0 months to about 2 years old, just as it did in children 5 years old to 11 years old. EX1035, Abstract, Figure 2; EX1007, 105; EX1017, 1526; EX1005, 26.

85. Further, a POSA would have also known that NPR-B (the receptor for CNP) signaling is important for bone growth in the first 2 years of life. For example, “[acromesomelic dysplasia, type Maroteaux (AMDM)] results from loss-of-function mutations in the natriuretic peptide receptor B (NPR-B).” EX1031, 28. “In patients with AMDM, skeletal growth falls off sharply after birth, so that a skeletal disorder is strongly suspected in most affected individuals by 1 year of age.” EX1031, 27. Here, similar to above, a POSA would have understood that FGFR3 mutations cause achondroplasia in the age population about 0 months to about 2 years old, as evidenced by AMDM patients displaying the AMDM phenotype before age 2. As such, A POSA would have known that that the same CNP signaling pathway modulated in Savarirayan’s children (aged 5 to 14 years) is also active in children with achondroplasia about 0 months to about 2 years old, and is responsible for the attenuated bone growth associated with achondroplasia. This is consistent with achondroplasia diagnoses occurring in utero and/or shortly after birth. EX1012, 296; EX1010, 4.

86. The teachings of Savarirayan also would have provided a POSA with a reasonable expectation of success in treating achondroplasia in patients aged

about 0 months old to about 2 years old. Savarirayan teaches that treatment with vosoritide showed “promising preclinical findings” for achondroplasia, and describes success in clinical trials with children aged 5-11 years old:

The increased annualized growth velocity observed in the patients who received the 15.0-μg-per-kilogram dose or the 30.0-μg-per-kilogram dose for up to 42 months approximated the annualized growth velocity of average-height children of similar age. Height z scores continued to improve over 42 months, in contrast to the decline observed during the pretreatment period.

EX1005, 26, 34. In light of these teachings, a POSA would have had a reasonable expectation of success that the increased height z-scores and growth velocity exhibited by this patient population would translate to the patent population of infants, as the root cause of this short stature—FGFR3 mutation—remains the same, independent of the age of the patient population. Indeed, Savarirayan suggests that the patient population of about 0 months old to about 2 years old is a suitable population for vosoritide treatment, disclosing that “an ongoing phase 2 ... clinical trial [] of vosoritide in infants and younger children (age range, 0 to <60 months) may provide further insights into the effects of treatment[.]” EX1005, 34. In the context of this teaching, a POSA would have understood that there was a reasonable expectation of success in treating infants and younger children with vosoritide, given the existing clinical trial.

87. A POSA also would have independently expected to successfully treat

achondroplasia in subjects about 0 months to about 2 years old because the art taught that CNP can reduce or eliminate the abnormal endochondral ossification that causes foramen magnum stenosis. A POSA would have understood that the foramen magnum stenosis observed in patients with achondroplasia is likely directly caused by the constitutive activation of FGFR3 and is treatable with a CNP peptide. Indeed, Yamanaka describes that “the developmental mechanisms of midfacial hypoplasia and *foramen magnum stenosis in achondroplasia are related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes.*” EX1017, 1526 (emphasis added). A POSA would further understand that CNP treatment, and vosoritide specifically, were known to rescue the effects of constitutively active FGFR3. Specifically, Yamanaka teaches that “*CNP reverses the effects of FGFR3 signaling*, which suppresses the proliferation and differentiation of growth plate chondrocytes and ultimately endochondral bone growth *by inhibiting the MAPK pathway* in tibiae.” EX1017, 1533 (emphasis added). Yamanaka further discloses that achondroplasia mice with “elevated levels of circulatory CNP” (Fgfr3^{ach}/SAP-Nppc-Tg mice) had “significantly ameliorated” foramen magnum stenosis compared to achondroplasia mice ((Fgfr3^{ach} mice), such that the “narrowed foramen magnum of Fgfr3^{ach} [(achondroplasia mice)] was rescued in Fgfr3^{ach}/SAP-Nppc-Tg mice [(achondroplasia mice with elevated CNP)]” by the time mice were 12-weeks old. EX1017, Abstract, 1532, FIG. 4. And

Savarirayan discloses that vosoritide was shown to work through this same mechanism: “C-type natriuretic peptide–based therapy explicitly addresses the underlying pathophysiologic mechanisms of achondroplasia by ***down-regulating FGFR3 signaling through the MAPK pathway and counteracting the effects of constitutively active FGFR3.***” EX1005, 34 (emphasis added). As such, a POSA would have expected vosoritide to down-regulate FGFR3 signaling through the MAPK pathway, rescuing foramen magnum stenosis in 0–1-year-old achondroplasia patients.

88. A POSA would have known from established mouse models of achondroplasia that overexpressing CNP reduced or eliminated the narrowed foramen magnum. EX1017, 1532 (“[t]he ***narrowed foramen magnum... was rescued***” by 12 weeks old.); EX1017, FIG. 4 caption; *see also* EX1017, Abstract (“These results clearly demonstrate the ***therapeutic potential of CNP for treatment of midfacial hypoplasia and foramen magnum stenosis*** in achondroplasia.”) (emphasis added).

89. A POSA also would have generally understood that the epiphyses remain open in 0-2 yr olds with achondroplasia, making them prime candidates for successful treatment. EX1016, Abstract; EX1051, 8.

90. In sum, Savarirayan and Högler disclose each and every element of claim 1. A POSA would have had a motivation to combine the patient population

disclosed by Höglér and Savarirayan, achondroplasia patients aged 0-2 years old (Hogler) and 0 to <5 years old (Savarirayan), with the vosoritide treatment disclosed in Savarirayan to address short stature and increased risk of foramen magnum stenosis. This because the primary loss of height compared to mean or average growth for children with achondroplasia occurs in the first two years of life, and foramen magnum stenosis is a major risk to infants with achondroplasia. And a POSA would have had a reasonable expectation of success in making this combination because the underlying FGFR3 mutation in patients that causes short stature and foramen magnum stenosis is the same in the successful clinical trial described in both Savarirayan and Höglér and for the patient population of about 0 months old to about 2 years old. Further, a POSA would have understood vosoritide was already in clinical trials for treating achondroplasia in pediatric subjects aged 0 to < 60 months, as disclosed by Savarirayan and Höglér. Thus, Höglér in view of Savarirayan render claims 1 of the '106 patent obvious.

91. I understand from my review of the '106 patent's file history that BioMarin argued that "the specification provides unexpected benefits of the claimed invention," and that the claimed method's "surprising therapeutic benefits would not have been predicted from the cited art." EX1002, 936-937. I disagree that these results would have been unexpected. As explained in Section VI.C and above in Sections X.A.1.b and X.A.1.c, (i) CNPs, such as vosoritide, were known

to target the constitutively active FGFR3 signaling that caused achondroplasia and its complications, such as foramen magnum stenosis, upper airway narrowing and sleep disorders, and short stature, (ii) CNP signaling was known to be crucial for bone growth in first 2 years of life, and (iii) POSAs knew that vosoritide successfully treated achondroplasia and its complications in mouse models of achondroplasia and in children. EX1007, Abstract, 105; EX1005, Abstract, 34-35;. Therefore, a POSA would have reasonably expected vosoritide to successfully treat achondroplasia in the claimed age group, contrary to arguments of unexpected results.

92. Additionally, I understand from counsel that evidence of unexpected results must be reasonably commensurate in scope with the claims. As I discuss below in Section X.F, the claims of the '106 patent are extremely broad due to encompassing three enormous genera of subjects, CNP variants, and skeletal dysplasias. BioMarin's evidence of unexpected results involves a single skeletal dysplasia (achondroplasia), in a single type of subject (human children), administered a single CNP variant (vosoritide). EX1002, 936-937; EX1001, 39:30-50:12. Therefore, in my opinion, the evidence of unexpected results is not commensurate in scope with the '106 patent claims.

2. Högler and Savarirayan render dependent claims 2-10 and 13-14 obvious.

a. Högler and Savarirayan render claims 2-4 obvious.

93. Högler and Savarirayan teach or suggest each and every element of claims 2-4. As discussed above in Section X.A.1.a, Högler and Savarirayan teach or suggest each and every element of claim 1. Claim 2 depends from claim 1 and further recites that the composition is administered “once daily;” “once daily over a period of at least 6 months;” or “once daily over a period of at last 12 months.” EX1001, 67:40-46. Savarirayan discloses the elements of claim 2 because Savarirayan discloses that “vosoritide was administered subcutaneously at *once-daily* doses[.]” EX1005, 34. Högler also discloses this element because Högler teaches that vosoritide was administered “once daily.” EX1007, 108.

94. Claim 3 depends from claim 1 and recites that the composition is administered “via subcutaneous administration. EX1001., 67:47-48. Savarirayan discloses the elements of claim 3 because Savarirayan discloses that “vosoritide was administered *subcutaneously* at once-daily doses[.]” EX1005, 34 (emphasis added). Högler also teaches that vosoritide was administered by “subcutaneous” injection. EX1007, 108.

95. Claim 4 depends from claim 1 and recites that the composition is administered “daily, daily every other day, 3 times weekly, 2 times weekly, or once weekly.” EX1001, 67:50-52. Savarirayan discloses the elements of claim 4 because

Savarirayan discloses that “vosoritide was administered subcutaneously at *once-daily* doses[.]” EX1005, 34 (emphasis added). Högler also discloses this element because Högler teaches that vosoritide was administered “once daily.” EX1007, 108.

96. Given the successful treatment of achondroplasia in Högler’s and Savarirayan’s disclosed method, a POSA would have been motivated to also administer vosoritide subcutaneously once-daily (daily) to infants with achondroplasia. Further, the rationales for motivation and expectation of success for claim 1 discussed in Sections X.A.1.b and X.A.1.c also apply to claims 2-4. And POSA would have reasonably expected success because Savarirayan teaches that the same dosing and routes successfully treated 5-yr-old children, and a POSA would have generally known that (i) CNP and FGFR3 signaling are active in 0-2 yrs olds with achondroplasia (EX1031, 27; EX1032, 283), and (ii) epiphyses remain open in 0-2 yr olds with achondroplasia, making them prime candidates for successful treatment (EX1016, Abstract; EX1051, 8).

97. Accordingly, claims 2-4 would have been obvious.

b. Högler and Savarirayan render claims 5 and 8 obvious.

98. Högler and Savarirayan teach or suggest all the elements of claims 5 and 8. Claim 5 depends from claim 1 and further requires that “the composition is administered at a dose of 30 µg/kg.” EX1001, 67:53-54. Claim 8 depends from

claim 5 and further recites that “the dosage may be decreased to 15 µg/kg when the subject is 2 years old.”³ EX1001, 67:59-60.

99. Savarirayan teaches administering vosoritide at a dose of “30.0 µg per kilogram,” teaching the element of claim 5. EX1005, Abstract, 27, Fig. 1. Högler teaches administering vosoritide at “a dose of 15 mcg/kg,” which meets the dose of claim 8. EX1007, 108. Savarirayan, too, discloses administering vosoritide at a dose of “15.0 µg per kilogram.” EX1005, Abstract, 25, 34.

100. As discussed below in Section X.G-F, it is my opinion that claim 8 is unpatentable as indefinite due to the unclear term “about 0 month” old and for failing to further limit the claim from which it depends. However, I understand that, even though claim 8 is unpatentable for these reasons, it can also be unpatentable as obvious.

101. For the purposes of this obviousness analysis, I interpret claim 8 as decreasing the dosage from 30 µg/kg to 15 µg/kg when the subject is 2 years old. As discussed above, Savarirayan and Högler teach or suggest each and every element of claims 1 and 5. Savarirayan further teaches the limitation recited in

³ Although claim 8 recites “may,” for the purposes of obviousness it is interpreted to require that the dosage is decreased to 15 µg/kg when the subject is 2 years old.

claim 8, a dosage that “may be decreased to 15 µg/kg when the subject is 2 years old.” EX1001, 67:59-60. Savarirayan teaches that “[n]o difference in efficacy or safety could be identified between the once-daily doses of 15.0 and 30.0 µg per kilogram; thus, *our findings support the choice of the lower dose* for further evaluation in ongoing studies.” EX1005, 34. A POSA would understand this teaching as expressing a preference for a 15 µg/kg dose in subjects 5-14 years old and would have interpreted this teaching as an effective dose for subjects at the age of 2 years old. Högler also discloses administering vosoritide at “a dose of 15 mcg/kg,” satisfying claim 8. EX1007, 108.

102. Additionally, a POSA would have generally known that infants often have a higher metabolic threshold for certain drugs compared to older children, and thus infants can “require higher drug exposures than those needed in older children and adults to achieve adequate treatment effect,” followed by reduced dosing amounts as the child ages. EX1033, 11; EX1059, 738. As such, a POSA would have been motivated to use the “lower dose” selected by Savarirayan as the subject turns 2 years old and older. EX1005, 34.

103. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.A.1.b and X.A.1.c also apply to claims 5 and 8. Accordingly, claims 5 and 8 would have been obvious in view of Högler and Savarirayan.

c. Högler and Savarirayan render claims 6-7 obvious.

104. Högler and Savarirayan teach or suggest each and every element of claims 6-7. As discussed above in Section X.A.1.a, Högler and Savarirayan teach or suggest each and every element of claim 1. Claims 6 and 7 depend from claim 1. Claim 6 recites the subject age of “about 6 months to about 2 years old,” and claim 7 recites the age of “about 0 to about 6 months old.” EX1001, 67:53-58. As discussed in Section X.A.1.a, Högler discloses both the achondroplasia patient population of “the first 2 years of life” and the population of 0-1 year old, because he discloses that “the main loss of height [in achondroplasia] occurs in the first 2 years of life.” EX1007, 105. And as discussed above, Högler teaches that “[g]iven the occurrence of complications from foramen magnum stenosis very early in life, the timing of future interventions would need to be shortly after, or before, birth.” EX1007, 106. A POSA would thus understand this disclosure as suggesting teaching both of the age ranges recited in claims 6 and 7, by identifying the age range of 0 to 2 years old. This range overlap with both the ranges recited in the additional limitations of claim 6 and 7. Thus, Högler discloses the additional limitations of claims 6 and 7. Further, Savarirayan discloses an ongoing clinical trial (NCT03583697) treating achondroplasia in “infants and younger children (age range, 0 to <60 months)” with vosoritide (EX1005, 34), which also satisfies the age ranges cited above.

105. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.A.1.b and X.A.1.c also apply to claims 6-7. Accordingly, claims 6-7 would have been obvious.

d. Högler and Savarirayan render claims 9-10 obvious.

106. Högler and Savarirayan teach or suggest each and every element of claims 9-10. As discussed above in Section X.A.1.a, Högler and Savarirayan teach or suggest each and every element of claim 1. Claim 9 depends from claim 1, and recites that the skeletal dysplasia is selected from a group of over 40 types of skeletal dysplasia, including “achondroplasia.” EX1001, 67:61-68:14. Claim 10 depends from claim 9 and recites that the skeletal dysplasia is achondroplasia. EX1001, 68:15-16.

107. As I discuss above in claim 1, both Högler and Savarirayan teach treating achondroplasia. *See* Section X.A.1; EX1007, 106; EX1005, Abstract, 25, 35.

108. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.A.1.b and X.A.1.c also apply to claims 9-10. Accordingly, claims 9-10 would have been obvious.

e. Högler and Savarirayan render claims 13-14 obvious.

109. Högler and Savarirayan teach or suggest each and every element of claims 13-14. As discussed above in Section X.A.1.a, Högler and Savarirayan

teach or suggest each and every element of claim 1. Claim 13 depends from claim 1, limiting the CNP variant to a group that contains SEQ ID NO: 1 (vosoritide). EX1001, 68:24-66. Claim 14 depends from claim 13, limiting the CNP variant to a group of two CNP variants, one of which is SEQ ID NO: 1 (vosoritide). EX1001, 60:1-10. As discussed above for claim 1, both Högler and Savarirayan teach administering vosoritide, which was known in the art as Pro-Gly-CNP37 and is the CNP variant of SEQ ID NO: 1 recited in claims 13 and 14. EX1007, 108; EX1005, 35; *See* Section X.A.1.

110. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.A.1.b and X.A.1.c also apply to claims 13-14. Accordingly, claims 13-14 would have been obvious.

B. Ground II: Claims 11-12 of the '106 patent would have been obvious over Högler, Savarirayan, and Bullens.

111. Högler, Savarirayan, and Bullens teach or suggest each and every element of claims 11-12. Claim 11 depends from claim 1, and claim 12 depends from claim 11. As discussed above in Section X.A.1.a, Högler and Savarirayan teach or suggest each and every element of claim 1. Claim 11 recites that the composition “further comprises one or more pharmaceutical excipients.” EX1001, 68:17-19. And claim 12 specifies that the composition comprises “citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.” EX1001, 68:20-23. Bullens discloses the

following composition:

Pro-Gly-CNP37 peptide [vosoritide] was formulated into a sterile, preservative-free composition comprising either 2.0 mg/ml or 10 mg/ml of the CNP peptide in combination with 0.28 mg/ml *citric acid monohydrate*, 1.08 mg/ml *sodium citrate dihydrate*, 58.01 mg/ml *trehalose dihydrate*, 15 mg/ml *D-mannitol*, 0.73 mg/ml *L-methionine* and 0.05 mg/ml *polysorbate 80*, pH 5.5.

EX1008, 25:62-26:1 (emphasis added); see also, EX1008, 19:21-37.

112. A POSA would have generally known from the art that each of the additional elements of the composition recited in Bullens are “pharmaceutical excipients” as recited in claim 11. Indeed, Bullens discloses that “[t]he use of excipients, diluents and carriers in the formulation of pharmaceutical compositions is known in the art.” EX1008, 19:32-34. As such, Bullens discloses the additional elements of claim 11 and 12, and the combination of Högler, Savarirayan, and Bullens teach or suggest each and every element of claims 11 and 12.

113. The rationale for combining Savarirayan and Högler is discussed above in Ground I. A POSA would have been further motivated to combine Bullens with Savarirayan and Högler because Bullens expressly teaches compositions for formulating vosoritide. A POSA following Savarirayan and Högler would have naturally looked to Bullens for guidance on vosoritide compositions, because Bullens teaches compositions for vosoritide. A POSA would further have been motivated to use the composition described by Bullens

when treating achondroplasia patients aged 0-2 years old considering its favorable efficacy. Specifically, Bullens teaches that daily administration of the composition described above at a dose of 15 µg/kg resulted in “an increase in annualized growth velocity of 50% above baseline.” EX1008, 27:33-36.

114. A POSA combining Savarirayan, Högler, and Bullens would have reasonably expected success because Bullens explains that treatment of children aged 5-14 years old with achondroplasia with this composition resulted in “a statistically significant increase ... in standing height growth velocity” when treated with “15 µg/kg [per] day of Pro-Gly-CNP-37” as well as “no significant adverse effect on overall body proportionality.” EX1008, 29:17-23.

115. The additional rationales for motivation and expectation of success for claim 1 discussed above in Section X.A.1.b and X.A.1.c also apply to claims 11-12. Accordingly, claims 11-12 would have been obvious.

116. As discussed above in Section X.A.1.c, the publicly available objective indicia of nonobviousness do not support patentability.

C. Ground III: Claims 1-10 and 13-14 of the '106 patent would have been obvious over Pauli and Savarirayan.

117. Claims 1-10 and 13-14 of the '106 patent would have been obvious over Pauli and Savarirayan. As I discuss below, Pauli and Savarirayan disclose each and every element of claims 1-10 and 13-14. And, a POSA would have been motivated to modify Savarirayan in view of Pauli to arrive at the claimed methods,

with a reasonable expectation of success. Thus, the combination of Pauli and Savarirayan renders claims 1-10 and 13-14 of the '106 patent obvious.

1. Pauli and Savarirayan render claim 1 obvious.

a. Pauli and Savarirayan teach or suggest each and every element of independent claim 1.

118. Again, claim 1 has four elements:

- [1.1] “A method of treating skeletal dysplasia...”
- [1.2] “in a subject about 0 month to about 2 years old...”
- [1.3] “comprising administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject...”
- [1.4] “wherein the CNP variant is selected from the group consisting of SEQ ID NO: 1 (Pro-Gly-CNP37)...” [i.e., vosoritide].

EX1001, 63:36-67:40.

i. A method of treating skeletal dysplasia...

119. As discussed in Section X.A.1.a, Savarirayan teaches claim element [1.1], because it discloses treatment of a skeletal dysplasia (achondroplasia). EX1005, Abstract, 25, 34. Savarirayan discloses “once-daily subcutaneous administration of vosoritide” (one of the claimed CNP variants as explained below) to “children (5 to 14 years of age) with achondroplasia” treats achondroplasia through “a sustained increase in the annualized growth velocity” that

“approximated the annualized growth velocity of average-height children of similar age.” EX1005, Abstract, 25, 34. Savarirayan goes on to explain that the treatment resulted in “[p]roportional growth between the upper-body and lower-body segments [], with no clinically relevant change in the body-segment ratio.” EX1005, 34. Pauli also teaches element [1.1]. Pauli provides a “comprehensive clinical review” of achondroplasia, and teaches a method of treating achondroplasia. EX1006, Title, Abstract. POSAs understood that achondroplasia is a type of skeletal dysplasia. For example, Pauli expressly discloses that “[a]chondroplasia is the most common of the *skeletal dysplasias* that result in marked short stature (dwarfism).” EX1006, Abstract; *see also*, EX1005, 26. The ’106 patent claims 13 and 14 confirm this understanding by reciting achondroplasia as a type of skeletal dysplasia. EX1001, claims 13-14.

ii. in a subject about 0 month to about 2 years old...

120. A POSA would have understood that Pauli suggests treating “a subject about 0 month to about 2 years old...” (claim element [1.2]) because Pauli discloses deaths of infant with achondroplasia “*between 3 and 11 months of age*,” due to “craniocervical junction constriction and restrictive pulmonary disease,” and suggests that “if preventive assessments are to be effective they must be completed early in infancy.” EX1006, 9 (emphasis added). Pauli goes on to discuss the serious complications of this craniocervical junction constriction, noting that that

the “foramen magnum is often abnormal in shape” in infants with achondroplasia, potentially leading to “apneic deaths aris[ing] from compression of the vertebral arteries at or near the craniocervical junction.” EX1006, 9. Pauli discloses some reports that “*the risk for death in the first year of life* may be as high as 7.5%. While that may be ... an overestimate, nonetheless, without special assessment and, when needed, surgical intervention, that risk is likely at least 2-3%.” EX1006, 9 (emphasis added). Further, Pauli discloses that “an expanded phase 2 trial” of treating achondroplasia “in *infants* and young children” with CNP variant vosoritide was ongoing. EX1006, 41. A POSA would have understood this disclosure to identify an achondroplasia patient population between the age of 0 months old and 1 year old. I understand from counsel that, when a prior art range (0 to 1 year old) is subsumed within a claimed range (here, about 0 month to about 2 years old), the prior art range is considered to disclose the given element. As such, Pauli discloses claim element [1.2].

121. Savarirayan also suggests element [1.2]. Savarirayan discloses an on-going clinical trial (NCT03583697) of treating achondroplasia in “*infants* and younger children (age range, *0 to <60 months*)” with vosoritide. EX1005, 34. As discussed above, Savarirayan’s disclosure of treating “infants” (<1 year old) falls within the claimed age range, and Savarirayan’s disclosure of treating “0 to <60 months” old children overlaps with the claimed age range.

- iii. administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject...**

122. Pauli and Savarirayan disclose claim element [1.3]. Pauli reports that CNP analogs are the “most advanced” of therapeutic options for achondroplasia. EX1006, 41. Pauli further states that treating with vosoritide “reversed the achondroplasia phenotype in the mouse model of this disorder and appeared to enhance bone growth in normal cynomolgus monkeys, including increases in growth plate thickness and increase in lumbar vertebral foraminal size.” EX1006, 41. Pauli also discloses administering vosoritide in “[h]uman trials.” EX1006, 41.

123. As discussed in Section X.A.1.a, Savarirayan also discloses claim element [1.3]. First, Savarirayan discloses the results of the same clinical trial referenced in Pauli. In particular, Savarirayan reports the effects of administering “15.0 µg per kilogram” or “30.0 µg per kilogram” doses of “vosoritide in children (5 to 14 years of age) with achondroplasia.” EX1005, Abstract. Savarirayan explains that “vosoritide is a biologic analogue of C-type natriuretic peptide.” *Id.*

124. A POSA would have understood that Savarirayan discloses an “amount effective to treat skeletal dysplasia” because Savarirayan discloses that vosoritide treatment resulted in “a sustained increase in the annualized growth velocity for up to 42 months.” EX1005, Abstract, 25, 34. As discussed above in Section IX.B, a POSA would have construed “amount effective to treat” as a

dosage sufficient to produce a desired result in a health condition, pathology, or disease of a subject or for a diagnostic purpose and comprising a subjective or objective improvement in the recipient of the dosage for prophylactic or therapeutic or diagnostic treatment. EX1001, 4:19-26, 29:4-6. Savarirayan discloses “a sustained increase in the annualized growth velocity” that “approximated the annualized growth velocity of average-height children of similar age” such that there was “[p]roportional growth between the upper-body and lower-body segments [], with no clinically relevant change in the body-segment ratio,” and thus teaches an amount effective to treat, according to the ’106 patent’s criteria for this term. EX1005, Abstract, 25, 34.

iv. wherein the CNP variant is selected from the group consisting of SEQ ID NO: 1 (Pro-Gly-CNP37)...

125. Pauli and Savarirayan teach claim element [1.4] because both Pauli and Savarirayan teach administering *vosoritide* (BMN-111) to children with achondroplasia. EX1006, 41; EX1005, Abstract . As discussed above, before July 9, 2021, POSAs generally knew that vosoritide consisted of the “37 C-terminal amino acids of human CNP plus the amino acids glycine and proline added to the N-terminal portion of the peptide,” and thus was also known in the art as “Pro-Gly-CNP37.” EX1026, 460; EX1053, Abstract, 197; EX1063, 1108, Fig. S2. A POSA would have understood that vosoritide as taught in Pauli and Savarirayan has the

same amino acid sequence as Pro-Gly-CNP-37 (SEQ ID NO: 1), as recited in claim 1.

b. A POSA would have been motivated to treat achondroplasia in infants as taught in Pauli and Savarirayan using the methods taught in Savarirayan.

126. As discussed in Section VI.D, a POSA would have known that foramen magnum stenosis is a co-morbidity of achondroplasia. For example, a POSA would have generally known that “achondroplasia is ... characterized by ... foramen magnum stenosis”; “Craniofacial features of achondroplasia include ... foramen magnum stenosis[.]” EX1017, Abstract, 1526. The ’106 patent defines “treatment” as “prophylactic treatment or therapeutic treatment or therapeutic treatment.” EX1001, 17:45-50. The ’106 patent further defines therapeutic treatment, in part, as “treatment administered to a subject who exhibits signs or symptoms of [a] pathology for the purpose of diminishing or eliminating those signs or symptoms.” EX1001, 17:58-61. Thus, according to the ’106 patent, diminishing or eliminating foramen magnum stenosis would be consistent with “treating” achondroplasia.

127. A POSA would have been motivated to treat the patient population 0-1 years old with vosoritide to treat achondroplasia. Pauli explains that “nearly all instances of achondroplasia are caused by FGFR3 mutations,” which cause activation of FGFR3. EX1006, 3. Pauli explains that FGFR3 is a “negative

regulator” of chondrocytic bone growth, and that “[v]irtually all of the clinical features and medical problems of achondroplasia arise because of the consequent abnormalities of cartilaginous bone growth – either directly, or because of disproportionate growth of cartilaginous bone compared with nearby structures derived from other tissues.” EX1006, 3. In addition, Pauli teaches:

It was already known that infants with achondroplasia have ... a small foramen magnum ... Furthermore, the foramen magnum is often abnormal in shape, frequently being “key holed” in appearance. This probably effectively diminishes even further the space actually available ... Therefore, we postulated that those deaths [of infants with achondroplasia] arose from either acute or chronic compression of vasculature at the craniocervical junction resulting in hypoxic damage to the central respiratory control centers in the medulla. In turn, such hypoxic damage can result in diminished central respiratory control, and, in the most severe instances, irreversible apnea.

EX1006, 9. Thus a POSA would understand that foramen magnum stenosis is caused by the activation mutation in FGFR3.

128. In short, a POSA would have understood that the foramen magnum stenosis and irregular shape (“small foramen magnum” and “key holing” discussed in Pauli) can cause severe complications from achondroplasia, including “irreversible apnea.” EX1006, 9. A POSA further would have understood that the majority of these extreme/irreversible apneic events occur within the first year of life, as taught by Pauli: “the risk for death in the first year of life ... is at least 2-

3%.” EX1006, 10. Indeed, Pauli estimates that the risk for death in the first year of life of achondroplasia patients “is likely ... 2-3%.” EX1006, 10. Pauli’s teachings are consistent with the general understanding in the art. For example, Yamanaka advises that “early administration [of CNP] may be an important determinant of clinical effectiveness[,]” strengthening the position that a POSA would want to treat a patient with achondroplasia patient early in life. A POSA thus would have been motivated to treat a patient with achondroplasia in the first year of life to reduce or eliminate foramen magnum stenosis, thereby lowering the risk of death in the first year of life due to complications such as cervicomedullary cord compression, sleep apnea, and/or other respiratory complications.

129. Further, Yamanaka discloses that “the foramen magnum stenosis observed in FGFR3^{ach} mice was significantly ameliorated in Fgfr3^{ach}/SAP-Nppc-Tg mice due to enhanced endochondral bone growth of the anterior intraoccipital synchondrosis. These results clearly demonstrate the therapeutic potential of **CNP for treatment** of midfacial hypoplasia and **foramen magnum stenosis in achondroplasia.**” EX1017, Abstract (emphasis added). Here, a POSA would understand that FGFR3^{ach} mice are an achondroplasia mouse model, which display “dwarfism and short limb bones.” EX1017, 1528. This mouse model was also shown to exhibit a “significantly smaller” foramen magnum compared to wild-type mice. EX1017, 1532. However, by overexpressing CNP in these achondroplasia

mice models, “[t]he narrowed foramen magnum... was rescued[.]” EX1017, 1532.

Further, a POSA would understand that the prevention of foramen magnum stenosis, as shown in Yamanaka’s mouse models, would also be a beneficial treatment for children with achondroplasia under the age of 2 years old, because of the higher rate of foramen magnum stenosis and its often fatal complications in this age group (vs patient population).

130. In terms of which CNP treatment to use, a POSA would have known that vosoritide had already demonstrated success in treating achondroplasia in children. Pauli teaches that CNP is “the most advanced ... therapeutic option” for the treatment of achondroplasia, teaching that “BMN-111 (i.e., vosoritide) reversed the achondroplasia phenotype in the mouse model of this disorder.” EX1006, 41. Pauli also teaches that “CNP in many ways acts as a counterbalance to the effects of FGFR3 on the growth plate” and that “increasing CNP activity could counteract the excess negative signal of FGFR3 mutations,” as shown by vosoritide that “reversed the achondroplasia phenotype in the mouse model.” EX1006, 41. Pauli also describes the “greater stability” of vosoritide compared to CNP22, and notes that human trials for people with achondroplasia who are “infants and young children” are ongoing. EX1006, 4. As such, a POSA would have been motivated to treat achondroplasia and prevent foramen magnum stenosis in infants 0-1 years old, as taught by Pauli and Savarirayan, with the method comprising vosoritide, as

taught by Savarirayan, to reduce the co-morbidity of foramen magnum stenosis and mitigate the incidence of potentially fatal complications.

c. A POSA would have had a reasonable expectation of success in treating achondroplasia in infants as taught in Pauli and Savarirayan with vosoritide as taught in Savarirayan.

131. When treating with children 0-1 year of age with achondroplasia with vosoritide, a POSA would have had a reasonable expectation of success for several reasons which I discuss in detail below: (1) POSAs knew that the underlying pathophysiologic mechanism that causes achondroplasia (FGFR3 activation) is addressed by treatment with vosoritide, and (2) treatment with CNP in young mice and human children successfully treated achondroplasia..

132. *First*, a POSA would have had a reasonable expectation of success in treating achondroplasia with vosoritide because the underlying mutation that causes achondroplasia, and abnormal bone growth including foramen magnum stenosis, was shown to be counteracted by vosoritide. Pauli teaches that “nearly all instances of achondroplasia are caused by FGFR3 mutations.” EX1006, 3. Specifically, Pauli teaches that “[t]he mutation that results in achondroplasia is a gain of function mutation [that] most likely results in ... activation of FGFR3 []. This, then, is constitutive activation of an inhibitory signal.” EX1006, 3. Pauli also explains that FGFR3 is a “negative regulator” of chondrocytic bone growth, and that “[v]irtually all of the clinical features and medical problems of achondroplasia

arise because of the consequent abnormalities of cartilaginous bone growth – either directly, or because of disproportionate growth of cartilaginous bone compared with nearby structures derived from other tissues.” EX1006, 3. A POSA would understand, then, that the foramen magnum stenosis observed in patients with achondroplasia is likely directly caused by the constitutive activation of FGFR3, as the foramen magnum is dependent on endochondral ossification whereas the bones of the cranial vault grow by intramembranous ossification. Indeed, Yamanaka describes that “the developmental mechanisms of midfacial hypoplasia and *foramen magnum stenosis in achondroplasia [is] related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes.*” EX1017, 1526 (emphasis added).

133. A POSA would further understand that CNP treatment, and vosoritide specifically, were known to rescue the effects of constitutively active FGFR3. Specifically, Yamanaka teaches that “*CNP reverses the effects of FGFR3 signaling*, which suppresses the proliferation and differentiation of growth plate chondrocytes and ultimately endochondral bone growth by *inhibiting the MAPK pathway* in tibiae.” EX1017, 1533 (emphasis added). And Savarirayan discloses that vosoritide was shown to work through this same mechanism: “C-type natriuretic peptide–based therapy explicitly addresses the underlying pathophysiologic mechanisms of achondroplasia by *down-regulating FGFR3*

signaling through the MAPK pathway and counteracting the effects of constitutively active FGFR3.” EX1005, 34 (emphasis added). And Pauli teaches that “CNP in many ways acts as a *counterbalance to the effects of FGFR3* on the growth plate” and that “increasing CNP activity could *counteract the excess negative signal of FGFR3 mutations.*” EX1006, 41. As such, a POSA would have expected vosoritide to down-regulate FGFR3 signaling through the MAPK pathway, rescuing foramen magnum stenosis in 0–1-year-old patients with achondroplasia.

134. *Second*, a POSA would have known from established mouse models of achondroplasia that overexpressing CNP reduced or eliminated the stenosis of the foramen magnum. EX1017, 1532 (“[t]he *narrowed foramen magnum [] was rescued*” by 12 weeks old.); EX1017, FIG. 4; *see also* EX1017, Abstract (“These results clearly demonstrate the *therapeutic potential of CNP for treatment of midfacial hypoplasia and foramen magnum stenosis* in achondroplasia.” (emphasis added)). Yamanaka teaches that achondroplasia mice with “elevated levels of circulatory CNP” (*Fgfr3^{ach}/SAP-Nppc-Tg* mice) had “significantly ameliorated” foramen magnum stenosis compared to the achondroplasia mice ((*Fgfr3^{ach}* mice), such that the “narrowed foramen magnum of *Fgfr3^{ach}* [(achondroplasia mice)] was rescued in *Fgfr3^{ach}/SAP-Nppc-Tg* mice [(achondroplasia mice with elevated CNP)]” by the time mice were 12-weeks old.

EX1017, Abstract, 1532, FIG. 4; Pauli also teaches that that CNP is “the most advanced ... therapeutic option” for the treatment of achondroplasia, and that “BMN-111 (i.e., vosoritide) reversed the achondroplasia phenotype in the mouse model of this disorder.” EX1006, 41. A POSA would have reasonably expected success in treating achondroplasia this this “advanced” therapeutic option, as taught by Pauli.

135. In sum, a POSA would have known from Pauli that infants aged 0-1 year old with achondroplasia have an increased risk of foramen magnum stenosis and death. A POSA would have understood from Pauli that the CNP peptide vosoritide is an effective treatment for achondroplasia and for improving bone growth, and would have understood from Yamanaka that CNP treatment can reduce or eliminate foramen magnum stenosis in achondroplasia mouse models. And a POSA would have had a reasonable expectation of success in treating foramen magnum stenosis in infants with vosoritide because of the successful clinical results of vosoritide discussed by Pauli and Savarirayan, the mouse models of Yamanaka, and the knowledge that vosoritide treatment counteracts the effects of constitutively active FGFR3. As such, Pauli, in view of Savarirayan, renders claim 1 of the '106 patent obvious.

136. As discussed above in Section X.A.1.c, the publicly available objective indicia of nonobviousness do not support patentability.

2. Pauli and Savarirayan render dependent claims 2-10 and 13-14 obvious.

a. Pauli and Savarirayan render claims 2-4 obvious.

137. Pauli and Savarirayan teach or suggest each and every element of claims 2-4. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or suggest each and every element of claim 1. Claim 2 depends from claim 1 and further recites that the composition is administered “once daily;” “once daily over a period of at least 6 months;” or “once daily over a period of at last 12 months.” EX1001, 67:40-46. Savarirayan discloses the elements of claim 2 because Savarirayan discloses that “vosoritide was administered subcutaneously at *once-daily* doses[.]” EX1005, 34 (emphasis added).

138. Claim 3 depends from claim 1 and recites that the composition is administered “via subcutaneous administration.” EX1001, 67:47-48. Savarirayan discloses the elements of claim 3 because Savarirayan discloses that “vosoritide was administered *subcutaneously* at once-daily doses[.]” EX1005, 34 (emphasis added).

139. Claim 4 depends from claim 1 and recites that the composition is administered “daily, every other day, 3 times weekly, 2 times weekly, or once weekly.” EX1001, 67:48-51. Savarirayan discloses the elements of claim 4 because Savarirayan discloses that “vosoritide was administered subcutaneously at *once-daily* doses[.]” EX1005, 34 (emphasis added).

140. Given the successful treatment of achondroplasia in Savarirayan's disclosed method, a POSA would have been motivated to also administer vosoritide subcutaneously once-daily (daily) to infants with achondroplasia. Further, the rationales for motivation and expectation of success for claim 1 discussed in Sections X.C.1.b and X.C.1.c also apply to claims 2-4. And POSA would have reasonably expected success because Savarirayan teaches that the same dosing and routes successfully treated 5-yr-old children, and a POSA would have generally known that (i) CNP and FGFR3 signaling are active in 0-2 yrs olds with achondroplasia (EX1031, 27; EX1032, 283), and (ii) epiphyses remain open in 0-2 yr olds with achondroplasia, making them prime candidates for successful treatment (EX1016, Abstract; EX1051, 8).

141. Accordingly, claims 2-4 would have been obvious.

b. Pauli and Savarirayan render claims 5 and 8 obvious.

142. Pauli and Savarirayan teach or suggest all the elements of claims 5 and 8. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or suggest each and every element of claim 1. Claim 5 depends from claim 1 and further requires that "the composition is administered at a dose of 30 µg/kg." EX1001, 67:53-54. Claim 8 depends from claim 5 and further recites that "the

dosage may be decreased to 15 µg/kg when the subject is 2 years old.”⁴ EX1001, 67:59-60.

143. Savarirayan teaches administering vosoritide at a dose of “30.0 µg per kilogram,” teaching the element of claim 5. EX1005, Abstract, 27, Fig. 1.

Savarirayan also discloses administering vosoritide at a dose of “15.0 µg per kilogram,” teaching the dose of claim 8. EX1005, Abstract, 25, 34. Thus a POSA would be motivated to administer these doses of vosoritide to infants or 2-year olds.

144. As discussed below in Section X.G-F, it is my opinion that claim 8 is unpatentable as indefinite due to the unclear term “about 0 month” old and for failing to further limit the claim from which it depends. However, I understand that, even though claim 8 is unpatentable for these reasons, it can also be unpatentable as obvious.

145. For the purposes of this obviousness analysis, I interpret claim 8 as decreasing the dosage from 30 µg/kg to 15 µg/kg when the subject is 2 years old. As discussed above, Pauli and Savarirayan teach or suggest each and every

⁴ Although claim 8 recites “may,” for the purposes of obviousness it is interpreted to require that the dosage is decreased to 15 µg/kg when the subject is 2 years old.

element of claims 1 and 5. Savarirayan further teaches that “[n]o difference in efficacy or safety could be identified between the once-daily doses of 15.0 and 30.0 µg per kilogram; thus, *our findings support the choice of the lower dose* for further evaluation in ongoing studies.” EX1005, 34. A POSA would have understood this teaching as expressing a preference for a 15 µg/kg dose in subjects 5-14 years old and would have interpreted this teaching as an effective dose for subjects at the age of 2 years old. EX1005, 34.

146. Additionally, a POSA would have generally known that infants often have a higher metabolic threshold for certain drugs compared to older children, and thus infants can “require higher drug exposures than those needed in older children and adults to achieve adequate treatment effect,” followed by reduced dosing amounts as the child ages. EX1033, 11; EX1059, 738. As such, a POSA would have been motivated to use the “lower dose” selected by Savarirayan as the subject turns 2 years old and older. EX1005, 34.

147. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.C.1.b and X.C.1.c also apply to claims 5 and 8. Accordingly, claims 5 and 8 would have been obvious.

c. Pauli and Savarirayan render claims 6-7 obvious.

148. Pauli and Savarirayan teach or suggest each and every element of claims 6-7. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or

suggest each and every element of claim 1. Claims 6 and 7 depend from claim 1.

Claim 6 recites the subject age of “about 6 months to about 2 years old,” and claim 7 recites the age of “about 0 to about 6 months old.” EX1001, 67:53-58.

149. As discussed in Section X.C.1.a, Pauli teaches or suggests treating patients with achondroplasia in “the first year of life[,]” which a POSA would understand is the age range of 0 months to 2 year old (i.e., infants). This range encompasses the age range claimed in claim 7 and overlaps with the age range claimed in claim 6. Thus, Pauli discloses the additional limitations of claims 6 and 7. Savarirayan discloses an ongoing clinical trial (NCT03583697) treating achondroplasia in “*infants* and younger children (age range, 0 to <60 months)” with vosoritide. EX1005, 34. Thus, Savarirayan’s age range of infant also encompasses the range of claim 7, and Savarirayan’s age range of 0 to <60 months overlaps with the age range of claim 6.

150. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.C.1.b and X.C.1.c also apply to claims 6-7. Accordingly, claims 6-7 would have been obvious.

d. Pauli and Savarirayan render claims 9-10 obvious.

151. Pauli and Savarirayan teach or suggest each and every element of claims 9-10. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or suggest each and every element of claim 1. Claim 9 depends from claim 1, and

recites that the skeletal dysplasia is selected from the group of

“...achondroplasia...[.]” EX1001, 67:61-68:14. Claim 10 depends from claim 9 and recites that the skeletal dysplasia is achondroplasia. EX1001, 68:15-16.

152. As discussed above, both Pauli and Savarirayan expressly teach methods of treating achondroplasia. EX1005, Abstract, 25, 34; EX1006, Abstract; Section X.C.1. Savarirayan describes “In children with *achondroplasia*, once-daily subcutaneous administration of vosoritide ... resulted in a sustained increase in the annualized growth velocity for up to 42 months.” EX1005, 1 (emphasis added). Pauli provides a “comprehensive clinical review” of achondroplasia, and teaches a method of treating achondroplasia. EX1006, Title, Abstract Thus, Pauli and Savarirayan disclose the additional limitations of claims 9 and 10.

153. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.C.1.b and X.C.1.c also apply to claims 9-10. Accordingly, claims 9-10 would have been obvious.

e. Pauli and Savarirayan render claims 13-14 obvious.

154. Pauli and Savarirayan teach or suggest each and every element of claims 13-14. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or suggest each and every element of claim 1. Claim 13 depends from claim 1, limiting the CNP variant to a group of 12 different CNP variants, including SEQ ID NO: 1 (vosoritide). EX1001, 68:24-66. Claim 14 depends from claim 13,

further limiting the CNP variant to a group of vosoritide and one other peptide, CNP-38. EX1001, 60:1-10.

155. As discussed above in Section VI.C, both Pauli and Savarirayan teach administering vosoritide, which was known in the art as Pro-Gly-CNP37 and is the CNP variant of SEQ ID NO: 1 recited in claims 13 and 14. EX1006, 41; EX1005, 35; *See* Section X.C.1.

156. The rationales for motivation and expectation of success for claim 1 discussed in Sections X.C.1.b and X.C.1.c also apply to claims 13-14. Accordingly, claims 13-14 would have been obvious.

D. Ground IV: Claims 11-12 of the '106 patent would have been obvious over Pauli, Savarirayan, and Bullens.

157. Pauli, Savarirayan, and Bullens teach or suggest each and every element of claims 11-12. Claim 11 depends from claim 1, and claim 12 depends from claim 11. As discussed above in Section X.C.1.a, Pauli and Savarirayan teach or suggest each and every element of claim 1. Claim 11 recites that the composition “further comprises one or more pharmaceutical excipients.” EX1001, 68:17-19. And claim 12 specifies that the composition comprises “citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.” EX1001, 68:20-23. Bullens discloses the following composition:

Pro-Gly-CNP37 peptide [vosoritide] was formulated into a sterile,

preservative-free composition comprising either 2.0 mg/ml or 10 mg/ml of the CNP peptide in combination with 0.28 mg/ml *citric acid monohydrate*, 1.08 mg/ml *sodium citrate dihydrate*, 58.01 mg/ml *trehalose dihydrate*, 15 mg/ml *D-mannitol*, 0.73 mg/ml *L-methionine* and 0.05 mg/ml *polysorbate 80*, pH 5.5.

EX1008, 25:62-26:1 (emphasis added); see also, EX1008, 19:21-37.

158. A POSA would understand that each of the additional elements of the composition recited in Bullens are “excipients” as recited in claim 11. Indeed, Bullens discloses that “[t]he use of excipients, diluents and carriers in the formulation of pharmaceutical compositions is known in the art.” EX1008, 19:32-34. As such, Bullens discloses the additional elements of claim 11 and 12, and the combination of Pauli, Savarirayan, and Bullens teach or suggest each and every element of claims 11 and 12.

159. The rationale for combining Pauli and Savarirayan is discussed above in Ground III. A POSA following Pauli and Savarirayan would have naturally looked to Bullens for guidance on vosoritide compositions, because Bullens teaches compositions for vosoritide. A POSA would further have been motivated to use the composition described by Bullens when treating achondroplasia patients aged 0-2 years old considering its favorable efficacy. For example, Bullens teaches that daily administration of the composition described above at a dose of 15 µg/kg resulted in “an increase in annualized growth velocity of 50% above baseline.”

EX1008, 27:33-36.

160. A POSA combining Savarirayan, Pauli, and Bullens would have reasonably expected success because Bullens explains that treatment of achondroplasia patients aged 5-14 years old with this composition resulted in “a statistically significant increase ... in standing height growth velocity” when treated with “15 µg/kg [per] day of Pro-Gly-CNP-37” as well as “no significant adverse effect on overall body proportionality.” EX1008, 29:17-23.

161. The additional rationales for motivation and expectation of success for claim 1 discussed above in Sections X.C.1.b and X.C.1.c also apply to claims 11-12.

162. Accordingly, Savarirayan, Pauli, and Bullens render claims 11-12 obvious.

E. Ground V: Claims 1-7 and 9-14 of the '106 patent are anticipated by Wendt-242.

163. I understand from counsel that, if each and every claim element of a given claim is disclosed in a single prior art document, arranged as claimed, then this claim is unpatentable as anticipated. I further understand that for anticipation, the reference must be enabling for the anticipatory subject matter. I also understand that prior art patents as anticipatory references are presumed enabled.

164. Here, U.S. Patent No. 8,198,242 (“Wendt-242”) discloses each and every one of the limitations of claims 1-7 and 9-14 of the '106 patent, arranged as claimed. Thus, Wendt-242 anticipates claims 1-7 and 9-14. There are numerous

embodiments of Wendt-242 that anticipate the challenged claims, including, but not limited to, Examples 19 and 13, which are discussed in more detail below.

165. Wendt-242 Example 13 is entitled “Efficacy in Mouse Model of Mild Achondroplasia.” EX1023, 127:42. Wendt-242 Example 13 discloses treating mice that have achondroplasia with CNP variants, including the CNP variant CNP-37. Wendt-242 Example 19 is titled “Clinical Evaluation of CNP Variants.” EX1023, 139:4. Wendt-242 Example 19 discloses treating achondroplasia patients with “CNP22 or variants thereof” variants disclosed in Wendt-242. EX1023, 139:11-14. Both the mice in Example 13 and the humans in Example 19 are mammals. As shown in the table below, each example independently discloses every element of claim 1, arranged as claimed.

Claim Element	Wendt-242 Example 13	Wendt-242 Example 19
[1.1], “a method of treating skeletal dysplasia”	“[t]he efficacy of CNP variants in enhancing growth and correcting achondroplasia was tested in a mouse model of mild achondroplasia ” EX1023, 126:20-41, Table 13 (emphasis added).	“compositions comprising CNP22 or variants thereof in therapeutic methods” EX1023, 139:9-11 “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone. ” EX1023, 139:10-15 (emphasis added). “A specific example of a potentially CNP-responsive, bone-related disorder is achondroplasia. ” EX1023,

Claim Element	Wendt-242 Example 13	Wendt-242 Example 19
		140:1-5 (emphasis added).
[1.2], “in a subject about 0 month to about 2 years old”	mice “ <i>[a]t 3 weeks of age</i> ” received “once daily subcutaneous (s.c.) administration of designated test article (vehicle or 200 nmol/kg CNP variant) for 5 weeks.” EX1023, 126:41-51 (emphasis added).	“[t]he ideal range of achondroplasia patients will be from <i>infant (<1 year of age) to pre-adolescent (<13 years of age.</i> ” EX1023, 140:6-8 (emphasis added).
[1.3], “comprising administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject”	<p>Table 13 of Wendt-242 shows that achondroplasia mice “statistically increased body length (FIG. 51), tail length (FIG. 52), distal bone (ulna and tibia) lengths (FIGS. 53A and B), and proximal bone (humerus and femur) lengths (FIGS. 54A and B).” EX1023, 127:17-21. The femus, tibia, humerus, and ulna were known to be long bones.</p> <p>Table 13 from Wendt-242, which is copied below, “summarizes the percentage change in tail length, body (naso-anal) length, and bone (femur, tibia, humerus and ulna) lengths in [achondroplasia] mice injected s.c. once daily with 200 nmol/kg of [] CNP37 ... for 5 weeks, relative to a value of 100% for [achondroplasia] mice</p>	<p>“The initial dose for the trials will vary from about 0.001 to about 1.0 mg/kg/ week.” EX1023, 139:20-21.</p> <p>Wendt-242 also teaches that “CNP22 or variants thereof will be used in <i>the treatment of disorders responsive to CNP.</i>” EX1023, 139:10-15 (emphasis added).</p> <p>And further, “In the event that the initial dose in this range does not produce a significant direct clinical benefit, the dose should be increased within this range or beyond this range as necessary.” EX1023, 139:20-27 (emphasis added).</p>

Claim Element	Wendt-242 Example 13	Wendt-242 Example 19																												
	<p>treated with vehicle only.” EX1023, 127:28-34</p> <table><tr><th colspan="7">TABLE 13</th></tr><tr><th></th><th>Tail</th><th>Naso- Anal</th><th>Femur</th><th>Tibia</th><th>Humerus</th><th>Ulna</th></tr><tr><td>CNP37</td><td>115%**</td><td>109%**</td><td>112%**</td><td>107%**</td><td>105%*</td><td>106%**</td></tr><tr><td>CNP27- PEO24</td><td>100%</td><td>99%</td><td>100%</td><td>102%</td><td>100%</td><td>101%</td></tr></table> <p>**p < 0.01, *p < 0.05</p> <p>EX1023, 127:15-35, Table 13.</p> <p>Mice received “once daily <i>subcutaneous (s.c.) administration</i> of designated test article (vehicle or 200 nmol/kg CNP variant) for 5 weeks.” EX1023 126:41-51 (emphasis added).</p>	TABLE 13								Tail	Naso- Anal	Femur	Tibia	Humerus	Ulna	CNP37	115%**	109%**	112%**	107%**	105%*	106%**	CNP27- PEO24	100%	99%	100%	102%	100%	101%	
TABLE 13																														
	Tail	Naso- Anal	Femur	Tibia	Humerus	Ulna																								
CNP37	115%**	109%**	112%**	107%**	105%*	106%**																								
CNP27- PEO24	100%	99%	100%	102%	100%	101%																								
[1.4], “wherein the CNP variant is selected from the group consisting of: ... (Pro-Gly-CNP-37) (SEQ ID NO: 1 PGQEHPNAR KYKGANKKG LSKGCFGLKL DRIGSMSGLG C ... (CNP-37) (SEQ ID NO: 21 QEHPNARKY KGANKKGLS KGCFGLKLD RIGSMSGLGC)...”	<p>Wendt treats the achondroplasia subjects of Example 13 with CNP37. EX1023, 126:45-50.</p> <p>The amino acid sequence of CNP37, QEHPNARKYKGANKKG LSKGCFGLKLD RIGSMS GLGC, as listed in Wendt (EX1023, col. 54, SEQ ID NO: 60) is identical to the SEQ ID NO: 21 as claimed in element [1.4].</p>	<p>“<i>CNP22 or variants thereof</i> will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 139:10-15 (emphasis added).</p> <p>Wendt teaches that “Non-limiting examples of CNP variants [] include: [] (SEQ ID NO, 145) PGQEHPNARKYKGANKKG LSKGCFGLKLD RIGSMSGL GC (<i>Pro-Gly-wtCNP37</i>).” EX1023, 58:15-59:10. As such, the embodiment of Example 19 in which the CNP variant selected is Pro-Gly-CNP37 anticipates claim 1.</p>																												

Claim Element	Wendt-242 Example 13	Wendt-242 Example 19
		Further, Wendt specifically highlights the CNP variant Pro-Gly-CNP37 by claiming it in the patent claims. <i>See</i> Wendt, 266:59-64 (“17. A CNP variant useful for increasing long bone growth or treating achondroplasia in a subject, the CNP variant consisting of PGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC (Pro-Gly-CNP37) (SEQ ID NO: 145).”).

166. Accordingly, Wendt-242 discloses each and every element of claim 1, arranged as claimed. And I understand that Wendt-242 is presumed enabled. Therefore, claim 1 is anticipated by Wendt-242.

1. Wendt-242 anticipates claims 2-4 of the '106 patent.

167. Wendt-242 also discloses each and every element of claims 2-4 of the '106 patent.

168. Claim 2 depends from claim 1, and further recites that the composition is administered “once daily”; “once daily over a period of at least 6 months”; or “once daily over a period of at last 12 months.” EX1001, 67:40-46. Wendt-242 Example 13 discloses that the mice were treated “once daily.” EX1023, 126:48. Wendt-242 also teaches that “[t]he doses of CNP variants described herein can be administered according to the dosing frequency/frequency of administration

described herein, including without limitation **daily**, 2 or 3 times per week, weekly every 2 weeks, every 3 weeks, monthly, etc.” EX1023, 25:15-24 (emphasis added). As such, Wendt-242 discloses each and every element of claim 2, arranged as claimed. Claim 2 is anticipated by Wendt

169. Claim 3 depends from claim 1 and further recites that the composition is administered “via subcutaneous administration.” EX1001, 67:47-48. Wendt-242 Example 13 discloses that the mice received “subcutaneous (s.c.) administration.” EX1023, 126:47-50. Wendt-242 also teaches that “[t]he CNP variants ... can be administered to subjects ... such as, e.g. by injection subcutaneously...” EX1023, 90:38-45. As such, Wendt-242 discloses each and every element of claim 3, arranged as claimed. Wendt anticipates claim 3.

170. Claim 4 depends from claim 1, and recites that the administration of the CNP variant is “daily, every other day, 3 times weekly, 2 times weekly, or once weekly.” EX1001, 67:48-51. Wendt-242 Example 13 discloses that the mice were treated “once daily.” EX1023, 126:47. Wendt-242 also teaches that “the doses of CNP variants described herein can be administered according to the dosing frequency/frequency of administration described herein, including without limitation **daily**, 2 or 3 times per week, weekly, every 2 weeks, every 3 weeks, monthly, etc.” EX1023, 25:15-24 (emphasis added). Wendt-242 further teaches “The trial will be conducted for a minimum, but not necessarily limited to, 24

weeks[.]” EX1023, 139:15-20. As such, Wendt-242 discloses each and every element of claim 4, arranged as claimed, and thus Wendt-242 anticipates claim 4.

2. Claim 5 is anticipated by Wendt-242

171. Claim 5 depends from claim 1 and recites that “the composition is administered at a dose of 30 µg/kg.” EX1001, 67:51-54. Example 19 of Wendt-242 teaches “The initial dose for the trials will vary from about 0.001 to about 1.0 mg/kg/ week.” EX1023, 139:20-22. A dose of 30 µg/kg falls within the range disclosed by Wendt-242 Example 19. The range of “0.001 to about 1.0 mg/kg/ week” corresponds to a weekly dose of 1 µg/kg to 1000 µg/kg, which includes a dose of 30 µg/kg. Thus, a POSA reading Wendt-242’s disclosed dose range would have immediately envisaged a dose of 30 µg/kg. EX1023, 139:20-22 As such, Wendt-242 Example 19 discloses each and every element of claim 5, arranged as claimed, and Wendt-242 anticipates claim 5.

3. Claim 6 is anticipated by Wendt-242.

172. Claim 6 depends from claim 1 and recites that “the subject is about 6 months to about 2 years old.” EX1001, 67:55-56. Example 19 of Wendt-242 teaches that “[t]he ideal range of achondroplasia patients will be from *infant (<1 year of age) to pre-adolescent (<13 years of age)*.” EX1023, 140:5-10 (emphasis added). Wendt-242’s disclosure of the age range “<1 year of age” to “<13 years of age” subsumes the claimed range of “about 6 months to about 2 years old.” And I

am not aware of any evidence that the claimed range of “about 0 month to about 2 years old” is critical for the method to work. As such, Wendt-242 Example 19 discloses each and every element of claim 6, arranged as claimed, and Wendt-242 anticipates claim 6.

4. Claim 7 is anticipated by Wendt-242.

173. Claim 7 depends from claim 1 and recites that “the subject is about 0 to about 6 months old.” EX1001, 67:57-58. Example 13 of Wendt-242 teaches that mice “[a]t 3 weeks of age” received “once daily subcutaneous (s.c.) administration of designated test article (vehicle or 200 nmol/kg CNP variant) for 5 weeks.” EX1023, 126:45-50. The subject age of “3 weeks of age” is subsumed within the claimed range “about 0 month to about 6 months old.” Example 19 of Wendt-242 teaches that “[t]he ideal range of achondroplasia patients will be from *infant (<1 year of age) to pre-adolescent (<13 years of age)*.” EX1023, 140:5-10 (emphasis added). This range subsumes the claimed range of about 0 to about 6 months old. And I am not aware of any evidence that the claimed range is critical for the method to work. As such, Wendt-242 discloses each and every element of claim 7, arranged as claimed, and Wendt-242 anticipates claim 7.

5. Claims 9-10 are anticipated by Wendt-242.

174. Claim 9 depends from claim 1 and recites that “the skeletal dysplasia is selected from the group consisting of [] achondroplasia[.]” EX1001, 67:61-

68:13. And claim 10 depends from claim 9 and recites that the skeletal dysplasia is achondroplasia. EX1001, 68:15-16. Wendt-242 Example 13 discloses that “[t]he efficacy of CNP variants in enhancing growth and *correcting achondroplasia* was tested in *a mouse model of mild achondroplasia*.” EX1023, 126:20-42, Table 13. And Wendt-242 Example 19 teaches: “[a] specific example of a potentially CNP-responsive, bone-related disorder is achondroplasia. EX1023, 140:2-5. As such, Wendt-242 discloses each and every element of claims 9-10, and Wendt-242 anticipates claims 9-10.

6. Claim 11 is anticipated by Wendt.

175. Claim 11 depends from claim 1 and recites that “the composition further comprises one or more pharmaceutical excipients.” Wendt-242 Example 13 describes that there is a “vehicle” used to administer CNP37 to the achondroplasia mice. EX1023, 126:45-50. This vehicle is not described in Example 13, but it is described in Example 14, which teaches that the vehicle is “30 mM acetic acid/acetate buffer, 1% benzyl alcohol, 10% sucrose, pH 4.0.” EX1023, 127:65-66. A POSA would understand that sucrose is an excipient, and thus Wendt-242 discloses each and every element of Claim 11, arranged as claimed. Wendt-242 also teaches that “the disclosure provides pharmaceutical compositions comprising a CNP variant, and one or more pharmaceutically acceptable excipients, carriers, or diluents.” EX1023, 85:33-37. As such, Wendt-242 discloses each and every

element of claim 11, arranged as claimed. Thus, Wendt anticipates claim 11.

7. Claim 12 is anticipated by Wendt-242.

176. Claim 12 depends from claim 11 and recites that the composition comprises “citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.” EX1001, 68:20-23.

177. Embodiments of CNP compositions are described, *e.g.*, Wendt-242 Example 18, which describes “liquid formulations of CNP” according to the following table:

TABLE 17

Ingredient Class	Ingredient	Concentration Range
Active ingredient	CNP variant	10 mg/mL $\pm$ 9.9 mg/mL
Buffering agent	Acetic acid/acetate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1
Buffering agent	Citric acid/citrate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1
Isotonicity-adjusting agent/bulking agent	Sorbitol	5% $\pm$ 3%
Isotonicity-adjusting agent/bulking agent	Mannitol	5% $\pm$ 3%
Isotonicity-adjusting agent/bulking agent	Sucrose	10% $\pm$ 5%
Preservative	m-Cresol	0.4% $\pm$ 0.2%
Preservative/anti-adsorbent	Benzyl alcohol	1.5% $\pm$ 0.5%
Stabilizer	Glycerin (glycerol)	5%-100% (neat) ¹
Stabilizer	Methionine	0.01%-0.2%
Stabilizer	Ascorbic acid/ascorbate salt	0.1%-1%
Stabilizer	Thioglycerol	0.1%-1%
Anti-adsorbent	Polysorbate 20	0.001%-0.5%
	Polysorbate 80	0.001%-0.5%
	Benzyl alcohol	0.5%-1.5%

¹Glycerin is used to minimize or prevent water-driven hydrolysis, deamidation, isomerization or cleavage of CNP variants.

EX1023, Table 17.

178. As can be seen from the table above, the composition disclosed by Wendt-242 includes “citric acid/citrate” which would lead a POSA to immediately envisage “citric acid monohydrate” and “sodium citrate dihydrate” as examples of citric acid/citrate. The table also includes methionine, mannitol, and polysorbate 80. *Id.* Wendt-242 also teaches that “[e]xemplary bulking agents include without limitation ...trehalose...” EX1023, 87:65. As such, Wendt-242 discloses each and every element of claim 12, arranged as claimed, and Wendt-242 anticipates claim 12. Thus, Wendt-242 would have led a POSA to immediately envisage a pharmaceutical composition comprising “citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80,” as claimed in claim 12. EX1003.

8. Claim 13 is anticipated by Wendt-242.

179. Claim 13 depends from claim 1 and recites that “the CNP variant is selected from the group consisting of: ...(Pro-Gly-CNP37) ... (CNP-37) ...” EX1001, 68:24-66. Example 13 of Wendt-242 discloses treating the achondroplasia subjects with CNP37 (i.e., SEQ ID NO: 21, as claimed). EX1023, 126:45-47. As such, Wendt-242 Example 13 discloses each and every element of claim 13, arranged as claimed. Example 19 of Wendt-242 teaches “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 139:10-15. Wendt-242 teaches that

“Non-limiting examples of CNP variants [] include: [] (SEQ ID NO, 145)

PGQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC (Pro-Gly-wtCNP37).” EX1023, 58:15-59:10. As such, Wendt-242 discloses each and every element of claim 13. Thus, Wendt-242 anticipate claim 13.

9. Claim 14 is anticipated by Wendt-242.

180. Claim 14 depends from claim 1 and recites that “the CNP variant is selected from the group consisting of: ... (Pro-Gly-CNP-37) ...” EX1001, 69:1-10. Example 19 of Wendt-242 teaches “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 140:38-39. Wendt-242 teaches that “Non-limiting examples of CNP variants [] include: [] (SEQ ID NO: 145) PGQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC (Pro-Gly-wtCNP37).” EX1023, 58:15-59:10. Further, Wendt-242 specifically highlights the CNP variant Pro-Gly-CNP37 by claiming it in the patent claims. *See* EX1023, 266:59-64. As such, Wendt-242 discloses each and every element of claim 14. Thus, Wendt-242 Example 19 anticipates claim 14.

F. Ground VI: Claims 1-14 of the ’106 patent lack enablement.

181. I understand from counsel that, for a claim to be enabled, the patent specification must enable those in the art to make and use the full claim scope without undue experimentation. Here, claims 1-14 lack enablement because each

and every claim encompasses immense genera of which a POSA would not have been able to practice without undue experimentation.

1. Claim 1 of the '106 patent lacks enablement.

a. The claim element “subject about 0 month to about 2 years old,” as recited in claim 1, creates an enormous scope.

182. The claim term, “subject” endows the claim with enormous scope. The specification defines “subject” extremely broadly, and “encompasses mammals and non-mammals.” EX1001, 18:55-65. The specification lists several examples of mammals, including humans, non-human primates, farm animals, and laboratory animals. EX1001, 18:55-65. Regarding non-mammals, the specification states that examples “include, but are not limited to, birds, fish, and the like.” EX1001, 18:63-65. In my opinion, the definition of subject as “mammals and non-mammals” results in the term having an enormous scope, as there are estimated to be more than 5000 species of mammals alone. EX1061, Table S1. As discussed above in Section IX.A, the term “non-mammals” would have been understood to include non-mammalian vertebrate species—e.g., birds, amphibians, reptiles, and fish. This includes over 10,000 species of birds and over 30,000 species of fish. EX1061, 1, Table S1; EX1050, 2. Thus, the scope of “mammal and non-mammal”

subjects⁵ of the '106 patent is enormous. And as discussed below, the specification provides no guidance on treating achondroplasia across this vast and diverse genera of subjects.

b. The claim term “CNP variant,” as recited in claim 1, creates a large genus of peptides with divergent pharmaceutical properties

183. Claim 1 recites the claim element “a C-type natriuretic peptide (CNP) variant” which is further limited by a group of CNP variants consisting of 65 members. The members of the group include wild-type CNP sequences ranging from CNP-52 – CNP -18 (excluding CNP-22), 12 PEGylated CNP variants, and vosoritide (Pro-Gly-CNP37). As discussed below, the prior art shows that the several members of this group have markedly different properties than other members, which would require experimentation to determine the how to use these CNP peptides as therapeutics.

184. The claimed CNP variants have a wide range of half-lives, leading to a varied pharmacokinetic profile and dosing regimen. The group of Claim 1 includes short CNP peptides, and it was known before 2019 that shorter CNP

⁵ To the extent “non-mammals” is construed to include *all* non-mammals, the scope of the term “subject” would extend to encompass over 7 million different species of animals. EX1050, 2.

peptides were more susceptible to proteolysis *in vivo*. Neutral endopeptidase (NEP) is a protease known to cleave the natriuretic peptides, including CNP, resulting in their deactivation. EX1049, FIG. 3; EX1020, 211. In reference to CNP-22, the naturally-occurring CNP variant in that circulates in blood, Pejchalova stated that “the [*in vivo*] half-life of CNP is only 2.6 min due to its rapid degradation by neutral endopeptidase.” EX1020, 213. However, it was also known before 2019 that “the majority of the natural substrates of NEP are restricted to about 3000 Da[.]” EX1045, 343. Typically, a peptide of roughly 28 amino acids will be 3000 Da. EX1052, 87. Therefore, a POSA would expect shorter CNP peptides, below 28 amino acids, to have a much shorter *in vivo* half-life than CNP peptides longer than 28 amino acids. *See e.g.*, EX1062, 346 (“differences in half-life (*longer in larger peptides*) are likely to materially affect their potency *in vivo*.”). Put another way, a POSA would have known that CNPs smaller than 3000 Da would have shorter half-life than CNPs larger than 3000 Da. EX1045, 343; EX1052, 87; EX1062, 346.

185. BioMarin’s own publications support this understanding. For example, Wendt 2015 shows that, among the claimed CNP variants, CNP27(K4,5,9R) (called “CNP27, K4R, K5R, K9R” in Wendt 2015) has markedly lower NEP resistance than CNP-33, CNP-36–CNP-40, and Pro-Gly-CNP-37 (called “BMN-111” in Wendt 2015). EX1009, Table 1. Notably, the only examples in the specification use vosoritide (BMN-111 in Wendt 2015), which is NEP

resistant. Ultimately, a POSA would have needed to perform extensive amounts of trial-and-error experimentation to understand the therapeutic properties of CNP-18 – CNP-27. Table 1 from Wendt 2015 is reproduced below, with annotations in red.

TABLE 1
In vitro potency and NEP resistance for CNP variants
Data are expressed $\pm$ S.D. values as applicable.

Description	Molecular Mass	Potency ^a (EC ₅₀)	NEP Resistance ^b
	<i>kDa</i>	<i>nM</i>	% Intact
CNP22	2.2	13 $\pm$ 5.4	2.4 $\pm$ 1.8
CNP27, K4R, K5R, K9R ^c	2.8	8.7 $\pm$ 1.8	<5
CNP28	3.1	>2000	<5
CNP22, Cys6-methylene ^d	2.2	44 $\pm$ 6.2	<5
CNP22, N-methyl-Phe7 ^d	2.2	860 $\pm$ 380	<5
CNP22, 20 kDa PEG	22	>2000	100
CNP22, 5 kDa PEG	7.2	>2000	84
CNP22, 2 kDa PEG	4.2	>2000	100
CNP22, 1 kDa PEO24	3.2	640 $\pm$ 320	90
CNP22, 0.6 kDa PEO12	2.8	210 $\pm$ 30	40
CNP27, 2 kDa PEG	4.8	>2000	100
CNP27, 1 kDa PEO24	3.8	16 $\pm$ 2.8	103 $\pm$ 2.7
CNP27, 0.6 kDa PEO12	3.4	7.8 $\pm$ 1.4	69 $\pm$ 1.6
CNP30	3.1	8.4 $\pm$ 3.9	36 $\pm$ 1.9
CNP33	3.5	11 $\pm$ 0.1	99 $\pm$ 1.2
CNP36	3.8	5.8 $\pm$ 3.5	98 $\pm$ 2.2
CNP37	3.9	11 $\pm$ 2.0	97 $\pm$ 8.3
CNP38	4.1	6.8 $\pm$ 0.4	105 $\pm$ 7.7
CNP39	4.2	17 $\pm$ 1.6	95 $\pm$ 6.8
CNP40	4.3	10 $\pm$ 2.6	101 $\pm$ 6.3
CNP53	5.8	7.1 $\pm$ 0.5	106 $\pm$ 20
BMN 1B2	4.0	8.7 $\pm$ 0.5	110 $\pm$ 0.02
BMN 1B2(QQ)	4.0	188 $\pm$ 28	182
BMN 111 ^e	4.1	4.9 $\pm$ 1.5	99 $\pm$ 0.6
HSA ₍₂₃₁₋₂₄₅₎ -CNP22 ^f	3.9	11 $\pm$ 3.2	20 $\pm$ 0.6
IgG1 ₍₂₂₄₋₂₃₇₎ -CNP22 ^f	3.7	72 $\pm$ 5.9	75
IgG1 ₍₂₂₄₋₂₃₃₎ -CNP27(QQ) ^f	3.9	920 $\pm$ 50	40
HSA ₍₂₇₋₃₆₎ -CNP27 ^f	4.0	6.9 $\pm$ 2.1	105 $\pm$ 6.4

NT, not tested.
^aMean EC₅₀ (*n* $\geq$ 2) of cGMP production in murine NIH3T3 fibroblasts after 15-minute exposure to CNP variants (10⁻¹⁰ M to 10⁻⁵ M), with nonlinear curve fit using the Hill equation (Erithacus Software).
^bNEP resistance was determined by measuring the amount of intact peptide remaining after exposure to human NEP for 140 minutes in PBS at 37°C (*n* = 2, for variants with near native potency; *n* = 1 for all other variants). Peptide digests were analyzed by liquid chromatography/mass spectrometry.
^cPeptides used for PEGylation variants.
^dNon-native Cys6-Phe7 peptide bond analogs were synthesized based on reported initial NEP cleavage site (Watanabe et al., 1997).
^eBiologic synthesis (all other analogs in this table were prepared by chemical synthesis).
^fChimeric sequences were synthesized on the amino terminus of CNP (IgG, Ac P01857, PDB ID 2TWG; HSA Ac P02768, PDB ID 1BM0).

EX1009, Table 1 (annotated).

186. The inclusion of PEGylated CNP peptides further expand the scope of the “CNP variant.” The Markush group of claim 1 contains 12 PEGylated CNP peptides, however each one of these PEGylated CNP peptides actually represents

several molecular species. The specification states that the PEG can “optionally have an alkylene group, $(CH_2)_m$, where m is an integer from 1 to 5.” EX1001, 19:5-9. Thus, each PEGylated peptide can have several forms, with 0, 1, 2, 3, 4, or 5 CH_2 groups between the PEG polymer and the CNP peptide. In addition, the patent also discloses that the “hydrophilic polymers [e.g., PEG] can be branched or unbranched” and that PEG can be attached to “various sites,” “including but not limited to: (1) only at the N-terminus; (2) only at the C-terminus; (3) only at an internal site (e.g., Lys4 and/or Lys 10); (4) at both the N-terminus and the C-terminus; (5) at the N-terminus and an internal site; and (6) at the C-terminus and an internal site.” EX1001, 24:51-61. Thus, the claimed PEGylated CNP variants can have branched and/or unbranched PEGs coupled to one or more sites on CNP, terminal, internal, or both. Further, according to the specification “[i]n various embodiments, the variant comprises a synthetic polymeric group [e.g., PEG] coupled to the variant through a hydrolysable linker.” EX1001, 12:12-15.

Therefore, because the language “various embodiments” is open ended, the linkage that connects the PEG molecule to the CNP peptide can be hydrolysable or non-hydrolysable. In total, the scope of “CNP variant” is vastly larger than just the 65 listed members, as each one of the PEGylated variants encompasses at least a dozen different molecules. As exemplified in Wendt 2015 by the varied NEP degradation of PEGylated CNPs, this diverse group of PEGylated peptides would

have varied half-life and pharmacokinetic profile. EX1009, Table 1.

187. PEGylated CNP peptides have different pharmaceutical properties than unPEGylated CNP peptides. Indeed, two PEGylated variants in the Markush group of claim 1 were known before 2019 to be *non-functional* according to BioMarin's own publication. PEO24-CNP27(K4,5,9R)⁶ was tested in mice and "it failed to provide a significant growth benefit in wild-type mice compared with the placebo control." EX1009, 137. According to Wendt 2015, this failure prompted BioMarin to pursue other CNP peptides for developing an achondroplasia therapeutic. EX1009, 137. In addition, Wendt 2015 determined that PEO12-CNP27(K4,5,9R) "was the least pharmacologically active of the variants tested, potentially due to poor tissue bioavailability associated with PEGylated proteins." EX1009, 137. Determining the therapeutic properties for PEGylated CNP peptides cannot be easily determine from vosoritide data, in part because vosoritide is unPEGylated.

- c. The term "skeletal dysplasia," as recited in claim 1 refers to a very large genus, including members that CNP would not be a suitable treatment for.**

188. As if the enormous breadth of "subject" and "CNP variant," were not

⁶ CNP27(K4,5,9R), which is SEQ ID NO: 62 in the '106 patent is referred to as CNP27 in Wendt 2015. *See* EX1009, Table 1, footnote c.

enough, claim 1 extends breadth even further due to the term “skeletal dysplasia,” which represent another extremely large and diverse group of disorders. The prior art shows that there are at least 450 different skeletal dysplasias which can be caused by mutations in at least 437 different genes. EX1025, 2394. Furthermore, a POSA would have understood that the wide variety of skeletal dysplasias are not linked by a single molecular pathogenesis that would lead one to believe that a single therapeutic modality could treat them all. This is because the mutations that give rise to skeletal dysplasias “not only code for tissue-specific proteins that are essential for the formation and maintenance of bone and cartilage but also encode proteins that have a more ubiquitous role such as regulating gene transcription, cell division, or intracellular transport.” EX1025, 2417. For many of these genes, “the skeletal roles [] are not yet clear.” EX1025, 2417. The ’106 patent does not provide an explicit definition for “skeletal dysplasia” but instead lists at least 40 non-limiting examples of skeletal dysplasias. EX1001, 4:27-47, claim 9.

189. Some skeletal dysplasias are so severe that they result in death shortly after, or even before, birth. Hypophosphatasia, which is encompassed by the claims, has seven distinct phenotypes (at least “six different forms of the disease”) including a perinatal form that is often lethal in the neonatal period. EX1036, Abstract. Short ribbed polydactyly syndromes, which are also encompassed by the claims, “are incompatible with postnatal life.” EX1037, 515.

190. Some diseases categorized as skeletal dysplasias would not be treatable using a CNP variant, including any of the claimed CNP variants. For example, the '106 patent specifically recites acromesomelic dysplasia as a skeletal dysplasia both in the specification and in claim 9, which depends from claim 1. EX1001, 4:41-42, claim 9. However, “acromesomelic dysplasia type Maroteaux, is caused by loss of function mutations *in the GC-B gene (NPR2)*” which encodes for the receptor that CNP binds to. EX1038, 662. Consequently, “it is supposed that CNP therapy is not effective for acromesomelic dysplasia type Maroteaux, which is caused by loss-of-function mutations in the [NPR-B] gene.” EX1038, 664. In addition, some skeletal dysplasias, such as Marfan syndrome, are characterized by bone *overgrowth*. EX1025, 2410. Because “C-type natriuretic peptide [] increase [sic] long-bone growth,” a POSA would understand that it is an inappropriate treatment for bone overgrowth disorders. EX1005, 26. Indeed, a mutation that causes “overexpression of the CNP” results in a disease similar to Marfan syndrome, referred to as “a marfanoid syndrome, characterized by excessively tall stature, arachnodactyly, scoliosis, and marked overgrowth of long bones.” EX1039, 2793. Similarly, Miura reported “a four-generation family with an overgrowth syndrome [] caused by a gain-of-function mutation at NPR2.” EX1040, Abstract. This NPR2 gain-of-function mutation was known to cause an “overgrowth syndrome characterized by tall stature . . . similar to those previously

reported in association with CNP/NPR2 overactivity.” EX[Miura], Abstract. A POSA would understand that administering a CNP variant to skeletal dysplasia patients with tall stature, such as those with overgrowth syndromes, would likely result in a *worsening* of symptoms (e.g., additional skeletal overgrowth), rather than a reduction in symptoms.

191. In sum, the scope of “skeletal dysplasia” is huge and the individual diseases are not linked by a universal mechanism that would suggest CNP as appropriate therapy. Indeed, there are several skeletal dysplasias for which, due to the underlying pathophysiology, would not be appropriate candidates for CNP therapy.

d. Analysis of the Wands factors show that undue experimentation would have been required to practice the full scope of claim 1.

192. I understand from counsel that claims are not enabled if they require undue experimentation for a POSA to practice their full scope. I further understand from counsel that 8 factors, the so-called Wands factors, are weighed to make a determination of claim enablement. The Wands factors are 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of ordinary skill in the relevant field, 5) the level of predictability in the art, 6) the amount of guidance given by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed. In Sections X.F.1-X.F.3 above, I

have described the 1) breadth of the claims. The claim element “an amount effective to treat,” when applied to the vast scope of the other elements, demands undue experimentation from a practitioner seeking to practice the full scope of the claims.

193. The '106 patent is clear that the “amount effective to treat” can change depending on the particular circumstances of the patient and disease. Specifically, the '106 patent states that: “[i]t will be understood that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors, including the activity of **the specific compound employed**; the bioavailability, metabolic stability, rate of excretion and **length of action of that compound**; the mode and time of administration of the compound; the **age**, body weight, general health, sex, and diet of the patient; and the **severity of the particular condition**.” EX1001, 17:37-45 (emphasis added). However, the specification does not provide sufficient guidance for how to determine “the amount effective to treat” for the huge genus encompassed by the claims.

i. Quantity of experimentation needed and the nature of the invention

194. The quantity of experiments needed to determine the “amount effective to treat” is high. As described above, the scope of the claimed invention is enormous. A POSA would need to determine the “amount effective to treat” for

more than 65 different CNP peptides, for all mammals and non-mammals (spanning millions of species of animals), and for more than 450 different skeletal dysplasias. The guidance and working examples in the specification are meager, and the teachings cannot be extrapolated to the full scope of the claims. Therefore, the quantity of experimentation needed is as enormous as the scope of the claims.

195. The specification acknowledges that dosage (*i.e.*, the “amount effective to treat”) should be adjusted based on the “severity of the particular condition” in the subject. Despite this, the ’106 patent provides no guidance for selecting the dose for each of the more than 450 skeletal dysplasia, excluding achondroplasia. Skeletal dysplasias were known to have a broad range of severity, with some as mild as “idiopathic short stature” and some so severe that they are “incompatible with postnatal life.” EX1001, 4:46; EX1037, 515. Furthermore, the various skeletal dysplasias do not share a unifying pathophysiology and consequently a POSA would not expect the teachings that apply to achondroplasia to reasonably extend to other skeletal dysplasias. Section VI.A. Indeed, some skeletal dysplasias are expected to be untreatable with CNP peptides. Section VI.A.

196. The list of claimed CNP peptides includes members with divergent properties. Further, these members are very different from the exemplified CNP variant, vosoritide, which is an unPEGylated CNP peptide of 39 amino acids. The

claimed CNP peptides include several short CNP peptides (28 amino acids or shorter) that are expected to be susceptible to NEP, resulting in a much shorter *in vivo* half-life. Section X.F.2. For example, CNP-37 was known to be resistant to NEP and displays an *in vivo* half-life almost 35 times longer than CNP-22 (1.42 minutes for CNP-22 compared to 49.5 minutes for CNP-37). EX1024, 123:25-35. Indeed, vosoritide was developed “to have a longer half-life than its endogenous form [CNP-22].” EX1005, 26. A POSA would know that the dosage guidance provided by vosoritide data would not be instructive for determining the “amount effective to treat” for CNP peptides with a fraction of vosoritide’s half-life. Furthermore, some claimed variants are PEGylated, whereas vosoritide is not. Two of the claimed PEGylated CNP peptides were known before 2021 to be ineffective for treatment of achondroplasia, as PEO24-CNP27(K4, 5, 9R) “failed to provide a significant growth benefit in wild-type mice” and PEO14-CNP27(K4, 5, 9R) “performed similarly” to PEO24-CNP27(K4, 5, 9R). EX1009, 137.

197. Therefore, determining the “amount effective to treat” would demand a POSA perform seemingly endless trial-and-error testing on each skeletal dysplasia type in each subject type, and with each CNP variant of the claims. The quantity of experimentation would have been enormous and weighed against enablement.

ii. Guidance from the specification and working examples

198. Despite the vast number of skeletal dysplasias, CNP peptides, and subjects encompassed by claim 1, the specification only provides a single working example, narrowly drawn to a specific embodiment of treating a human with achondroplasia. EX1001, Example 1. Example 1 describes a clinical trial for treating achondroplasia. EX1001, Example 1. The only exemplified CNP variant in the specification is vosoritide (also called Pro-Gly-CNP37 or BMN 111). EX1001, 39:40-48, 39:54-58, 39:59-40:4, 40:5-9, Table 2, Table 3, 46:33-35, Table 4, 47:58-59, 48:61-64, 50:1-5. Furthermore, only two doses, 15 µg/kg and 30 µg/kg, were tested in human patients. EX1001, 39:59-40:9, Table 4. While the specification describes testing in a cohort aged birth to <6 months, treatment did not begin in these patients until after a 3-month observation period. EX1001, 40: 5-9. Therefore, a POSA would understand that the specification provides an example of a single CNP peptide, testing for treatment efficacy in a single skeletal dysplasia, with only two doses of the CNP peptide, and no examples of the 0-3 month age group.

199. The specification provides minimal guidance for determining the “amount effective to treat” the many skeletal dysplasias humans aged 0 month to 2 years, let alone *any mammal or non-mammal* about 0 month to about 2 years old. The specification contemplates broad dosing ranges, from 3 nmol/kg up to 300

nmol/kg, or 3 mg/kg to 1000 mg/kg. EX1001, 35:51; 35:66-36:4. Beyond a single CNP peptide applied to a single disease, no guidance is provided for determining which dose in these ranges, which span two orders of magnitude, would be “an amount effective to treat” for each of the hundreds of “skeletal dysplasias,” dozens of “CNP variants,” or the millions of “subjects” encompassed by the claims.

iii. The nature and predictability of the field

200. Given the enormous scope of the claims due to the millions of mammal and non-mammal “subjects” (even when limiting to the phylum chordata), the varying pharmacodynamics in the genus of “CNP variants,” and the hundreds of different “skeletal dysplasias” with different pathophysiologies, a POSA would have found practicing the full scope of the claims to be highly unpredictable. The differences in pharmacokinetic responses among the millions of different subject types alone would have created enormous unpredictability for a POSA attempting to practice the full scope of the claimed method. The variability of the CNP variants and vast array of skeletal dysplasia conditions would have further exacerbated this unpredictability.

iv. Level of ordinary skill in the art

201. Despite the high level of skill of a POSA, practicing the full scope of the claim would have been outside of a POSA’s capacity. The term “subject” encompasses all mammals and non-mammals. Section IX.B. Thus, the term

“subject” encompasses animals not commonly studied in skeletal dysplasia (*e.g.*, birds, fish, reptiles, or amphibians). The nearly infinite possibilities of mammalian and non-mammalian “subjects,” according to taxonomy, far exceeds the level of skill of a POSA. EX1001, 18:62-65. Therefore, the level of ordinary skill in the art weighs in favor of non-enablement.

v. Weighing the Wands factors

202. Practicing the full scope of the claim would have required undue experimentation from a POSA. As described above, the quantity of experimentation required is extremely high, while the guidance in the specification is limited in view of the vast breadth of the claims. Therefore, no matter how carefully planned the research, practicing the full scope of the claims would require trial and error discovery. The experimentation that POSA would need to engage in to practice the full scope of the claims would be undue.

2. Claim 2-14 of the '106 patent lack enablement.

203. As discussed above, claim 1 of the '106 patent contains enormous scope. Claims 2-8 and 11-12 all depend directly or indirectly from claim 1 and do not narrow the terms discussed above (“subject,” “CNP variant,” or “skeletal dysplasia”) and thus claims 2-8 and 11-12 are not enabled for the same reasons discussed above for claim 1.

204. Claim 9 depends from claim 1 and limits the “skeletal dysplasia” to a

list of 42 skeletal dysplasias. And Claim 10 depends from claim 3, limiting the skeletal dysplasia to just achondroplasia. However, these claims still derive enormous scope from the terms “subject” and “CNP variant,” and are no more enabled than the subject matter of claim 1.

205. Claim 13 depends from claim 1 and limits the “CNP variant” to a list of 12 CNP variants, and claim 14 depends from claim 1 and limits the “CNP variant” to a list of 2 variants. However, these claims still derive enormous scope from the terms “subject” and “skeletal dysplasia,” and are no more enabled than the subject matter of claim 1.

206. As such, each of dependent claims 2-14 lack enablement.

G. Ground VIII: Claim 8 of the '106 patent is unpatentable because it fails to further limit claim 5 from which it depends.

207. Claim 5 depends from claim 1 and is directed to a method of treating skeletal dysplasia in a subject of “about 0 month to about 2 years old” comprising administering a composition comprising CNP variant recited in claim 1 at a dose of 30 µg/kg. Claim 8 further limits the method of claim 5 to a method wherein “the dosage may be decreased to 15 µg/kg when the subject is 2 years old.”

208. Initially, the use of the word “may” implies that this dosage recited in claim 8 is optional, and thus claim 8 does not necessarily limit the scope of claim 5.

209. Moreover, claim 8 requires decreasing the dose of claim 5 to 15

µg/kg. But claim 5 requires administering a fixed dose 30 µg/kg and explicitly does not encompass the 15 µg/kg dose. As such, claim 8 is unpatentable for failing to further limit claim 5.

XI. CONCLUSION

210. In signing this declaration, I recognize that the declaration will be filed as evidence in a post-grant review before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required, I will appear for cross-examination within the United States during the time allotted.

211. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on this 24th day of November 2025.

M. Jennifer Abuzzahab, MD

Dr. Mary Jennifer Abuzzahab, M.D.

XII. APPENDIX A – CLAIM LISTING

Claim Element No.	Claim Element
[1.1]	A method of treating skeletal dysplasia
[1.2]	in a subject about 0 month to about 2 years old
[1.3]	comprising administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the skeletal dysplasia in the subject,
[1.4]	<p>wherein the CNP variant is selected from the group consisting of:</p> <p>(Pro-Gly-CNP37) (SEQ ID NO: 1) PGQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(Gly-CNP53) (SEQ ID NO: 2) GDLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(Pro-CNP53) (SEQ ID NO: 3) PDLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(Met-CNP53) (SEQ ID NO: 4) MDLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>[CNP-53(M48N)] (SEQ ID NO: 5) DLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SNSGLGC;</p> <p>(CNP-52) (SEQ ID NO: 6) LRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-51) (SEQ ID NO: 7) RVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-50) (SEQ ID NO: 8) VDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-49) (SEQ ID NO: 9) DTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-48) (SEQ ID NO: 10) TKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-47) (SEQ ID NO: 11) KSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-46) (SEQ ID NO: 12) SRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-45) (SEQ ID NO: 13) RAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-44) (SEQ ID NO: 14) AAWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-43) (SEQ ID NO: 15) AWARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-42) (SEQ ID NO: 16) WARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-41) (SEQ ID NO: 17) ARLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p> <p>(CNP-40) (SEQ ID NO: 18) RLLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC;</p>

Claim Element No.	Claim Element
	<p>(CNP-39) (SEQ ID NO: 19) LLQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-38) (SEQ ID NO: 20) LQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-37) (SEQ ID NO: 21) QEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-36) (SEQ ID NO: 22) EHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-35) (SEQ ID NO: 23) HPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-34) (SEQ ID NO: 24) PNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-33) (SEQ ID NO: 25) NARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-32) (SEQ ID NO: 26) ARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-31) (SEQ ID NO: 27) RKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-30) (SEQ ID NO: 28) KYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-29) (SEQ ID NO: 29) YKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-28) (SEQ ID NO: 30) KGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-27) (SEQ ID NO: 31) GANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-26) (SEQ ID NO: 32) ANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-25) (SEQ ID NO: 33) NKKGLSKGCFGLKLDRI SMSGLGC; (CNP-24) (SEQ ID NO: 34) KKGLSKGCFGLKLDRI SMSGLGC; (CNP-23) (SEQ ID NO: 35) KGLSKGCFGLKLDRI SMSGLGC; (CNP-21) (SEQ ID NO: 36) LSKGCFGLKLDRI SMSGLGC; (CNP-20) (SEQ ID NO: 37) SKGCFGLKLDRI SMSGLGC; (CNP-19) (SEQ ID NO: 38) KGCFGLKLDRI SMSGLGC; (CNP-18) (SEQ ID NO: 39) GCFGLKLDRI SMSGLGC; [CNP37(M32N)] (SEQ ID NO: 40)</p>

Claim Element No.	Claim Element
	<p>QEHPNARKYKGANKKGLSKGCFGLKLDRIGSNSGLGC; (Pro-CNP37) (SEQ ID NO: 41) PQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC; (Met-CNP37) (SEQ ID NO: 42) MQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC; (Gly-CNP37) (SEQ ID NO: 43) GQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC; [Gly-CNP37(M32N)] (SEQ ID NO: 44) GQEHPNARKYKGANKKGLSKGCFGLKLDRIGSNSGLGC; (Met-Gly-CNP37) (SEQ ID NO: 45) MGQEHPNARKYKGANKKGLSKGCFGLKLDRIGSMSGLGC; (HSA-CNP27) (SEQ ID NO: 46) GHKSEVAHRFKGANKKGLSKGCFGLKLDRIGSMSGLGC; [HSA-CNP27(M22N)] (SEQ ID NO: 47) GHKSEVAHRFKGANKKGLSKGCFGLKLDRIGSNSGLGC; (Pro-HSA-CNP27) (SEQ ID NO: 48) PGHKSEVAHRFKGANKKGLSKGCFGLKLDRIGSMSGLGC; (Met-HSA-CNP27) (SEQ ID NO: 49) MGHKSEVAHRFKGANKKGLSKGCFGLKLDRIGSMSGLGC; [CNP27(K4, 5, 9R)] (SEQ ID NO: 50) GANRRGLSRGCFGLKLDRIGSMSGLGC; [CNP27(K4, 5, 9R, M22N)] (SEQ ID NO: 51) GANRRGLSRGCFGLKLDRIGSNSGLGC; [Pro-CNP27(K4, 5, 9R)] (SEQ ID NO: 52) PGANRRGLSRGCFGLKLDRIGSMSGLGC; [Met-CNP27(K4, 5, 9R)] (SEQ ID NO: 53) MGANRRGLSRGCFGLKLDRIGSMSGLGC; [PEG1K-CNP27(K4, 5, 9R)] (SEQ ID NO: 54) PEG1K-GANRRGLSRGCFGLKLDRIGSMSGLGC; [PEG1K-CNP27(K4, 5, 9R, M22N)] (SEQ ID NO: 55) PEG1K-GANRRGLSRGCFGLKLDRIGSNSGLGC; [PEG1K-Pro-CNP27(K4, 5, 9R)] (SEQ ID NO: 56) PEG1K-PGANRRGLSRGCFGLKLDRIGSMSGLGC; [PEG1K-Met-CNP27(K4, 5, 9R)] (SEQ ID NO: 57) PEG1K-MGANRRGLSRGCFGLKLDRIGSMSGLGC; [PEO12-CNP27(K4, 5, 9R)] (SEQ ID NO: 58) PEO12-GANRRGLSRGCFGLKLDRIGSMSGLGC; [PEO12-CNP27(K4, 5, 9R, M22N)] (SEQ ID NO: 59) PEO12-GANRRGLSRGCFGLKLDRIGSNSGLGC; [PEO12-Pro-CNP27(K4, 5, 9R)] (SEQ ID NO: 60) PEO12-PGANRRGLSRGCFGLKLDRIGSMSGLGC; [PEO12-Met-CNP27(K4, 5, 9R)] (SEQ ID NO: 61) PEO12-MGANRRGLSRGCFGLKLDRIGSMSGLGC;</p>

Claim Element No.	Claim Element
	[PEO24-CNP27(K4, 5, 9R)] (SEQ ID NO: 62) PEO24-GANRRGLSRGCFGLKLDRI SMSGLGC; [PEO24-CNP27(K4, 5, 9R, M22N)] (SEQ ID NO: 63) PEO24-GANRRGLSRGCFGLKLDRI SNSGLGC; [PEO24-Pro-CNP27(K4, 5, 9R)] (SEQ ID NO: 64) PEO24-PGANRRGLSRGCFGLKLDRI SMSGLGC; and [PEO24-Met-CNP27(K4, 5, 9R)] (SEQ ID NO: 65) PEO24-MGANRRGLSRGCFGLKLDRI SMSGLGC.
[2]	The method of claim 1, wherein (a) said composition is administered once daily; (b) said composition is administered once daily over a period of at least 6 months; or (c) said composition is administered once daily over a period of at least 12 months.
[3]	The method of claim 1, wherein the composition is administered to the subject via subcutaneous administration.
[4]	The method of claim 1, wherein the composition is administered daily, every other day, 3 times weekly, 2 times weekly, or once weekly.
[5]	The method of claim 1, wherein the composition is administered at a dose of 30 µg/kg.
[6]	The method of claim 1, wherein the subject is about 6 months to about 2 years old.
[7]	The method of claim 1, wherein the subject is about 0 to about 6 months old.
[8]	The method of claim 5, wherein the dosage may be decreased to 15 µg/kg when the subject is 2 years old.
[9]	The method of claim 1, wherein the skeletal dysplasia is selected from the group consisting of hypophosphatemic rickets, achondroplasia, hypochondroplasia, short stature, dwarfism, osteochondrodysplasias, thanatophoric dysplasia, osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, campomelic dysplasia, congenital lethal hypophosphatasia, perinatal lethal type of osteogenesis imperfecta, short-rib polydactyly syndromes, hypochondroplasia, rhizomelic type of chondrodysplasia punctata, Jansen-type metaphyseal dysplasia, spondyloepiphyseal dysplasia congenita, atelosteogenesis, diastrophic dysplasia, congenital short femur, Langer-type mesomelic dysplasia, Nievergelt-type mesomelic dysplasia, Robinow syndrome, Reinhardt syndrome, acrodysostosis, peripheral dysostosis, Kniest dysplasia, fibrochondrogenesis, Roberts syndrome, acromesomelic dysplasia, micromelia, Morquio syndrome, Kniest syndrome, metatrophic dysplasia, spondyloepimetaphyseal dysplasia, NPR2 mutation, SHOX mutation, Turner's syndrome/Leri Weill, PTPN11 mutations, Noonan's syndrome, and idiopathic short stature.
[10]	The method of claim 3, wherein the skeletal dysplasia is achondroplasia.
[11]	The method of claim 1, wherein the composition further comprises one or more pharmaceutical excipients.
[12]	The method of claim 11, wherein the composition comprises citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.
[13]	The method of claim 1, wherein the CNP variant is selected from the group consisting of: (Pro-Gly-CNP-37) (SEQ ID NO: 1) PGQEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (Gly-CNP-37) (SEQ ID NO: 43)

Claim Element No.	Claim Element
	<p> GQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-38) (SEQ ID NO: 20) LQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; [CNP-37(M32N)] (SEQ ID NO: 40) QEHNPARKYKGANKKGLSKGCFGLKLDRI SNSGLGC; (Met-CNP-37) (SEQ ID NO: 42) MQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (Pro-CNP-37) (SEQ ID NO: 41) PQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; [Gly-CNP-37(M32N)] (SEQ ID NO: 44) GQEHNPARKYKGANKKGLSKGCFGLKLDRI SNSGLGC; (Met-Gly-CNP-37) (SEQ ID NO: 45) MGQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-37) (SEQ ID NO: 21) QEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-36) (SEQ ID NO: 22) EHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; (CNP-35) (SEQ ID NO: 23) HPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC; and (CNP-34) (SEQ ID NO: 24) PNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC. </p>
[14]	<p> The method of claim 1, wherein the CNP variant is selected from the group consisting of: (SEQ ID NO: 1) PGQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC (Pro-Gly-CNP-37); and (SEQ ID NO: 20) LQEHNPARKYKGANKKGLSKGCFGLKLDRI SMSGLGC (CNP-38). </p>

XIII. APPENDIX B – TABULATED WENDT ANTICIPATORY DISCLOSURE OF EXAMPLES 13 AND 19

Claim or Claim Element	Wendt Example 13	Wendt Example 19
[1.1], “a method of treating skeletal dysplasia”	“[t]he efficacy of CNP variants in enhancing growth and <i>correcting achondroplasia</i> was tested in <i>a mouse model of mild achondroplasia</i> ” EX1023, 126:20-25, Table 13.	Wendt Example 19 teaches that “CNP22 or variants thereof will be used in the <i>treatment of disorders responsive to CNP, including disorders of the bone.</i> ” EX1023, 139:6-11. Further, “A specific example of a potentially CNP-responsive, bone-related disorder is <i>achondroplasia.</i> ” EX1023, 140:2-6.
[1.2], “in a subject about 0 month to about 2 years old”	mice “[a]t 3 weeks of age” received “once daily subcutaneous (s.c.) administration of designated test article (vehicle or 200 nmol/kg CNP variant) for 5 weeks.” EX1023, 126:42-54.	Example 19 of Wendt teaches that “[t]he ideal range of achondroplasia patients will be from <i>infant (<1 year of age) to pre-adolescent (<13 years of age.</i> ” EX1023, 140:6-8.
[1.3], “comprising administering to the subject a composition comprising a C-type natriuretic peptide (CNP) variant in an amount effective to treat the	Table 13 of Wendt shows that achondroplasia mice treated with CNP37 showed a statistically significant increase in tail, bone, and femur length, thus treating the mice. EX1023, 127:40-60, Table 13.	Example 19 of Wendt teaches “The initial dose for the trials will vary from about 0.001 to about 1.0 mg/kg/ week.” EX1023, 139:20-22. Wendt also teaches that “CNP22 or variants thereof will be used in <i>the treatment of disorders responsive to CNP.</i> ” EX1023, 139:11-14. And further, “In the event that the initial dose in this range does not produce a significant direct clinical benefit , the dose should be increased within this range or beyond this range as necessary.” EX1023, 139:22-36.

skeletal dysplasia in the subject”		
[1.4], “wherein the CNP variant is selected from the group consisting of: ... (Pro-Gly-CNP-37) ... (CNP-37) ...”	Example 13 of Wendt treats the achondroplasia subjects with CNP37. EX1023, 126:20-21.	Example 19 of Wendt teaches “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 139:11-14. Wendt teaches that “Non-limiting examples of CNP variants [] include: [] (SEQ ID NO, 145) PGQEHPNARKYKGANKKGLSKGCFGLK LDRIGSMSGLGC (<i>Pro-Gly-wtCNP37</i>).” EX1023, 58:15-59:10. As such, the embodiment of Example 19 in which the CNP variant selected is Pro-Gly-CNP37 anticipates claim 1.
2, administration is “once daily;” “once daily over a period of at least 6 months;” or “once daily over a period of at last 12 months.”	Wendt Example 13 discloses that the mice were treated “once daily.” EX1023, 126:47-49.	Wendt Example 19 does not discuss specific dosing schedules. An embodiment of Wendt teaches that “[i]n other embodiments ... the doses of CNP variants described herein can be administered according to the dosing frequency/frequency of administration described herein, including without limitation daily, 2 or 3 times per week, weekly every 2 weeks, every 3 weeks, monthly, etc.” EX1023, 25:5-15, <i>see also</i> EX1023, 90:24-29. Example 19 of Wendt further teaches “The trial will be conducted for a minimum, but not necessarily limited to, 24 weeks[.]” EX1023, 139:18-20. As such, the embodiment of Wendt Example 19 in which a daily dosing frequency is selected anticipates Claim 2.
3, “via subcutaneous administration”	Wendt Example 13 discloses that the mice received “subcutaneous (s.c.) administration.” EX1023, 126:48-50.	Wendt Example 19 does not discuss administration routes. Wendt teaches that “[t]he CNP variants ... can be administered to subjects such as, e.g. by injection subcutaneously...” EX1023, 90:39-42. As such, the embodiment of Wendt Example 19 in which the CNP variant is administered subcutaneously anticipates claim 3.

4, “daily, every other day, 3 times weekly, 2 times weekly, or once weekly.”	Wendt Example 13 discloses that the mice were treated “once daily.” EX1023, 126:47-49.	Example 19 does not discuss dosing schedule. As discussed above, Wendt teaches that “CNP variants described herein can be administered according to the dosing frequency/frequency of administration described herein, including without limitation daily ...[.]” EX1023, 25:10-15. As such, the embodiment of Wendt Example 19 in which a daily dosing frequency is selected anticipates Claim 4.
5, “the composition is administered at a dose of 30 µg/kg.”	NA	Example 19 of Wendt teaches “The initial dose for the trials will vary from about 0.001 to about 1.0 mg/kg/ week.” EX1023, 139:20-22. A dose of 30 µg/kg falls within the range disclosed by Wendt Example 19. As such, Wendt Example 19 anticipates claim 5.
6, “the subject is about 6 months to about 2 years old”	NA	Example 19 of Wendt teaches that “[t]he ideal range of achondroplasia patients will be from <i>infant (<1 year of age) to pre-adolescent (<13 years of age).</i> ” EX1023, 140:6-8. This range overlaps with 6 months to 2 years old.
7, “the subject is about 0 to about 6 months old.”	mice “[a]t 3 weeks of age” received “once daily subcutaneous (s.c.) administration of designated test article (vehicle or 200 nmol/kg CNP variant) for 5 weeks.” EX1023, 126:42-54.	Example 19 of Wendt teaches that “[t]he ideal range of achondroplasia patients will be from infant (<1 year of age) to pre-adolescent (<13 years of age.” EX1023, 140:6-8. <1 to 13 years of age overlaps with about 0 to about 6 months old. As such, Wendt Example 19 anticipates claim 7.
8, “the dosage may be decreased to 15 µg/kg when the subject is 2 years old”	NA	NA

9, “the skeletal dysplasia is selected from the group consisting of ... achondroplasia ...”	“[t]he efficacy of CNP variants in enhancing growth and <i>correcting achondroplasia</i> was tested in <i>a mouse model of mild achondroplasia</i> ” EX1023, 126:20-25, Table 13.	Wendt Example 19 teaches: “[a] specific example of a potentially CNP-responsive, bone-related disorder is achondroplasia EX1023, 141:1-6.
10, “the skeletal dysplasia is achondroplasia .”	“[t]he efficacy of CNP variants in enhancing growth and <i>correcting achondroplasia</i> was tested in <i>a mouse model of mild achondroplasia</i> ” EX1023, 126:20-25, Table 13.	Wendt Example 19 teaches: “[a] specific example of a potentially CNP-responsive, bone-related disorder is achondroplasia.” EX1023, 141:1-6.
11, “the composition further comprises one or more pharmaceutical excipients.”	Wendt Example 13 describes that there is a “vehicle” used to administer CNP37 to the achondroplasia mice. EX1023, 127:55-60. This vehicle is not described in Example 13, but it is described in Example 14, which teaches that the vehicle is “30 mM acetic acid/acetate buffer, 1% benzyl alcohol, 10% sucrose, pH 4.0.”	Wendt Example 19 does not describe excipients, but does describe “clinical evaluation of <i>compositions</i> .” EX1023, 139:8-11. Wendt also teaches that “[i]n additional embodiments, the disclosure provides pharmaceutical compositions comprising a CNP variant, and one or more pharmaceutically acceptable excipients, carriers, or diluents.” EX1023, 85:33-36. As such, when a pharmaceutically acceptable excipient is selected for use in Wendt Example 19, it anticipates Claim 11.

	EX1023, 128:27-33. A POSA would understand that sucrose is an excipient.																																																	
12, the composition comprises “citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.”	NA	<p>Wendt Example 19 does not describe excipients, but does describe “clinical evaluation of compositions.” EX1023, 139:7-11. Embodiments of CNP compositions are described, e.g., Wendt Example 18, which describes “liquid formulations of CNP” according to the following table:</p> <p style="text-align: center;">TABLE 17</p> <table> <tr> <th>Ingredient Class</th><th>Ingredient</th><th>Concentration Range</th></tr> <tr> <td>Active ingredient</td><td>CNP variant</td><td>10 mg/mL $\pm$ 9.9 mg/mL</td></tr> <tr> <td>Buffering agent</td><td>Acetic acid/acetate</td><td>10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1</td></tr> <tr> <td>Buffering agent</td><td>Citric acid/citrate</td><td>10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1</td></tr> <tr> <td>Isotonicity-adjusting agent/bulking agent</td><td>Sorbitol</td><td>5% $\pm$ 3%</td></tr> <tr> <td>Isotonicity-adjusting agent/bulking agent</td><td>Mannitol</td><td>5% $\pm$ 3%</td></tr> <tr> <td>Isotonicity-adjusting agent/bulking agent</td><td>Sucrose</td><td>10% $\pm$ 5%</td></tr> <tr> <td>Preservative</td><td>m-Cresol</td><td>0.4% $\pm$ 0.2%</td></tr> <tr> <td>Preservative/anti-adsorbent</td><td>Benzyl alcohol</td><td>1.5% $\pm$ 0.5%</td></tr> <tr> <td>Stabilizer</td><td>Glycerin (glycerol)</td><td>5%-100% (neat)¹</td></tr> <tr> <td>Stabilizer</td><td>Methionine</td><td>0.01%-0.2%</td></tr> <tr> <td>Stabilizer</td><td>Ascorbic acid/ascorbate salt</td><td>0.1%-1%</td></tr> <tr> <td>Stabilizer</td><td>Thioglycerol</td><td>0.1%-1%</td></tr> <tr> <td>Anti-adsorbent</td><td>Polysorbate 20</td><td>0.001%-0.5%</td></tr> <tr> <td></td><td>Polysorbate 80</td><td>0.001%-0.5%</td></tr> <tr> <td></td><td>Benzyl alcohol</td><td>0.5%-1.5%</td></tr> </table> <p>¹Glycerin is used to minimize or prevent water-driven hydrolysis, deamidation, isomerization or cleavage of CNP variants.</p> <p>EX1001, 137:40-63, 139:1-25. As can be seen from the table above, the composition disclosed by Wendt includes “citric acid/citrate” which a POSA would understand is synonymous with “citric acid monohydrate” and “sodium citrate dihydrate.” The table also includes methionine (which a POSA would understand encapsulates both L-methionine and D-methionine), mannitol (which a POSA would understand encapsulates both L-</p>	Ingredient Class	Ingredient	Concentration Range	Active ingredient	CNP variant	10 mg/mL $\pm$ 9.9 mg/mL	Buffering agent	Acetic acid/acetate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1	Buffering agent	Citric acid/citrate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1	Isotonicity-adjusting agent/bulking agent	Sorbitol	5% $\pm$ 3%	Isotonicity-adjusting agent/bulking agent	Mannitol	5% $\pm$ 3%	Isotonicity-adjusting agent/bulking agent	Sucrose	10% $\pm$ 5%	Preservative	m-Cresol	0.4% $\pm$ 0.2%	Preservative/anti-adsorbent	Benzyl alcohol	1.5% $\pm$ 0.5%	Stabilizer	Glycerin (glycerol)	5%-100% (neat) ¹	Stabilizer	Methionine	0.01%-0.2%	Stabilizer	Ascorbic acid/ascorbate salt	0.1%-1%	Stabilizer	Thioglycerol	0.1%-1%	Anti-adsorbent	Polysorbate 20	0.001%-0.5%		Polysorbate 80	0.001%-0.5%		Benzyl alcohol	0.5%-1.5%
Ingredient Class	Ingredient	Concentration Range																																																
Active ingredient	CNP variant	10 mg/mL $\pm$ 9.9 mg/mL																																																
Buffering agent	Acetic acid/acetate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1																																																
Buffering agent	Citric acid/citrate	10 mM $\pm$ 5 mM, or pH 5 $\pm$ 1																																																
Isotonicity-adjusting agent/bulking agent	Sorbitol	5% $\pm$ 3%																																																
Isotonicity-adjusting agent/bulking agent	Mannitol	5% $\pm$ 3%																																																
Isotonicity-adjusting agent/bulking agent	Sucrose	10% $\pm$ 5%																																																
Preservative	m-Cresol	0.4% $\pm$ 0.2%																																																
Preservative/anti-adsorbent	Benzyl alcohol	1.5% $\pm$ 0.5%																																																
Stabilizer	Glycerin (glycerol)	5%-100% (neat) ¹																																																
Stabilizer	Methionine	0.01%-0.2%																																																
Stabilizer	Ascorbic acid/ascorbate salt	0.1%-1%																																																
Stabilizer	Thioglycerol	0.1%-1%																																																
Anti-adsorbent	Polysorbate 20	0.001%-0.5%																																																
	Polysorbate 80	0.001%-0.5%																																																
	Benzyl alcohol	0.5%-1.5%																																																

		mannitol and D-mannitol), and polysorbate 80. While trehalose dihydrate is not included in this list, Wendt also teaches that “[e]xemplary bulking agents include without limitation ...trehalose...” EX1023, 87:63-65. As such, when the embodiment composition comprising trehalose, citric acid/citrate, methionine, mannitol, and polysorbate 80 is selected, Wendt Example 19 anticipates claim 12.
13 “the CNP variant is selected from the group consisting of: ... (Pro-Gly-CNP-37) ... (CNP37) ...”	Example 13 of Wendt treats the achondroplasia subjects with CNP37. EX1023, 126:20-21.	Example 19 of Wendt teaches “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 139:11-14. Wendt teaches that “Non-limiting examples of CNP variants [] include: [] (SEQ ID NO, 145) PGQEHPNARKYKGANKKGLSKGCFGLK LDRIGSMSGLGC (Pro-Gly-wtCNP37).” EX1023, 58:15-59:10. As such, when the CNP variant Pro-Gly-CNP37, as described in Wendt, is selected for use in Wendt Example 19, it anticipates claim 13.
14, “the CNP variant is selected from the group consisting of: ... (Pro-Gly-CNP-37) ...”	NA	Example 19 of Wendt teaches “CNP22 or variants thereof will be used in the treatment of disorders responsive to CNP, including disorders of the bone.” EX1023, 139:11-14. Wendt teaches that “Non-limiting examples of CNP variants [] include: [] (SEQ ID NO, 145) PGQEHPNARKYKGANKKGLSKGCFGLK LDRIGSMSGLGC (Pro-Gly-wtCNP37).” EX1023, 58:15-59:10. As such, when the CNP variant Pro-Gly-CNP37, as described in Wendt, is selected for use in Wendt Example 19, it anticipates claim 13.