

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ZYDUS LIFESCIENCES LIMITED, ZYDUS
LIFESCIENCES GLOBAL FZE, and ZYDUS
PHARMACEUTICALS (USA) INC.,
Petitioners

v.

BIOMARIN PHARMACEUTICAL INC.
Patent Owner

Case No. PGR2026-00055
Patent 12,233,106

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 12,233,106

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I. INTRODUCTION

Zydus Lifesciences Limited, Zydus Lifesciences Global FZE, and Zydus Pharmaceuticals (USA) Inc. (“Zydus” or “Petitioners”) petitions for Post-Grant Review (“PGR”) of Claims 1-14 of U.S. Patent No. 12,233,106 (the “’106 Patent”) (EX1001). In particular, Zydus respectfully seeks to join *Ascendis USA, Inc. et al v. BioMarin Pharmaceutical Inc.*, PGR2026-00013, which was instituted on May 6, 2026 (*see* EX1065), as a party pursuant to the joinder provisions of 37 C.F.R. §42.222(b), as explained in the motion for joinder filed concurrently with this Petition.

This Petition is substantively identical to Ascendis’s petition filed in PGR2026-00013 (EX1064), except for Petitioner-specific mandatory notices and minor changes to comply with word limitations.

The ’106 patent is directed to C-type natriuretic peptide (CNP) variants for treating skeletal dysplasia in children. Skeletal dysplasia is a class of genetic disorders affecting bone and/or cartilage growth, and includes achondroplasia—the most common form of short limb dwarfism in humans. Claim 1 of the ’106 patent recites a method of treating skeletal dysplasia in “a subject about 0 month to about 2 years old” comprising administering to the subject a CNP variant selected from a Markush group of 65 different peptides. As this Petition shows, the ’106 patent’s claimed method uses a CNP variant that was already known in the prior art for treating skeletal dysplasia in children: vosoritide, also known as “Pro-Gly-CNP37.”

Before the '106 patent was ever filed, vosoritide was already in phase 3 clinical trials for treating children as young as 5 years old and was in phase 2 clinical trials for treating children 0 to 5 years old—encompassing the '106 patent's claimed subpopulation of “about 0 month to about 2 years old.” As shown herein, the claimed methods are not only obvious over the prior art, they are expressly anticipated. The '106 patent should never have issued.

During examination, Patent Owner BioMarin Pharmaceutical Inc. (“PO”) conceded (i) that the prior art demonstrated that vosoritide could successfully treat achondroplasia in children as young as 5 years old; and (ii) that the prior art suggests administering vosoritide to treat achondroplasia in children between 0 to 2 years old, as claimed. PO, however, convinced the Examiner that a person of ordinary skill in the art would not have had a reasonable expectation of successfully treating the *claimed subpopulation* of about “0 month to about 2 years old.” New evidence presented with this Petition shows that PO's arguments were unfounded, and the Examiner erred in allowing the '106 patent to issue. It would have been obvious to treat the claimed subpopulation of subjects “about 0 month to about 2 years old” with the CNP variant known in the art as vosoritide. *See e.g., Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1099-01 (Fed. Cir. 2015) (finding that it would have been obvious to treat the claimed subpopulation of irritable bowel syndrome patients based on common practices in the field).

First, new evidence shows that claims 1-14 of the '106 patent would have been obvious over prior art that was not before the Examiner. Högler explains that infants with achondroplasia had significantly increased risk of fatal respiratory complications due to a condition known as foramen magnum stenosis (a narrowed opening at the bottom of the skull), which can cause cervical compression and “sudden infant death.” EX1007, 105. Pauli states that the risk of sudden death due to foramen magnum stenosis in infants with achondroplasia was considered “substantial,” and estimated to be “as high as 7.5%.” EX1006, 10. Before the '106 patent was filed, the field was already focused on using CNP variants to reduce or eliminate complications from foramen magnum stenosis in achondroplasia. EX1007, 108-109; EX1006, 41; EX1017, 1533. Meanwhile, the CNP variant vosoritide was in clinical trials demonstrating success in treating achondroplasia. Savarirayan disclosed in 2019 using vosoritide to successfully treat achondroplasia in children as young as 5 years old, and that phase 2 trials were underway for treating achondroplasia in children 0-5 years old. EX1005, 34. As Dr. Abuzzahab explains, there were at least two clear and strong motivations in the art to administer vosoritide to infants with achondroplasia (i) to reduce or eliminate fatal complications associated with foramen magnum stenosis and (ii) to mitigate the loss of height due to abnormal bone growth. Neither Högler nor Pauli were before the Examiner.

Also absent from the Examiner's assessment of the prior art was evidence related to the aberrant signaling pathway associated with achondroplasia irrespective of age. Achondroplasia is primarily caused by a mutation in the gene for fibroblast growth factor receptor 3 (FGFR3), resulting in constitutively active FGFR3 signaling that causes abnormal bone growth. CNP was known to counteract this FGFR3-dependent abnormal bone growth. Thus, CNP variants like vosoritide were developed to inhibit the constitutively active FGFR3 signal. Record evidence shows that the constitutive FGFR3 signaling present in, e.g., 5-year-old children with achondroplasia (who were known to be successfully treated with vosoritide), was also present in *infants* with achondroplasia. A skilled artisan would have had no reason to expect vosoritide to inhibit the FGFR3 signaling pathway any differently in infants than it was shown to do in 5-year-old children. Thus, contrary to PO's prosecution arguments, a person of ordinary skill in the art would have reasonably expected vosoritide to successfully treat achondroplasia in infants, (i.e., <1 year old) who fall within the claimed age range of "about 0 month to about 2 years old," just as it was already shown to work in children 5 years old. By 2019, PO had already initiated phase 2 clinical trials of vosoritide "in infants and younger children (age range, 0 to <60 months)" and stressed the "benefits of early treatment" of achondroplasia in "infants and toddlers ages 0-5 years." EX1005, 34; EX1043, 23, 26; EX1006, 41.

Second, the Examiner erred by failing to realize that the '106 patent's claimed method is anticipated by PO's own prior art patent, Wendt-242. While Wendt-242 was submitted to the Office in an IDS, the Examiner failed to raise it in an Office Action. As Dr. Abuzzahab explains, Wendt-242 expressly discloses each and every claim element of claims 1-7 and 9-14, arranged as claimed. The Examiner's failure to raise Wendt-242 as an anticipatory reference was another material error. *Ecto World, LLC v. Rai Strategic Holding Inc.*, IPR2024-01280, Paper 13 at 5-6 (PTAB May 19, 2025) (precedential).

Third claims 1-14 are unpatentable under 35 U.S.C. § 112(a) for lack of enablement. Claim 1 recites treating "skeletal dysplasia" in a "subject" with a "CNP variant" selected from a Markush group of 65 variants. The patent defines the "subject" of the claims as encompassing *mammals and non-mammals*, extending the scope of the challenged claims to encompass tens of thousands of different animal species. Meanwhile, the claim term "skeletal dysplasia" represents a diverse genus of *hundreds* of different conditions with varying pathologies, and the claimed Markush group of CNP variants introduces yet another vast genus of peptides with varying half-lives and pharmacokinetic properties. A claim reciting any one of these genera alone would have enormous scope, yet here, all three massive genera are combined in claim 1. None of the dependent claims limits at least the scope of "subject." While the level of skill in the art is high, the '106 patent fails to provide

any “meaningful guidance or working examples, across the full scope of the claim”—which encompasses treating hundreds of different skeletal dysplasias across myriad different animal species using a diverse genus of CNP variants with varying activities. *Id.*, 1162. The facts of this case can “only support a finding of non-enablement.” *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1161-1162 (Fed. Cir. 2019). There is no question that a skilled artisan would have had to engage in undue experimentation to practice the full scope of the claims. In fact, it would have been well-nigh impossible.

Fourth, claim 8 is unpatentable under § 112(d) for failing to further limit the claim from which it depends. As discussed herein, claim 8 recites optional language, failing to limit the claim from which it depends. Claim 8 also introduces inconsistency with the claim from which it depends, rendering claim 8 unpatentable.

Claims 1-14 of the ’106 patent are unpatentable and should be canceled.

II. REQUIREMENTS FOR PGR

A. Grounds for Standing

Pursuant to 37 C.F.R. §42.204(a), Zydus certifies that, while the ’106 patent issued more than 9-months ago and would not ordinarily be available for a PGR, under the present circumstances—because the Ascendis PGR on the ’106 patent was instituted on May 6, 2026—the ’106 patent is available for PGR under 37 C.F.R. §42.222(b), which permits requests for joinder “no later than one month after the

institution date of any post-grant review for which joinder is requested,” here June 6, 2026. Thus, Zydus respectfully requests that it be joined to Ascendis’s PGR as a party by virtue of the joinder provisions of 37 C.F.R. §42.222(b). Zydus believes this issue to be one of first impression—i.e., whether 37 C.F.R. §42.222(b) permits a party to join a PGR proceeding that is not within the 9-month window for filing a PGR.

Zydus is not barred or estopped from requesting PGR challenging Claims 1-14.

III. STATEMENT OF PRECISE RELIEF REQUESTED AND REASONS THEREFOR (37 C.F.R. §42.22(A))

Petitioners request PGR, seeking cancellation of claims 1-14 of the ’106 patent (EX1001), assigned to BioMarin Pharmaceutical Inc. Each claim is unpatentable under AIA 35 U.S.C. §§ 103 and 112. Claims 1-7 and 9-14 are also unpatentable under AIA 35 U.S.C. § 102. The Petition is supported by the declaration of Dr. Jennifer Abuzzahab, M.D. (EX1003), a pediatric endocrinologist and Board-certified physician in Pediatrics and Pediatric Endocrinology and an expert in pediatric endocrinology. EX1003, ¶¶4-8; EX1004.

IV. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. §42.204(B))

Petitioners request PGR based on the grounds summarized below.

Ground	35 U.S.C. Section	Claims	References
1	§ 103	1-10, 13-14	Högler and Savarirayan
2	§ 103	11-12	Högler, Savarirayan, and Bullens
3	§ 103	1-10, 13-14	Pauli and Savarirayan
4	§ 103	11-12	Pauli, Savarirayan, and Bullens
5	§ 102	1-7, 9-14	Wendt-242
6	§ 112(a) (enablement)	1-14	N/A
7	§ 112(d) (improper dependent claim)	8	N/A

The asserted references are prior art for at least the following reasons. Högler *et al.*, *Wiener Medizinische Wochenschrift*, 170:104-111(“Högler”; EX1007), published on March 6, 2020.

Pauli, *Orphanet Journal of Rare Diseases*, 14:1-49 (“Pauli”; EX1006), published on January 3, 2019.

Savarirayan *et al.*, *The New England Journal of Medicine*, 381:25-35 (“Savarirayan”; EX1005), published on July 4, 2019.

U.S. Patent No. 9,907,834 (“Bullens”; EX1008) issued on March 6, 2018.

U.S. Patent No. 8,198,242 B2 (“Wendt-242”; EX1023) issued on June 12, 2012.

Each of Högler, Pauli, Savarirayan, Bullens, and Wendt-242 published or were issued more than one year before the '106 patent's earliest claimed priority date (July 9, 2021). Thus, each reference is prior art to the '106 patent under AIA 35 U.S.C. § 102(a)(1), and none qualifies as an exception under AIA U.S.C. § 102(b)(1). Högler and Pauli were not cited during the '106 patent's prosecution. Savarirayan and Wendt-242 were submitted in an IDS during the '106 patent's prosecution, but the Examiner failed to rely on them for any rejections. *Ecto World*, at 5-6.

V. PERSON OF ORDINARY SKILL IN ART

A POSA is a hypothetical person, presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. Here, a POSA would have possessed a strong understanding of treating pediatric skeletal dysplasias, including achondroplasia. EX1003, ¶10. 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. *Id.*

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. *Id.*, ¶11. 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. *Id.*

VI. STATE OF THE ART BEFORE JULY 9, 2021

The following is a summary of what a POSA would have known before July 9, 2021, regarding the '106 patent's field of art.

A. Achondroplasia is a skeletal dysplasia, which is a genetic disorder that affect bones and cartilage

POSAs understood that skeletal dysplasias are a “clinically and genetically heterogeneous group of disorders of bone and/or cartilage.” EX1018, Abstract; EX1025, Abstract, 2417; EX1003, ¶¶12-17. The underlying genes involved in skeletal dysplasias were known to be “diverse” and a POSA would have understood the term “skeletal dysplasia” to include a broad set of indications, caused by a diverse mutations. EX1025, 2417; EX1003, ¶¶12-13.

Before July 9, 2021, achondroplasia was recognized both as the most common type of skeletal dysplasia and the most common form of dwarfism. EX1015, 8; EX1035, 162; EX1003, ¶14. Achondroplasia is characterized by short stature due to disproportionately short limbs, and abnormal growth in long bones (such as the femur and the humerus) and some craniofacial bones. EX1035, 162, 166; EX1012, 291; EX1010, 3-5; EX1003, ¶14. Some of the other common features of

achondroplasia include a narrowing of the opening in the base of the skull where the brain connects to the spinal cord (known as foramen magnum stenosis) and a narrowing of the backbone around the spinal cord (known as spinal stenosis). EX1012, 291; EX1010, 3-5; EX1003, ¶14. Foramen magnum stenosis and spinal stenosis were known to play a significant role in achondroplasia patient morbidity and mortality, particularly in infants. *Id.* For example, foramen magnum stenosis “can cause cervical cord compression leading to respiratory failure and sudden infant deaths.” EX1007, 105; EX1003, ¶¶14, 23, 61; *see also* EX1006, 9.

Short stature in achondroplasia is caused by a defect in “endochondral ossification,” a process by which long bones grow. EX1011, 1446; EX1042, 4977; EX1013, 1577, FIG. 1; EX1044, 439; EX1014, 2842; FIG. 2; EX1051, 8; EX1007, 109; EX1003, ¶¶15, 17. Endochondral ossification occurs in structures called “growth plates,” (also known as epiphyseal plates) found close to the ends of long bones. *Id.* Long bone growth depends on an “intricate balance between chondrocyte proliferation ... and chondrocyte death,” and this growth occurs until “epiphyseal closure,” when the growth plates close after puberty. EX1013, FIG. 1; EX1016, Abstract; EX1007, 109; EX1051, 8; EX1060, 5; EX1058, 5; EX1035, 166; EX1051, 10; EX1003, ¶¶15-17. Foramen magnum stenosis and spinal stenosis are caused by “premature closure of synchondroses (cartilaginous joints).” EX1007, 106; EX1003, ¶22. “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; EX1003, ¶22.

Before July 9, 2021, POSAs knew that achondroplasia and its features were caused by an autosomal dominant mutation in the gene for fibroblast growth factor receptor 3 (FGFR3) that made FGFR3 constitutively active. EX1035, Abstract, FIG. 3; EX1007, 105; EX1017, 1526; EX1005, 26; EX1003, ¶¶17, 26, 28. This constitutive FGFR3 signaling activates downstream MAPK signaling pathway and “inhibits chondrocyte differentiation and *puts a break on growth plate function*¹, in addition to causing serious medical complications such as *foramen magnum* and spinal *stenosis* and upper airway narrowing.” EX1007, Abstract, 105; EX1003, ¶¶17, 26, 77, 82; *see also* EX1042, FIG. 8, 4984 (noting that FGFR3 signaling “dramatically inhibit[ed] ... chondrocyte proliferation ... and differentiation,” slowing bone growth).

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

POSAs knew that in children with achondroplasia, the “[l]oss in height position ... occurred mainly during first 2 years of life.” EX1027, Abstract, 1725, 1728; EX1007, 105; EX1054, 401-402; EX1055, 4, 6; EX1003, ¶¶18-21. For

¹ Emphasis has been added throughout this Petition, unless stated otherwise.

example, Merker reported in 2018 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*.” EX1027, 1725, FIG. 2; EX1003, ¶¶18-19; *see also*, EX1055, 6.

POSAs understood that the reason for meaningful height loss occurring in the first 2 years of life was likely related to FGFR3 signaling. EX1003, ¶19. As Merker explained, “FGFR3 signaling might be more dominant during [infancy], or might play a different role than in later growth periods.” EX1027, 1728; EX1003, ¶¶19-21; EX1012, 299. Thus, the art taught that the greater chance of reducing height loss in children with achondroplasia was afforded when treating within the first 2 years of life. *Id.* Högler stated in 2020, “short stature syndromes by definition necessitate intervention in the young.” EX1007, 109; *see also*, EX1055, 4, 6; EX1054, 401; EX1012, 299; EX1003, ¶¶19-21.

C. The art taught that children with achondroplasia have an increased risk of death in the first two years of life due foramen magnum stenosis

Before July 9, 2021, POSAs understood that infants with achondroplasia often suffered from severe and life-threatening respiratory complications. EX1003, ¶¶22-25. Infants with achondroplasia have an increased risk of a narrowing of the opening in the base of the skull where the brain connects to the spinal cord, a condition known

as foramen magnum stenosis. EX1006, 9; EX1003, ¶22. Foramen magnum stenosis was known to cause “cervical cord compression leading to respiratory failure and sudden infant deaths.” EX1007, 105; EX1017, 1526 (“[f]oramen magnum stenosis can cause hydrocephalus, potentially resulting in brainstem compression, apnea, or sudden death.”); EX1006, 9 (discussing “apneic death” in infants with foramen magnum stenosis “aris[ing] from compression of vertebral arteries at or near the craniocervical junction.”); EX1003, ¶¶23-24, 61, 77. POSAs understood that the risk of death during the first year of life from foramen magnum stenosis complications is significant. As Pauli explained, “risk for death in the first year of life may be as high as 7.5%.” EX1006, 10; EX1007, 105 (“[t]he risk of death was increased approximately 6-fold....”); EX1003, ¶¶23-24, 120.

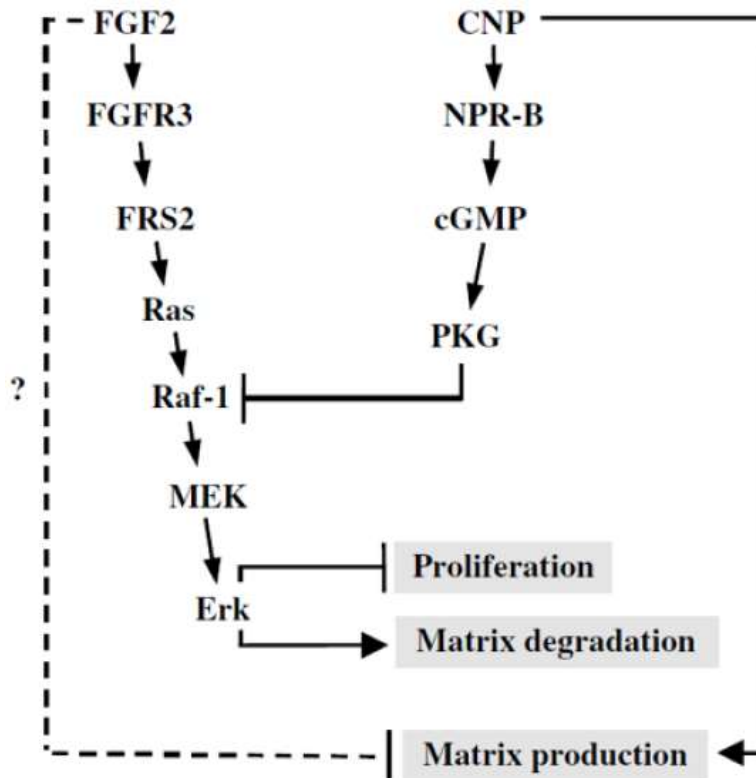
Before July 9, 2021, the art taught that treating achondroplasia with peptides called C-type natriuretic peptides (CNP) and variants thereof could reduce or eliminate foramen magnum stenosis and its associated complications. EX1003, ¶¶76, 133-135. For example, Yamanaka demonstrated that overexpressing CNP in a mouse model of achondroplasia resulted in “significantly ameliorated” foramen magnum stenosis. EX1017, Abstract, 1533; EX1003, ¶ 79, 129. Yamanaka’s results “clearly demonstrate the therapeutic potential of CNP for treatment of . . . foramen magnum stenosis in achondroplasia.” *Id.*; EX1003, ¶¶76-79, 129; *see also*, EX1007, 105, 108; EX1006, 10-11, 41.

POSAs also understood that, to increase the chances of preventing sudden death in infants with foramen magnum stenosis from achondroplasia, “preventative assessments ... must be completed *early in infancy*.” EX1006, 9; EX1003, ¶24, 120. As Hogler explained, “[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; *see also*, EX1017, 1533 (“*early administration* of CNP or a CNP analogue maybe an important determinant of clinical effectiveness.”); EX1012, 299; EX1003, ¶¶24-25, 62, 77-78, 128. Thus, POSAs knew that the sooner treatment could be administered to an infant, the better. *Id.*

D. The art taught that C-type natriuretic peptide (CNP) counters FGFR3 signaling and plays a role in bone growth in the first two years of life

Before July 9, 2021, POSAs understood that C-type natriuretic peptide (CNP) is a type of natriuretic peptide that plays an important role in bone and cartilage growth and counteracts the FGFR3 signaling pathway. EX1019, 5090; EX1020, 210; EX1003, ¶¶26-27. CNP was well known as an “important regulator of cartilage homeostasis and endochondral bone growth,” with animal studies demonstrating that eliminating CNP expression results in dwarfism, and overexpressing CNP leads to skeletal overgrowth. EX1020, Abstract, 212; EX1003, ¶26.

The art taught that upon binding to its cellular receptor NPR-B CNP causes bone growth by inhibiting FGFR3 signaling. EX1019, 5089. The figure below from Krejci 2005 illustrates the known interplay between CNP and FGFR3 signaling.



EX1019, FIG. 10; EX1003, ¶26.

CNP was known to be crucial for bone growth in the first two years of life. EX1003, ¶¶26-27, 85. Acromesomelic dysplasia, type Maroteaux (AMDM) patients were known to have a loss-of-function mutation in the CNP receptor (NPR-B), which prevents CNP from binding to NPR-B and triggering a cellular response. EX1031, 27-28; EX1003, ¶¶26-27, 85. As a result, in AMDM patients, the “skeletal growth falls off sharply after birth, so that a skeletal disorder is strongly suspected

in most affected individuals by 1 year of age” and “by years of age . . . abnormal growth plates and short, mis-shapen bones in the extremities [] and spine” are observed. *Id.*

Given CNP’s known interaction with the FGFR3 signaling pathway, CNP and variations of CNP were studied intensely and developed as therapeutic agents to inhibit FGFR3 signaling. *See e.g.*, EX1017, Abstract; EX1005, 25; EX1043, 23-27; EX1007, 108; EX1006, 41; EX1008, 25:36-3:39; EX1024, 140:30-142:22; EX1003, ¶¶28-31; EX1020, 213. CNP was identified as existing in two forms: a peptide consisting of 53 amino acids (CNP-53), and a truncated version of 22 amino acids (CNP-22). EX1021, 25852; EX1022, 608-09; EX1003, ¶27. Thus, before July 9, 2021, the art routinely identified CNP variants with a number next to the acronym “CNP” to indicate its length. EX1041, ¶[0018]; EX1026, Abstract, 459; EX1003, ¶27. Typically, intermediate numbers (*e.g.*, CNP-37) were known to refer to the number of amino acids in the sequence of CNP-53, counting from the C-terminus. *Id.* For example, the table below shows the sequences of CNP-53, CNP-37, and CNP-22, as they would have been understood to a POSA before July 9, 2021. *Id.*

NAME	SEQUENCE
CNP-53	DLRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLK LDRIGSMSGLGC
CNP-37	QEHPNARKYKGANKKGLSKGCFGLKLDRI SMSGLGC
CNP-22	GLSKGCFGLKLDRI SMSGLGC

EX1003, ¶27.

POSAs understood that different CNP variants had different pharmacokinetic characteristics, making some variants more viable therapeutic agents than others. EX1003, ¶27. For example, CNP-22 was known to have a short half-life of only a few minutes. EX1062, 346; EX1009, Abstract; EX1026, Abstract, 459. Longer CNPs were known to have longer half-lives. EX1062, 346 (“differences in half-life (longer in larger peptides) are likely to materially affect their potency in vivo ...”); EX1003, ¶¶27, 184.

E. The art taught that vosoritide, a CNP variant with a longer half-life than CNP-22, is useful for treating achondroplasia in children

Given the short half-life of naturally occurring CNP-22, the field developed modified versions of CNP to increase its half-life and suitability as a therapeutic agent for treating achondroplasia. EX1009, Abstract; EX1026, Abstract, 459-460; EX1012, 302; EX1063, 1108; EX1003, ¶¶28-31. Examples of such modified CNP variants included peptides longer than CNP-22, peptides with polyethylene glycol chains appended to them (PEGylated CNP peptides), or both. *Id.*

Before July 9, 2021, vosoritide (also known as “BMN-111”) was a well-known CNP variant already in clinical trials for treating children with achondroplasia. EX1005, 25; EX1007, 108; EX1043, 21-27; EX1006, 41; EX1003, ¶¶29-31. As Savarirayan explained, vosoritide is a CNP variant “developed to have a longer half-life than its endogenous form in order to prolong pharmacologic activity.” EX1005, 26; *see also* EX1063, 1108 (“BMN 111 [vosoritide] mimics CNP

pharmacological activity and has an extended half-life as a result of neutral-endopeptididase (NEP) resistance that allows one-daily SC administration.”). The amino acid sequence of vosoritide was known in the art since at least 2012, when Lorget disclosed that “BMN 111 is a 39 amino acid CNP pharmacological analogue. Its sequence is 1 PGQEHPNARK YKGANKKGLS KGCFGLKLDR IGSMSGGLGC 39.” EX1063, FIG. S2; EX1053, 197; EX1003, ¶¶29-31. Breinholt explained that “[v]osoritide 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; EX1003, ¶29. Thus, POSAs also referred to vosoritide as “PG-CNP37” or “Pro-Gly-CNP37.” EX1053, 196; EX1008, 4:44-45, 4:52-53, 14:54-55; EX1003, ¶29.

Before July 9, 2021, Savarirayan reported that treating pediatric achondroplasia patients with vosoritide “resulted in a sustained increase in the annualized growth velocity” at doses of 15.0 and 30.0 µg/kg of body weight. EX1005, 25; EX1003, ¶31. Savarirayan described “an ongoing ... clinical trial (NCT03583697) of vosoritide in infants and younger children (age range, 0 to <60 months).” EX1005, 34. Pauli similarly disclosed in 2019 that vosoritide was “currently” in an “expanded phase 2 trial in infants and young children” and there was “active recruitment for a phase 3 trial.” EX1006, 41; *see also*, EX1007, 108. PO itself disclosed in 2020 a phase 2 study “expanding [the] vosoritide patient

population to include infants and toddlers ages 0-5 years to provide maximum benefit.” EX1043, 26; EX1003, ¶31. According to PO’s 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; EX1003, ¶31.

VII. THE ’106 PATENT AND ITS PROSECUTION HISTORY

A. The ’106 patent

The ’106 patent issued on February 25, 2025, from U.S. Patent Application 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 C-type natriuretic peptide (CNP) variants to “treat skeletal dysplasias in children, for example, “children between 2 and 5 years old, and in particular children less than or about 2 years old,” or “about 6 months to about 2 years old,” “0 to about 6 months old,” or “about 3 to about 6 months old,” or “0 to about 3 months.” EX1001, 3:47-55, 4:1-18, 12:55-61. The ’106 patent lists achondroplasia (the most common form of dwarfism) as an example of skeletal dysplasia. *Id.*, 3:12-19; EX1003, ¶32.

As examples of CNP variants, the '106 patent discloses truncated versions of wild-type CNP-53 (e.g., CNP-18 through CNP-52), modified CNPs with substitutions or additions compared to the wild-type CNPs (such as vosoritide, also called Pro-Gly-CNP37 or BMN111), and CNPs conjugated to synthetic polymeric groups (e.g., PEG). EX1001, 5:20-9:30, 18:66-19:26, 19:50-23:14, 23:16-24:67; EX1003, ¶32. The '106 patent discloses a single working example, which is directed to a method of treating “[a]chondroplasia patients 0-5 years old” by administering the CNP variant, vosoritide. EX1001, 39:25-50:12. Claim 1 (the sole independent claim) recites:

A method of treating skeletal dysplasia in a subject about 0 month to about 2 years old 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, wherein the CNP variant is selected from the group consisting of:

(Pro-Gly-CNP37) (SEQ ID NO: 1)

PGQEHPNARKYKGANKKGLSKGCFGLKLD RIGSMSGLGC; ...

(CNP-52) (SEQ ID NO: 6)

LRVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLD RIGSMSGLGC;

(CNP-51) (SEQ ID NO: 7)

RVDTKSRAAWARLLQEHPNARKYKGANKKGLSKGCFGLKLD RIGSMSGL
GC; ...

(CNP-37) (SEQ ID NO: 21)

QEHPNARKYKGANKKGLSKGCFGLKLD RIGSMSGLGC; ... and

[PEO24-Met-CNP27 (K4, 5, 9R)] (SEQ ID NO: 65)

PEO24-MGANRRGLSRGCFGLKLD RIGSMSGLGC

EX1001, 63:37-67:40; EX1003, ¶33.

The dependent claims 2-14 add various elements, e.g., dosing regimen, administration route, dose, subject age, type of skeletal dysplasia, or CNP variant. EX1001, 67:41-69:10; EX1003, ¶33.

B. Prosecution History of the '106 Patent

The Examiner issued a single Office Action on the merits, rejecting the original claims under §§ 103 and 112. The Examiner rejected original claims 1 and 8-20 as obvious over US Patent No. 9,907,834 (Bullens; EX1008) and WO 2009/067639 (the '639 publication; EX1046). EX1002, 906-910; EX1003, ¶¶34-35. The Examiner found, *inter alia*, that Bullens teaches “instant SEQ ID NO: 1 [i.e., vosoritide] ... and instant SEQ ID NO: 41 ... for treating patients with skeletal

dysplasia,” including “achondroplasia.” EX1002, 907-908; EX1003, ¶34. The Examiner found that the ’639 publication teaches “CNP variants that are useful as therapeutics for treatment of ... achondroplasia,” and that “the ideal age range of achondroplasia patients will be from infant (<1 year of age) to preadolescent (< 13 years of age).” EX1002, 909, EX1003, ¶34. The Examiner concluded that it would have been obvious to combine the teachings of Bullens and the ’639 publication to arrive at the claimed method. EX1002, 909-910; EX1003, ¶34. The Examiner rejected dependent claims 12 and 14 for failing to further limit the claims from which they depend, and dependent claim 15 for indefiniteness. EX1002, 904-906; EX1003, ¶35.

In response, PO amended the claims to overcome the § 112 rejections. EX1002, 916-926, 934-935; EX1003, ¶36. In rebutting obviousness, PO admitted that the ’639 publication “discloses that younger children suffering from achondroplasia *could* benefit from treatment with CNP,” but argued that actual “treatment of the patient population in the claims had heretofore not been disclosed and the treatment effect could not have been predicted in this patient population.” EX1002, 936; EX1003, ¶36. PO conceded there was a suggestion in the prior art to treat achondroplasia in the subject population of the claims, but argued that Bullens and the ’639 publication “only disclose the effects of CNP therapy *in children over 5 years old*,” and that “[n]othing in the cited art would have provided a reasonable

expectation of success that the same or higher dosage of CNP would have been effective in children under the age of 2.” EX1002., 936l EX1003, ¶36.

After an Examiner Interview (EX1002, 938), the Examiner allowed the claims, stating 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; EX1003, ¶37.

As discussed below, the Examiner erred in failed to identify Högler and Pauli during examination, and failed to consider Wendt-242 as an anticipatory reference.

VIII. CLAIM CONSTRUCTION

Claim terms are generally given their ordinary and customary meaning—“the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc); 37 C.F.R. § 42.200(b).

A. “Subject”

Claims 1, 3, and 6-8 recite the term “subject.” EX1001, 63:36-67:60. The ’106 patent 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; EX1003, ¶52.

Thus, “subject” in the challenged claims should be construed as encompassing mammals and non-mammals. EX1003, ¶¶53-55.

B. “Amount effective to treat”

Claim 1 recites the term, “amount effective to treat.” EX1001, 63:37-42. The ’106 patent does not define this exact phrase. However, it defines the terms “effective amount” and “treatment” as follows:

The term “effective amount” means a dosage sufficient to produce a desired result on a health condition, pathology, or disease of a subject or for a diagnostic purpose. The desired result may comprise a subjective or objective improvement in the recipient of the dosage.

“Treatment” refers to prophylactic treatment or therapeutic treatment or diagnostic treatment. In certain embodiments, “treatment” refers to administration of a compound or composition to a subject for therapeutic, prophylactic or diagnostic purposes.

EX1001, 17:28-50; EX1003, ¶56.

Thus, “amount effective to treat” should be construed 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.
EX1003, ¶56.

IX. GROUND 1: CLAIMS 1-10 AND 13-14 WOULD HAVE BEEN OBVIOUS OVER HÖGLER AND SAVARIRAYAN

A. Claim 1

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

a. “A method of treating skeletal dysplasia in a subject about 0 month to about 2 years old”

Högler reviews “new developments in the management of achondroplasia.” EX1007, Title; EX1003, ¶60. Högler explains that achondroplasia is a form of skeletal dysplasia. 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.”); EX1003, ¶¶59-60; *see also*, EX1005, 26; EX1001, claims 13-14 (reciting achondroplasia as one of the claimed skeletal dysplasias).

Högler 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, 105. Högler teaches that “foramen magnum stenosis, which can cause cervical cord compression leading to respiratory failure and sudden *infant* deaths,” is one of the contributing factors to an “increased risk of *first-year* deaths in infants with achondroplasia,” with one study

reporting a 6-fold increased risk. *Id.*, 105. 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.*” *Id.*, 106.

Högler identifies short stature in achondroplasia patients, which though “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. Högler teaches that achondroplasia patients experience “the main loss of height [] *in the first 2 years of life*” and that “short stature syndromes [like achondroplasia] by definition *necessitate intervention in the young*, prior to epiphyseal closure.” EX1007, 105, 109. As Dr. Abuzzahab explains, epiphyseal plates remain open in “the first 2 years of life.” EX1003, ¶¶16, 63, 89; EX1016, Abstract; EX1051, 8.

Thus, Högler teaches or suggests treating achondroplasia (a skeletal dysplasia) in infants “shortly after ... birth” and in “the first 2 years of life” to mitigate foramen magnum stenosis complications and loss of height. EX1007, 105, 106; EX1003, ¶¶58-65. POSAs would have known infants to be 0 months to <1 year old. EX1003, ¶¶60-63, 65; EX1023, 140:6-8. Högler’s disclosure of treating achondroplasia in “infants” (i.e., 6 weeks to 2 years old) falls within the claimed age

range of subjects “about 0 month to about 2 years old” and thus teaches this claim element. EX1003, ¶¶60-65.

Savarirayan reports the results from clinical studies of treating “children (5 to 14 years of age) with achondroplasia.” EX1005, Abstract. Savarirayan discloses an on-going clinical trial (NCT03583697) treating achondroplasia in “*infants* and younger children (age range, *0 to <60 months*)” with vosoritide (one of the claimed CNP variants as explained below). EX1005, 34. Savarirayan’s disclosure of treating achondroplasia in “infants” (i.e., 0 months to 1 year old) falls within the claimed age range of subjects “about 0 month to about 2 years old” and thus teaches this claim element. EX1003, ¶65; EX1005, 34. Likewise, Savarirayan’s disclosure of treating achondroplasia in children “age range 0 to < 60 months” (i.e., 0 to < 5 years) overlaps with the claimed age range of “about 0 month to about 2 years old,” and renders this claim element obvious. *Id.*; *In re Peterson*, 315 F.3d 1325, 1329-1330 (Fed. Cir. 2003).

Thus, Högler and Savarirayan teach or suggest a method of treating achondroplasia (a skeletal dysplasia) in a subject about 0 month to about 2 years old, as claimed.

b. “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”

Högler discloses administering the CNP variant, vosoritide, in an amount effective to treat skeletal dysplasia. Specifically, Högler describes the results of clinical studies (“NCT02055157 and NCT02724228”) which involved treating “35 children with achondroplasia” by administering vosoritide at “a dose of 15mcg/kg.” EX1007, 108; EX1003, ¶66. A POSA would have understood that Högler discloses an “amount effective to treat skeletal dysplasia” because Högler teaches that the “first 6 months of treatment demonstrated a dose-dependent increase in the annualized growth velocity, and a sustained increase in annualized growth velocity of 1.5 cm/year.” EX1007, 108; EX1003, ¶66.

Savarirayan also discloses this claim element because, e.g., Savarirayan reports the results of the same clinical studies disclosed in Högler (along with a third study, NCT01603095). Savarirayan discloses 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; EX1003, ¶66. Savarirayan explains that “vosoritide is a biologic analogue of C-type natriuretic peptide.” *Id.* A POSA would have known that Savarirayan discloses an “amount effective to treat skeletal dysplasia” because Savarirayan teaches that the vosoritide treatment resulted in “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.” EX1005, Abstract, 25, 34; EX1003, ¶66.

As discussed above in Section VII, the phrase “amount effective to treat” should be construed 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. EX1003, ¶56. The ’106 patent discloses that “improvement in one or more symptoms of skeletal dysplasia” includes “*improved or increased growth velocity*.” EX1001, 4:19-26; *see also, id.*, 29:4-6 (disclosing that “efficacy is assessed as the change in *annualized growth velocity* from the baseline period to the intervention period”; EX1003, ¶56. Because Högler and Savarirayan each teaches that the vosoritide treatment improves annualized growth velocity, each reference teaches administering vosoritide in “an amount effective to treat” achondroplasia according to the ’106 patent’s criteria. EX1003, ¶66, 68. Thus, Högler and Savarirayan teach or suggest administering a CNP variant (vosoritide) in an amount effective to treat achondroplasia (a skeletal dysplasia). EX1003, ¶66, 68.

c. “wherein the CNP variant is selected from the group consisting of: Pro-Gly-CNP37 . . . ”

As discussed above, both Högler and Savarirayan teach administering vosoritide (BMN111) to children with achondroplasia. EX1007, 108; EX1005, Abstract, 34; EX1003, ¶¶67-68. Before July 9, 2021, POSAs 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”—thus the nomenclature, Pro-Gly-CNP37. EX1026, 460; EX1053, Abstract, 197; EX1063, 1108, FIG. S2; EX1003, ¶29. As Dr. Abuzzahab explains, a POSA would have understood that vosoritide has the same amino acid sequence as Pro-Gly-CNP-37 (SEQ ID NO: 1) recited in claim 1. EX1003, ¶¶29, 67.

Thus, Högler and Savarirayan teach or suggest administering the CNP variant, Pro-Gly-CNP37 (SEQ ID NO: 1), as claimed.

2. A POSA would have been motivated to treat achondroplasia in the infants taught in Högler and Savarirayan with the CNP variant vosoritide taught in Savarirayan

As discussed below, given the ample teachings in the prior art regarding foramen magnum stenosis complications and loss of height in early infancy, it would have been obvious for a POSA to treat achondroplasia in subjects “about 0 month to about 2 years old” with vosoritide. *See e.g., Prometheus*, 805 F.3d at 1099-01 (finding that it would have been obvious to treat the claimed subpopulation of

irritable bowel syndrome patients based on common practices in the field); *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. Of Rheumatology Trust*, 764 F.3d 1366, 1380–81 (Fed. Cir. 2014) (holding that the ordinary artisan would have easily envisaged the claimed subset of rheumatoid arthritis patients); EX1003, ¶¶57, 69–80.

As discussed above, Högler and Savarirayan teach or suggest treating achondroplasia in infants to improve achondroplasia symptoms, particularly foramen magnum stenosis and loss of height. EX1005, 34; EX1007, 105; EX1003, ¶¶58–80. Consistent with Högler, the prior art widely recognized foramen magnum stenosis necessitating treatment in early infancy in achondroplasia children. *See* Section V; EX1003, ¶¶76–80. For example, Yamanaka discloses that “*early administration* of CNP or a CNP analog may be an important determinant of *clinical effectiveness*” to treat narrowing of foramen magnum in achondroplasia subjects. EX1017, 1533. Thus, a POSA would have been motivated to treat achondroplasia in infants to improve achondroplasia symptoms, particularly foramen magnum stenosis and loss of height. EX1003, ¶¶69–80.

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. Similarly, Högler states that the activating FGFR3 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; EX1003, ¶77. In fact, the role of constitutively active FGFR3 signaling and MAPK pathway activation causing achondroplasia and its complications was well known in the art. See Section V; EX1003, ¶77. 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. Thus, a POSA would have been motivated to treat achondroplasia in infants with a therapeutic that counteracts the activated FGFR3 to improve achondroplasia symptoms, particularly foramen magnum stenosis and loss of height. EX1003, ¶¶ 75, 80.

CNPs, such as vosoritide, were known to counteract FGFR3 activation. For example, 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; EX1003, ¶72, 82-84. 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; EX1003, ¶¶74, 79, 81. Savarirayan similarly teaches successfully treating achondroplasia in 5–14-year-old children with vosoritide to increase annualized 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. Savarirayan teaches an on-going clinical trial treating “infants and younger children (age range, 0 to <60 months)” with vosoritide. EX1005, 34; EX1003, ¶¶74.

Thus, to diminish or eliminate the fatal symptom of foramen magnum stenosis and prevent the resulting apneic death or loss of height as early as possible, a POSA would have been motivated to administer vosoritide to treat achondroplasia in infants and young children. EX1003, ¶¶76-80.

3. A POSA would have had a reasonable expectation of successfully treating achondroplasia in the infants taught in Högler and Savarirayan with the CNP variant vosoritide taught in Savarirayan

A POSA reading Högler and Savarirayan would have had a reasonable expectation of successfully treating achondroplasia in infants using vosoritide for several reasons: (1) CNPs, such as vosoritide, were known to target the pathophysiological mechanism (FGFR3 activation) that caused achondroplasia and its complications, such as foramen magnum stenosis, upper airway narrowing and sleep disorders, and short stature; (2) CNP signaling was known to be crucial for

bone growth in first 2 years of life; and (3) CNP treatment was known to successfully treat achondroplasia and its complications in young mice and achondroplasia children. EX1003, ¶¶81-90.

First, CNP was known to rescue the pathophysiological mechanism causing achondroplasia and its symptoms. EX1003, ¶82. POSAs would have known that achondroplasia and its symptoms, such as foramen magnum stenosis and short stature, are caused by FGFR3 activating mutations. EX1003, ¶82. For example, 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; EX1003, ¶82. 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; EX1003, ¶¶77, 82-83; *see also* EX1017, 1526 (stating that the “developmental mechanisms of . . . foramen magnum stenosis in achondroplasia are related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes”).

POSAs would have known that CNPs, including vosoritide, treat achondroplasia and its symptoms by countering the FGFR3 activation. EX1003, ¶¶83-84, 87-88. For example, 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. Savarirayan teaches that “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. Similarly, 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.” EX1017, 1533. Thus, POSAs would have reasonably expected that vosoritide would inhibit FGFR3 signaling and reduce or eliminate the pathophysiological mechanism causing achondroplasia and its symptoms.

Second, based on the disorders in infants resulting from CNP receptor mutations, POSAs would have known that CNP signaling was crucial for bone growth in the first two years of life. EX1003, ¶85. Acromesomelic dysplasia, type Maroteaux (AMDM) patients were known to have a loss-of-function mutation of the cellular receptor to which CNP binds (NPR-B), which prevents CNP from binding

to the receptor and triggering a cellular response. EX1031, 27-28; EX1003, ¶85. In AMDM patients, the “skeletal growth falls off sharply after birth, so that a skeletal disorder is strongly suspected in most affected individuals by 1 year of age” and “by years of age . . . abnormal growth plates and short, mis-shapen bones in the extremities [] and spine” are observed. *Id.* Thus, POSAs would have known that CNP signaling was important for bone growth in 0-2 year old children with achondroplasia. EX1031, 27; EX1003, ¶85. Because epiphyseal plates remain open in 0-2-year-old children with achondroplasia, a POSA would have recognized 0-2-year-old children as prime candidates for successful treatment with vosoritide. EX1016, Abstract; EX1051, 8; EX1003, ¶89.

Third, a POSA would have known that CNP treatment successfully rescued achondroplasia complications, such as foramen magnum stenosis in young mice and bone length in children. EX1003, ¶87. For example, Yamanaka discloses 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; EX1003, ¶87. Höglér also reports that vosoritide treatment in mice with achondroplasia caused “a *significant recovery* of bone

growth” and in 5-14-year-old children caused a “sustained increase in annualized growth velocity.” EX1007, 106; EX1003, ¶¶74, 83. Savarirayan similarly discloses successful clinical results with vosoritide in 5-14 year old children, including a sustained increase in growth velocity. EX1005, 34. Savarirayan discloses “ongoing” clinical trials for treating achondroplasia in infants and younger children ages 0 to 5 years old with vosoritide. EX1005, 34; EX1003, ¶¶86.

Thus, POSAs would have had a reasonable expectation of successfully treating achondroplasia in infants and young children with the CNP variant, vosoritide. Högler and Savarirayan would have rendered claim 1 obvious.

B. Claims 2-4

Claims 2-4 depend from claim 1 and further require that the composition is administered “once daily” (claim 2) or “daily” (claim 4) or “via subcutaneous administration” (claim 3). EX1001, 67:41-52.

Högler and Savarirayan teach or suggest all the elements of claims 2-4. Högler teaches that vosoritide was administered “once daily [by] subcutaneous” injection. EX1007, 108; EX1003, ¶¶93-95. Savarirayan also discloses that children received “vosoritide at a once-daily subcutaneous dose.” EX1005, Abstract; EX1003, ¶¶93-95.

The rationales for obviousness of claim 1 apply to claims 2-4. *See* Section VIII.A. Given the successful treatment of achondroplasia in Högler’s and

Savarirayan's disclosed methods, a POSA would have been motivated to also administer vosoritide subcutaneously once-daily (daily) to infants with achondroplasia. EX1003, ¶¶96-97. A POSA would have had a reasonable expectation of successfully treating achondroplasia symptom, e.g., foramen magnum stenosis or shortened height, in infants. *Id.*

Claims 2-4 would have been obvious.

C. 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" for claim 1's "about 0 months to about 2 year old" subject. EX1001, 63:36-42, 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." EX1001, 67:59-60.

Högler and Savarirayan teach or suggest all the elements of claims 5 and 8. EX1003, ¶¶98-103. Savarirayan teaches administering vosoritide at a dose of "30.0 µg per kilogram," satisfying claim 5. EX1005, Abstract, 27, FIG. 1; EX1003, ¶99. Claim 8 recites that the dosage "*may be decreased* to 15 µg/kg," and thus recites an *optional* limitation. Because claim 8's dosage amount is optional, it does not further limit claim 5. *See In re Johnston*, 435 F.3d 1381, 1384 (Fed Cir. 2006); *Ex parte Schulhauser*, No. 2013-007847, at 9-10 (PTAB, April 28, 2016) (precedential).

Thus, Savarirayan's disclosure of administering vosoritide at 30 µg/kg teaches claim 8 for the same reasons it teaches claim 5.

Even if claim 8's recited dose of 15 µg/kg were limiting, it was taught in the art. Högler discloses administering vosoritide at "a dose of 15 mcg/kg," satisfying claim 8. EX1007, 108; EX1003, ¶¶100-101. Savarirayan similarly discloses administering vosoritide at a dose of "15.0 µg per kilogram." EX1005, Abstract, 25, 34; EX1003, ¶101.

Savarirayan discloses comparing the results of administering vosoritide in 15 µg/kg or 30 µg/kg and concluded 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; EX1003, ¶101.

The rationales for obviousness of claim 1 apply to claims 5 and 8. *See* Section VIII.A. Given the successful treatment of achondroplasia in children 5-14 years old with vosoritide doses of 15 µg/kg or 30 µg/kg in Högler's and Savarirayan's disclosed method, a POSA would have been motivated to also administer these doses of vosoritide to infants or 2-year-old children with achondroplasia. EX1003, ¶103. Infants were known to have a higher metabolic rate for certain drugs than the older children and thus require "higher drug exposures than those needed in older children and adults to achieve adequate treatment effect," with the dose decreasing as the

child ages. EX1033, 11; *see also* EX1059, 737. Thus, a POSA treating infants with vosoritide at a dose of 30 ug/kg (the dose taught in Savarirayan) would have been motivated to decrease the dose of vosoritide to the lower dose (15 µg/kg, as taught in Savarirayan and Högler) when the child turned 2 years old. EX1003, ¶102-103.

A POSA would have had a reasonable expectation of successfully treating achondroplasia symptoms, e.g., foramen magnum stenosis or shortened height, in infants and 2-year-old children. EX1003, ¶103.

Claims 5 and 8 would have been obvious.

D. Claims 6 and 7

Claims 6 and 7 depend from claim 1 and further require that the subject is “about 6 months to about 2 years old” (claim 6) or “about 0 to about 6 months old.” EX1001, 67:55-58.

Högler and Savarirayan teach or suggest all the elements of claims 6 and 7. 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; EX1003, ¶104. A POSA would have understood that treating an infant “shortly after ... birth” suggests treating an age between “about 0 month to about 2 years,” as claimed, because “infants” were generally understood to be 0 months to <1 year old. *See* Section VIII.A.1; EX1003, ¶65; EX1023, 140:6-8. Högler also teaches that “the main loss of height [in

achondroplasia] occurs in the *first 2 years of life*.” EX1007, 105; EX1003, ¶¶58-65. Savarirayan discloses an ongoing clinical trial (NCT03583697) treating achondroplasia in “*infants and younger children (age range, 0 to <60 months)*” with vosoritide. EX1005, 34; EX1003, ¶104. The age ranges taught in Högler and Savarirayan overlap with the claimed age ranges in claims 6 and 7. *Peterson*, 315 F.3d at 1329-1330.

The rationales for obviousness of claim 1 apply to claims 6 and 7. *See* Section VIII.A. Claims 6 and 7 would have been obvious.

E. Claims 9 and 10

Claims 9 and 10 depend from claims 1 and 3, respectively, and further limit the skeletal dysplasia. Claim 9 recites a list of over 40 different types of skeletal dysplasia that includes achondroplasia, and claim 10 is limited specifically to achondroplasia. EX1001, 67:61-68:16; EX1003, ¶106. Both Högler and Savarirayan expressly teach treating achondroplasia. *See* Section VIII.A; EX1007, 106; EX1005, Abstract, 25, 35; EX1003, ¶107.

The rationales for obviousness of claim 1 apply to claims 9 and 10. *See* Section VIII.A. Claims 9 and 10 would have been obvious.

F. Claims 13 and 14

Claims 13 and 14 depend from claim 1 and further limit the CNP variant to a group that includes Pro-Gly-CNP-37 (SEQ ID NO: 1). EX1001, 68:24-69:10. 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. *See* Sections V, VII.A; EX1003, ¶109; EX1007, 108; EX1005, 35.

The rationales for obviousness of claim 1 apply to claims 13 and 14. *See* Section VIII.A. Claims 13 and 14 would have been obvious.

G. Objective indicia do not outweigh the strong case of *prima facie* obviousness

Any potentially relevant objective indicia are insufficient to outweigh this strong *prima facie* case of obviousness. *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

During prosecution, PO 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. However, as explained in detail by Dr. Abuzzahab, the evidence of record contradicts PO’s allegations of unexpected results. *See* Section VIII.A; EX1003, ¶¶91-92. The evidence shows that a POSA would have had a reasonable expectation of successfully treating achondroplasia in subjects about 0 month to about 2 years old with vosoritide, because (i) CNPs, such as vosoritide, were known to target the pathophysiological mechanism (FGFR3 activation) 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) CNP (e.g., vosoritide) treatment was known to successfully treat achondroplasia and its symptoms in young mice and achondroplasia children. EX1007, Abstract, 105; EX1005, Abstract, 34-35; EX1003, ¶81-90; *see Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

PO's alleged evidence of unexpected results is not commensurate with the scope of the '106 patent's broad claims. As discussed below in Section XIII, the claimed method encompasses three enormous genera of subjects, CNP variants, and skeletal dysplasias, encompassing millions of wildly varying embodiments. PO's purported evidence of unexpected results, however, is limited to treating a single species of skeletal dysplasia (achondroplasia) in a single species of subject (human children) using a single species of CNP variant (vosoritide). EX1002, 936-937; EX1001, 39:30-50:12; EX1003, ¶92. "[O]bjective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014). That includes evidence of unexpected results. *Id.*; *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Thus, at least for this additional reason, PO's evidence of unexpected results cannot overcome the case of *prima facie* obviousness.

Should PO submit any alleged objective evidence or arguments in its preliminary response, the Board should nonetheless institute trial. *Amneal Pharms.*,

LLC v. Supernus Pharms., Inc., IPR2013-00368, Paper 8, at 12-13 (P.T.A.B., Dec. 17, 2013).

X. GROUND 2: CLAIMS 11-12 WOULD HAVE BEEN OBVIOUS OVER HÖGLER, SAVARIRAYAN, AND BULLENS

Claim 11 depends from claim 1 and requires that “the composition further comprises one or more pharmaceutical excipients.” EX1001, 68:17-18. Claim 12 depends from claim 11 and requires that “the composition comprises citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.” EX1001, 68:20-23.

Bullens teaches or suggests all the elements of claims 11 and 12 because Bullens discloses “Pro-Gly-CNP37 peptide” (vosoritide)—*see e.g.*, EX1008, 4:44-45, 4:52-53, 14:54-55—and vosoritide compositions comprising pharmaceutical excipients. EX1003, ¶¶157-162. Bullens discloses results from a clinical study in which vosoritide was formulated with the excipients of claim 12:

Pro-Gly-CNP-37 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; *see also, id.*, 19:21-37; EX1003, ¶157. Bullens also teaches that “[t]he use of excipients, diluents and carriers in the formulation of

pharmaceutical compositions is known in the art.” EX1008, 19:32-34; EX1003, ¶158.

The rationales for obviousness of claim 1 apply to claims 11-12. *See* Section VIII.A. A POSA would have been motivated to combine Bullens with Savarirayan and Högler because Bullens expressly teaches compositions for *vosoritide*, which the POSA would have sought when following the teachings Högler and Savarirayan. EX1003, ¶159.

A POSA combining Högler, Savarirayan, and Bullens would have reasonably expected success because Bullens explains that treatment of achondroplasia in children with the *vosoritide* composition resulted in “a statistically significant increase ... in standing height growth velocity” when treated with the composition “15 µg/kg per day of Pro-Gly-CNP-37.” EX1008, 29:20-32; EX1003, ¶¶160.

Claims 11 and 12 would have been obvious. Objective indicia do not outweigh the case of *prima facie* obviousness.

XI. GROUND 3: CLAIMS 1-10 AND 13-14 WOULD HAVE BEEN OBVIOUS OVER PAULI AND SAVARIRAYAN

A. Claim 1

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

a. “A method of treating skeletal dysplasia in a subject about 0 month to about 2 years old”

Pauli provides a “comprehensive clinical review” of achondroplasia EX1006, Title; EX1003, ¶119. Pauli explains that “[a]chondroplasia is the most common of the *skeletal dysplasias* that result in marked short stature (dwarfism).” EX1006, Abstract; *see also*, EX1005, 26; EX1001, claims 9-10 (reciting achondroplasia as one of the claimed skeletal dysplasias); EX1001, 67:61-68:16.

Pauli teaches that in achondroplasia subjects “certain complications can only be prevented through assessment in *early infancy*.” EX1006, 4. Pauli explains that one such complication in “*infants* with achondroplasia” is a “small” and “often abnormal in shape” foramen magnum at the base of the skull “aris[ing] directly from the decreased growth of cartilaginous bone” that leads to “apneic deaths aris[ing] from compression of the vertebral arteries at or near the craniocervical junction,” *Id.*; EX1003, ¶¶23-25, 120. Pauli discloses that this apneic death occurs “between 3 and 11 months of age.” *Id.*, 9; *see also, id.* (noting “irreversible apnea”); EX1003, ¶24, 120. Accordingly, Pauli teaches that for “preventive assessments [] to be effective they must be completed *early in infancy*.” *Id.* Pauli teaches that “an

expanded phase 2 trial” of treating achondroplasia “in *infants* and young children” with the CNP variant vosoritide was ongoing. EX1006, 41; EX1003, ¶120.

Thus, Pauli teaches or suggests a method of treating achondroplasia (a skeletal dysplasia) in infants to improve achondroplasia symptoms, particularly foramen magnum stenosis. EX1003, ¶¶118-120. POSAs would have understood infants to be 0 months to <1 year old. EX1003, ¶65; EX1023, 140:6-8; Section VIII.A. Pauli’s disclosure of infants (0 to <1 year old) falls within the claimed age range of “about 0 month to about 2 years old,” and thus teaches this claim element. EX1003, ¶120.

Savarirayan discloses that treating “children (5 to 14 years of age) with achondroplasia” with “once-daily subcutaneous administration of vosoritide” (one of the claimed CNP variants as explained below) caused “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; EX1003, ¶119. Savarirayan also discloses 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; EX1003, ¶119.

Savarirayan discloses an on-going clinical trial (NCT03583697) for treating achondroplasia in “*infants* and younger children (age range, 0 to <60 months)” with vosoritide. EX1005, 34. Savarirayan’s disclosure of treating achondroplasia in “infants” (i.e., 0 months to 1 year old) falls within the claimed range age range of

subjects “about 0 month to about 2 years old” and thus teaches this claim element. EX1003, ¶121; EX1005, 34. Likewise, Savarirayan’s disclosure of treating achondroplasia in children “age range 0 to <60 months” overlaps with the claimed age range of “about 0 month to about 2 years old,” and renders this claim element obvious. *Id.*; *Peterson*, 315 F.3d at 1329-1330.

Thus, Pauli and Savarirayan teach or suggest a method of treating achondroplasia (a skeletal dysplasia) in a subject about 0 month to about 2 years old, as claimed.

b. “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”

Pauli discloses administering vosoritide in an amount effective to treat skeletal dysplasia. Pauli discloses CNP analogs as the “most advanced” of therapeutic options for achondroplasia. EX1006, 41; EX1003, ¶122. Pauli explains that administering 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; EX1003, ¶122. Pauli also teaches administering vosoritide to humans. EX1006, 41 (discussing vosoritide “[h]uman trials.”); EX1003, ¶122.

Savarirayan also discloses this claim element. Savarirayan discloses the results of the same clinical studies referenced in Pauli. Savarirayan discloses 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; EX1003, ¶123. Savarirayan explains that “vosoritide is a biologic analogue of C-type natriuretic peptide.” *Id.* A POSA would have known 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” 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, 34; EX1003, ¶124.

As discussed above in Section VII, the term “amount effective to treat” should be construed 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. EX1003, ¶56. The ’106 patent discloses that “improvement in one or more symptoms of skeletal dysplasia” includes “*improved or increased growth velocity.*” EX1001, 4:19-26; *see also, id.*, 29:4-6 (disclosing that “efficacy is assessed as the change in *annualized growth velocity* from the

baseline period to the intervention period”; EX1003, ¶56. Because Savarirayan discloses that vosoritide treatment improves annualized growth velocity, Savarirayan teaches administering vosoritide in an amount effective to treat achondroplasia. EX1003, ¶124.

Thus, Pauli and Savarirayan teach or suggest administering a CNP variant (vosoritide) in an amount effective to treat achondroplasia (a skeletal dysplasia). EX1003, ¶¶117-124.

c. “wherein the CNP variant is selected from the group consisting of: Pro-Gly-CNP37 . . .”

As discussed above, both Pauli and Savarirayan teach administering vosoritide (BMN-111) to children with achondroplasia. EX1006, 41; EX1005, Abstract; EX1003, ¶125. Before July 9, 2021, POSAs 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”—thus the nomenclature, Pro-Gly-CNP37. EX1026, 460; EX1053, Abstract, 197; EX1063, 1108, FIG. S2; EX1003, ¶125. Thus, a POSA would have understood that vosoritide has the same amino acid sequence as Pro-Gly-CNP-37 (SEQ ID NO: 1), recited in claim 1. EX1003, ¶125.

Thus, Pauli and Savarirayan teach or suggest administering the CNP variant Pro-Gly-CNP37 (SEQ ID NO: 1), as claimed.

2. A POSA would have been motivated to treat achondroplasia in the infants taught in Pauli and Saarirayan with the CNP variant vosoritide taught in Savarirayan

Given the ample teachings in the prior art regarding foramen magnum stenosis and risk of death in early infancy, it would have been obvious for a POSA to treat achondroplasia in subjects “about 0 month to about 2 years old” with vosoritide. *See e.g., Prometheus*, 805 F.3d at 1099-01; *AbbVie*, 764 F.3d at 1380–81; EX1003, ¶¶126-136

Pauli discloses treating achondroplasia in early infancy to alleviate foramen magnum stenosis (i.e., narrowing of foramen magnum) that can cause severe complications such as “apneic death” or “irreversible apnea” such that “the risk of death in the first year of life” being “at least 2-3%,” and potentially “as high as 7.5%.” EX1006, 4, 9, 10; EX1003, ¶¶120, 127-128. Consistent with Pauli’s teachings, the prior art widely recognized foramen magnum stenosis as a dangerous complication in children with achondroplasia necessitating treatment in early infancy. *See* Section V; EX1003, ¶¶22-25, 128. For example, Yamanaka discloses that “*early administration* of CNP or a CNP analogue may be an important determinant of *clinical effectiveness*” for treating achondroplasia with CNP to address complications of foramen magnum stenosis. EX1017, 1533; EX1003, ¶¶128-129. Thus, a POSA would have been motivated to treat achondroplasia in

infants to reduce or eliminate achondroplasia complications, particularly foramen magnum stenosis. EX1003, ¶¶126-130.

Pauli teaches that “nearly all instances of achondroplasia are caused by FGFR3 mutations” that activate 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.” *Id.*; EX1003, ¶127. Thus, a POSA would have understood that the foramen magnum stenosis in achondroplasia patients is caused by the activating mutation of FGFR3. EX1003, ¶127. The role of activating FGFR3 mutation in triggering achondroplasia and its symptoms, including foramen magnum stenosis, was well known in the art. *See* Section V; EX1003, ¶¶17, 22. 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. Thus, a POSA would have been motivated to treat achondroplasia in infants with a therapeutic that counteracts the activated FGFR3 to improve achondroplasia complications, particularly foramen magnum stenosis. EX1003, ¶128.

CNPs, such as vosoritide, were known to counteract FGFR3 activation. EX1003, ¶¶129-130. Pauli teaches that CNP is “the most advanced ... therapeutic option” for achondroplasia treatment and “BMN-111 (now called Vosoritide by BioMarin) 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; EX1003, ¶130. As discussed above, Savarirayan teaches successfully treating achondroplasia in children with vosoritide to increase annualized 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; EX1003, ¶119. Savarirayan teaches an on-going clinical trial treating “infants and younger children (age range, 0 to <60 months)” with vosoritide. EX1005, 34; EX1003, ¶121.

Thus, to diminish or eliminate fatal complications of foramen magnum stenosis (which have a high risk in the first year of life), a POSA would have been motivated to also treat achondroplasia in early infancy with vosoritide, as taught in Pauli and Savarirayan. EX1003, ¶¶126-130.

3. A POSA would have had a reasonable expectation of successfully treating achondroplasia in infants taught in Pauli and Savarirayan with the CNP variant vosoritide taught in Savarirayan

A POSA reading Pauli and Savarirayan would have had a reasonable expectation of successfully treating achondroplasia in infants using vosoritide for several reasons: (1) CNPs, such as vosoritide, were known to target the pathophysiological mechanism (FGFR3 activation) that caused achondroplasia and its complications, such as foramen magnum stenosis; and (2) CNP treatment was known to successfully treat achondroplasia and its complications in young mice and in human children. EX1003, ¶131.

First, CNP treatment was known to rescue the pathophysiological mechanism causing achondroplasia and its complications, such as foramen magnum stenosis. EX1003, ¶132. Pauli teaches that “nearly all instances of achondroplasia are caused by FGFR3 mutations” that activate it. 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.” *Id.*; EX1003, ¶132. Thus, a POSA would have known that foramen magnum stenosis in achondroplasia patients is caused by the activating mutation of FGFR3. EX1003, ¶132; *see also*, EX1017, 1526 (“developmental

mechanisms of ... foramen magnum stenosis in achondroplasia are related to FGFR3 and mitogen-activated protein kinase (MAPK) signaling in chondrocytes.”).

POSAs would have also known that CNPs, including vosoritide, treat achondroplasia and its symptoms by counteracting the FGFR3 activation. EX1003, ¶¶28, 133. For example, 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; EX1003, ¶133. Similarly, Savarirayan teaches that “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; EX1003, ¶133; *see also*, EX1017, 1533 (“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.”). Thus, POSAs would have reasonably expected that vosoritide would inhibit FGFR3 signaling and reduce or eliminate the pathophysiological mechanism causing achondroplasia and its complications, such as foramen magnum stenosis. EX1003, ¶132-133.

Second, the art taught that CNP treatment successfully rescues achondroplasia symptom, such as foramen magnum stenosis, in young mice. EX1003, ¶134. Pauli

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; EX1003, ¶134. Yamanaka discloses 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; EX1003, ¶134.

Thus, a POSA reading Pauli and Savarirayan would have had a reasonable expectation of successfully treating achondroplasia in the infants with the CNP variant, vosoritide. EX1003, ¶¶131-136.

Pauli and Savarirayan would have rendered claim 1 obvious.

B. Claims 2-4

Savarirayan teaches or suggests all the elements of claims 2-4 because Savarirayan discloses a “*once-daily*” (claims 2 and 4) “subcutaneous administration” (claim 3) of vosoritide in children. EX1005, Abstract; *id.*, 25, 34; EX1003, ¶137.

The rationales for obviousness of claim 1 also apply to claims 2-4. *See* Section X.A. Given the successful treatment of achondroplasia in Savarirayan’s disclosed methods, a POSA would have been motivated to also administer vosoritide

subcutaneously once-daily (daily) to infants with achondroplasia. EX1003, ¶140. A POSA would have reasonably expected success as discussed above for claim 1. EX1003, ¶140.

Claims 2-4 would have been obvious.

C. Claims 5 and 8

Savarirayan discloses all the elements of claims 5 and 8. Savarirayan teaches administering vosoritide at a dose of “30.0 µg per kilogram,” satisfying claim 5. EX1005, Abstract, 27, FIG. 1; EX1003, ¶¶142-143. As discussed above in Ground 1, claim 8 recites that the dosage “*may be decreased* to 15 µg/kg,” and thus recites an *optional* limitation. Because claim 8’s dosage amount is optional, it does not further limit claim 5. *Johnston*, 435 F.3d at 1384; *Schulhauser*, at 9-10. Thus, Savarirayan’s disclosure of administering vosoritide at 30 µg/kg teaches claim 8 for the same reasons it teaches claim 5.

Even if claim 8’s recited dose of 15 µg/kg were limiting, it was taught in the art, because Savarirayan also discloses that achondroplasia was successfully treated with vosoritide at a dose of 15 µg/kg. EX1005, Abstract, 25, 34; EX1003, ¶145.

Savarirayan discloses comparing the results of administering vosoritide in 15 µg/kg or 30 µg/kg and concluded 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; EX1005, ¶145.

The rationales for obviousness of claim 1 also apply to claims 5 and 8. *See* Section X.A. Given the successful treatment of achondroplasia at a vosoritide dose of 15 µg/kg or 30 µg/kg in Savarirayan’s disclosed method, a POSA would have been motivated to also administer these doses of vosoritide to infants or 2-year-old children with achondroplasia. EX1003, ¶143. Infants were known to have a higher metabolic rate for certain drugs than the older children and thus require “higher drug exposures than those needed in older children and adults to achieve adequate treatment effect,” with the dose decreasing as the child ages. EX1033, 11; *see also* EX1059, 737; EX1003, ¶146. Thus, a POSA treating infants with vosoritide at a dose of 30 ug/kg (as taught in Savarirayan) would have been motivated to decrease the dose of vosoritide to the lower dose (15 µg/kg, also taught in Savariraryan) when the child turned 2 years old. EX1003, ¶146.

A POSA would have had a reasonable expectation of success as discussed above for claim 1. EX1003, ¶147.

Pauli and Savarirayan would have rendered claims 5 and 8 obvious.

D. Claims 6 and 7

Pauli and Savarirayan teach or suggest all the elements of claims 6 and 7. Pauli teaches an increased “risk for death in the first year of life” and suggests that

for “preventive assessments to be effective they must be completed early in *infancy*.” EX1006, 9, 10; EX1003, ¶128. Savarirayan discloses an ongoing clinical trial (NCT03583697) treating achondroplasia in “*infants* and younger children (age range, 0 to <60 months)” with vosoritide. EX1005, 34; EX1003, ¶149. The age ranges taught in Pauli and Savarirayan overlap with the claimed age ranges in claims 6 and 7. *Peterson*, 315 F.3d at 1329-1330.

The rationales for obviousness of claim 1 also apply to claims 6 and 7. *See* Section X.A. Claims 6 and 7 would have been obvious.

E. Claims 9 and 10

Both Pauli and Savarirayan expressly teach treating achondroplasia. *See* Section X.A; EX1006, 41; EX1005, Abstract, 25, 35; EX1003, ¶152.

The rationales for obviousness of claim 1 also apply to claims 9 and 10. *See* Section X.A. Claims 9 and 10 would have been obvious.

F. Claims 13 and 14

Savarirayan teaches administering vosoritide, which was known in the art as Pro-Gly-CNP37 and is the CNP variant of SEQ ID NO: 1. *See* Sections V, X.A; EX1003, ¶¶154-156; EX1005, 35.

The rationales for obviousness of claim 1 also apply to claims 13 and 14. *See* Section X.A. Claims 13 and 14 would have been obvious. Objective indicia do not outweigh the strong case of *prima facie* obviousness.

XII. GROUND 4: CLAIMS 11-12 WOULD HAVE BEEN OBVIOUS OVER PAULI, SAVARIRAYAN, AND BULLENS

Claim 11 depends from claim 1 and requires that “the composition further comprises one or more pharmaceutical excipients.” EX1001, 68:17-18. Claim 12 depends from claim 11 and requires that “the composition comprises citric acid monohydrate, sodium citrate dihydrate, trehalose dihydrate, D-mannitol, L-methionine and polysorbate 80.” EX1001, 68:20-23.

As discussed above in Ground 2, Bullens teaches or suggests all the elements of claims 11 and 12 because Bullens discloses “Pro-Gly-CNP37 peptide” (vosoritide)—*see e.g.*, EX1008, 4:44-45, 4:52-53, 14:54-55—and vosoritide compositions comprising pharmaceutical excipients. EX1003, ¶¶157-158. Bullens discloses results from a clinical study in which vosoritide was formulated with all the excipients of claim 12:

Pro-Gly-CNP-37 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; *see also, id.*, 19:21-37; EX1003, ¶157. Bullens also teaches that “[t]he use of excipients, diluents and carriers in the formulation of

pharmaceutical compositions is known in the art.” EX1008, 19:32-34; EX1003, ¶158.

The rationales for obviousness of claim 1 discussed above also apply to claims 11-12. *See* Section X.A. A POSA would have been motivated to combine Bullens with Savarirayan and Pauli because Bullens expressly teaches compositions for *vosoritide*, which the POSA would have sought when following the teachings Pauli and Savarirayan. EX1003, ¶159.

A POSA combining Pauli, Savarirayan, 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.” EX1008, 29:20-32; EX1003, ¶160.

Claims 11 and 12 would have been obvious. Objective indicia do not outweigh the strong case of *prima facie* obviousness.

XIII. GROUND 5: CLAIMS 1-7 AND 9-14 ARE ANTICIPATED BY WENDT-242

Wendt-242 is a patent directed to CNP variants and discloses methods for treating achondroplasia, including in mice and human children. *See, e.g.*, EX1023, Abstract, 126:20-127:52 (Example 13), 139:5-140:47 (Example 19). Wendt-242 in at least two embodiments (Example 13 and Example 19) teaches each and every limitation of claims 1-7 and 9-14, arranged as claimed, and thus anticipates claims

1-7 and 9-14. EX1003, ¶¶163-180. Wendt-242 is presumed enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1287, 1289 (Fed. Cir. 2012).

A. Claim 1

1. “A method of treating skeletal dysplasia in a subject about 0 month to about 2 years old”

Wendt-242 discloses this claim element. For example, in Example 13, Wendt-242 discloses administering “once daily subcutaneously” a composition comprising a CNP variant (CNP37) in a “mouse model of mild *achondroplasia*” at 200 nmol/kg dose starting at *3 weeks of age* for 5 weeks. EX1023, 126: 20-54; EX1003, ¶165. Wendt-242’s Example 13 teaches a method of treating achondroplasia in 3 to 8 weeks old subjects. EX1003, ¶165.

Wendt-242 also discloses this claim element in Example 19. Here, Wendt-242 discloses administering “compositions comprising CNP22 or variants thereof in therapeutic methods” for treating achondroplasia in “*infant[s] (<1 year of age)* to pre-adolescent (<13 years of age),” with the “initial dose ... vary[ing] from 0.001 to about 1.0 mg/kg/week.” EX1023, 139:5-140:9. As discussed above, infants were understood to be 0 months to <1 year old. EX1003, ¶65; EX1023, 140:6-8; Section VIII.A. Wendt-242’s Example 19 teaches a method of treating achondroplasia in 0 months to <13 year old children.

As discussed in Section VII above, the ’106 patent defines a subject as encompassing “mammals and non-mammals,” including “any member of the

mammalian class.” EX1001, 18:55-65; EX1003, ¶52. Mice (Wendt-242’s Example 13) and human children (Wendt-242’s Example 19) are mammals. EX1003, ¶165. Achondroplasia is a type of skeletal dysplasia. EX1023, Abstract (“skeletal dysplasias (e.g., achondroplasia)), 3:5-6 (achondroplasia, the most common form of the skeletal dysplasias”); EX1003, ¶¶13-17; *see* Section V.

Wendt-242 teaches two separate embodiments of a method of treating skeletal dysplasia in a subject about 0 month to about 2 years old, as claimed. EX1003, ¶165. Wendt-242’s mice age of 3-8 weeks falls within the claimed age of “about 0 month to about 2 years old” and anticipates the claimed age range. *See Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 666 (Fed. Cir. 2023). Wendt-242’s disclosure of children ages 0 months to <13 years encompasses the claimed age of “about 0 month to about 2 years old” and also anticipates the claimed age range. *Id.*; *see also, Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005).

2. “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”

In Example 13, Wendt-242 teaches administering the CNP variant, CNP37, to mice with achondroplasia, and that the treated mice showed a “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; EX1003, ¶165. Wendt-242’s Table 13 (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 treated with vehicle only.” EX1023, 127:28-34; EX1003, ¶165.

TABLE 13						
	Tail	Naso- Anal	Femur	Tibia	Humerus	Ulna
CNP37	115%**	109%**	112%**	107%**	105%*	106%**
CNP27- PEO24	100%	99%	100%	102%	100%	101%
**p < 0.01, *p < 0.05						

EX1023, 127:35-44; EX1003, ¶165.

As discussed above in Section VII, the term “amount effective to treat” should be construed 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. EX1003, ¶56; EX1001, 17:28-30. The ’106 patent discloses that “improvement in one or more symptoms of skeletal dysplasia” includes “*increased long-bone growth.*” EX1001, 4:19-26; EX1003, ¶56. As Dr.

Abuzzahab explains, tibia, femur, ulna, and humerus bone are long bones. EX1003, ¶165. Because Wendt-242's Example 13 teaches that vosoritide treatment increased long-bone growth, it teaches administering a CNP variant in "an amount effective to treat" a skeletal dysplasia (achondroplasia). EX1003, ¶165.

Wendt-242 also discloses this claim element in Example 19. Here, Wendt-242 teaches administering a CNP variant in an "initial dose ... vary[ing] from 0.001 to about 1.0 mg/kg/week" and increasing the dose within this range or beyond as necessary in the event that the initial dose "does not produce a significant direct *clinical benefit*." EX1023, 139:20-27. As discussed above in Section VII, the term "amount effective to treat" should be construed 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. EX1003, ¶56; EX1001, 17:28-30. Because Wendt-242's Example 19 teaches vosoritide treatment to produce clinical benefit, it teaches administering a CNP variant in "an amount effective to treat" skeletal dysplasia (achondroplasia). EX1003, ¶165.

3. "wherein the CNP variant is selected from the group consisting of: Pro-Gly-CNP37; ... CNP-37..."

Wendt-242 discloses this claim element in Examples 13 and 19. In Example 13, Wendt-242 teaches a method of treating achondroplasia in mice using CNP

variant “CNP-37” having the amino acid sequence, “(SEQ ID NO: 60 QEHPNARKYKGANKKGLSKGCFGLKLDRI GSMSGLGC.” EX1023, 54:1-67, 126:45-50; EX1003, ¶165. The CNP-37 variant disclosed in Wendt-242 the same as the CNP-37 variant recited in the Markush group of claim 1 as SEQ ID NO: 21. EX1001, 65:25-27; EX1003, ¶165.

In Example 19, Wendt-242 teaches a method of treating achondroplasia in children using “CNP22 or variants thereof.” EX1023, 139:8-11; EX1003, ¶165. Wendt-242 teaches “(SEQ ID NO, 145) PGQEHPNARKYKGANKKGLSKGCFGLKLDRI GSMSGLGC (*Pro-Gly-wtCNP37*)” as one of the “[n]on-limiting examples of CNP variants” and specifically claims it as a preferred CNP variant. EX1023, 58:15-59:10, claim 17; EX1003, ¶165. The Pro-Gly-wtCNP37 variant disclosed in Wendt-242 is the same as the Pro-Gly-CNP37 variant recited in the Markush group of claim 1 as SEQ ID NO: 1. EX1001, 63:4446; EX1003, ¶165. Each of Wendt-242’s Examples 13 and 19 teaches this claim element.

In sum, Wendt-242 teaches every limitation of claim 1, arranged as claimed and anticipates claim 1. EX1003, ¶¶165-166. Wendt-242 is presumed enabled. *Antor*, 689 F.3d at 1287, 1289.

B. Claims 2-4

In Example 13, Wendt-242 discloses administering “*once daily subcutaneously*” a composition comprising a CNP variant (CNP37) to mice with achondroplasia. EX1023, 126: 20-54; EX1003, ¶¶168-169. Wendt-242 anticipates claims 2-4. EX1003, ¶¶167-170.

C. Claim 5

In Example 19, Wendt-242 discloses administering initial dose for the trials will vary from about *0.001 to about 1.0 mg/kg/week*,” which corresponds to about 1 µg/kg to about 1000 µg/kg/week. EX1023, 139:20-22; EX1003, ¶171. The claimed dose of 30 µg/kg falls squarely within Wendt-242’s disclosed dose range, and a POSA would have thus immediately envisaged a dose of 30 µg/kg. EX1003, ¶171. *See e.g., In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006). Wendt-242 anticipates claim 5. EX1003, ¶171.

D. Claim 6

In Example 19, Wendt-242 teaches a method of treating achondroplasia in “infant[s] (<1 year of age) to preadolescent (<13 years of age).” EX1023, 140:6-8; EX1003, ¶172. The claimed age of about 6 months to about 2 years old falls within Wendt-242’s disclosed age range of “<1 year of age” to “<13 years of age.” EX1003, ¶172; *Petering*, 301 F.2d at 681; *Eli Lilly*, 471 F.3d at 1376. Wendt-242 anticipates claim 6. EX1003, ¶172.

E. Claim 7

Example 13 in Wendt-242 teaches a method of treating achondroplasia in mice (“subjects”) 3 to 8 weeks old. EX1023, 126:45-50; EX1003, ¶173. Wendt-242’s disclosed age range of 3-8 weeks old falls squarely within the claimed age range of about 0 to about 6 months old.” EX1003, ¶173; *Arbutus*, 65 F.4th at 666. In Example 19, Wendt-242 discloses treating achondroplasia in “*infant[s]* (<1 year of age) to pre-adolescent (<13 years of age),” an age range that subsumes the claimed age range. EX1023, 140:6-8; EX1003, ¶173; *Arbutus*, 65 F.4th at 666; *Perricone*, 432 F.3d at 1377.

Wendt-242 anticipates claim 7. EX1003, ¶¶173.

F. Claims 9 and 10

Claims 9 and 10 depend from claims 1 and 3, respectively, and further limit the skeletal dysplasia to a group that includes achondroplasia (claim 9) or specifically to achondroplasia (claim 10). EX1001, 67:61-68:16; EX1003, ¶174. Wendt-242 teaches a method of treating *achondroplasia*. EX1023, 126:20-42 (Example 13), Table 13, 140:2-5 (Example 19); EX1003, ¶174; Section XII. Wendt-242 anticipates claims 9 and 10. EX1003, ¶174.

G. Claim 11

Wendt-242’s Example 13 teaches using a “vehicle” to administer CNP37 to the achondroplasia mice. EX1023, 126:45-50; EX1003, ¶175. Example 14 in Wendt—another mouse study administering CNP37—teaches that the vehicle is “30

mM acetic acid/acetate buffer, 1% benzyl alcohol, 10% sucrose, pH 4.0.” EX1023, 127:65-66; EX1003, ¶175. Wendt-242 also states that “the disclosure provides pharmaceutical compositions comprising a CNP variant, and one or more pharmaceutically acceptable excipients, carriers, or diluents.” EX1023, 85:33-37; EX1003, ¶175. Wendt-242 anticipates claim 11. EX1003, ¶175.

H. Claim 12

Example 18 in Wendt-242 teaches “liquid formulations of CNP variants” that are “formulated according to any combinations of the ingredients and their amounts or concentrations in Table 16.” EX1023, 137:7-10; EX1003, ¶177. Table 16 is reproduced below:

TABLE 16		
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	NaCl	140 mM $\pm$ 20 mM
Isotonicity-adjusting agent	Sucrose	10% $\pm$ 5%
Preservative	m-Cresol	0.4% $\pm$ 0.1% or 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%
¹ Glycerin is used to minimize or prevent water-driven hydrolysis, deamidation, isomerization or cleavage of CNP variants. For lyophilized formulations, 4-6% or 6-20% mannitol or sucrose can be substituted for NaCl.		

EX1023, Table 17; EX1003, ¶177.

Table 16 discloses compositions comprising excipients “citric acid/citrate,” “mannitol,” “methionine,” and “polysorbate 80.” *Id.* Wendt-242 also teaches that “[e]xemplary *bulking agents* include ... *trehalose*...” EX1023, 87:65; EX1003, ¶178.

A POSA reading “methionine” disclosed in Wendt-242 would have at once envisaged L-methionine, D-methionine, or their mixture; and likewise for “mannitol” disclosed in Wendt-242, would have at once envisaged L-mannitol or D-mannitol or their mixture. EX1003, ¶178. *Petering*, 301 F.2d at 681 (“one skilled in this art would, on reading the [prior art], at once envisage each member of this limited class...”). A POSA also would have understood “citric acid/citrate” to disclose a limited class suitable for pharmaceutical formulations, including citric acid monohydrate and sodium citrate dihydrate; and “trehalose” to be a limited class suitable for pharmaceutical formulations, including trehalose dihydrate. EX1003, ¶178; *Petering*, 301 F.2d at 681.

“[A] reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art,

reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015); *Petering*, 301 F.2d at 681. A POSA reading Wendt-242 would have at once envisaged 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, ¶178.

Wendt-242 anticipates claim 12. EX1003, ¶¶176-178.

I. Claims 13 and 14

Wendt-242’s Example 19 teaches a method for treating achondroplasia using Pro-Gly-CNP-37, as claimed. EX1023, 58:15-59:10, 139:8-11, claim 17; EX1003, ¶¶179-180; *see* Section XII.A. Wendt-242 anticipates claims 13 and 14.

Wendt-242 (which is presumed enabled) teaches each and every element of claims 1-7 and 9-14, arranged as claimed and anticipates these claims. EX1003, ¶¶179-180; *Antor*, 689 F.3d at 1287, 1289.

XIV. GROUND 6: CLAIMS 1-14 ARE NOT ENABLED

Claims 1-14 are unpatentable for lacking enablement. “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.” *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013). The enablement requirement only allows for a specification to “call for a reasonable amount of

experimentation to make and use a patented invention.” *Amgen v. Sanofi*, 598 U.S. 594, 612 (2023). “[A] patentee ‘cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.’” *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (citation omitted).

Enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

If a claim encompasses significant numbers of inoperative embodiments, and a skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled. *Atlas Powder Co. v. E.I. du Pont De Nemours*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

A. Claim 1 is not enabled

1. Breadth of the claim

Claim 1 captures a massive and diverse genus of treatment methods.

a. “subject”

The claim term “subject” has an enormous scope. As discussed above in Section VII, the ’106 patent defines a “subject” extremely broadly as

“encompass[ing] *mammals and non-mammals*.” EX1001, 18:55-65. The patent specification discloses that mammals include “*any member of the mammalian class*,” which “include, but *are not limited to* ... 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.” EX1001, 18:55-65; EX1003, ¶¶52, 182. The specification discloses non-mammals to “include, but are not limited to, birds, fish, and the like.” *Id.*

As Dr. Abuzzahab explains, there are estimated to be more than 5,000 species of mammals alone, and non-mammal subjects of the '106 patent include over 10,000 species of birds and over 30,000 species of fish.² EX1061, Table S1; EX1050, 2; EX1003, ¶182. Scope of “subject” in claim 1 under the '106 patent’s definition is enormous. EX1003, ¶182. As discussed below, the specification provides no guidance for treating skeletal dysplasia (such as achondroplasia) in any subject other than human children.

² To the extent “non-mammals” is construed to include all non-mammals, including invertebrates, the scope of the term “subject” would extend to encompass over 7 million different species of animals. EX1050, 2; EX1003, ¶182.

b. “C-type natriuretic peptide (CNP) variant”

Claim 1 requires a “C-type natriuretic peptide (CNP) variant” selected from a 65-member Markush group of CNP variants. The Markush members include, for example, CNPs with wild-type sequence of CNP-52 – CNP-18 (excluding CNP-22), PEGylated CNP variants, and vosoritide (Pro-Gly-CNP37). EX1001, 63:44-46; EX1003, ¶183. However, as Dr. Abuzzahab explains, the claimed CNP variants were known to have markedly different properties, creating unpredictability and untenable amounts of experimentation in order to practice the full scope of the claimed method of treating skeletal dysplasia. EX1003, ¶¶183-187.

First, the claimed CNP variants have a wide range of half-lives, leading to a varied pharmacokinetic profile and dosing regimen. EX1003, ¶184. CNPs were known to undergo degradation by neutral endopeptidase (NEP). EX1049, FIG. 3; EX1020, 211. CNP-22 (CNP in circulation) was known to have a very short half-life of “2.6 min due to its rapid degradation by neutral endopeptidase.” EX1020, 213. Vosoritide was developed “to have a longer half-life than its endogenous form [CNP-22].” EX1005, 26. The art taught that “the majority of the natural substrates of NEP are restricted to about 3000 Da,” such that CNPs smaller than 3000 Da would have shorter half-life than CNPs larger than 3000 Da. EX1045, 343; EX1052, 87; EX1062, 346 (“differences in half-life (*longer in larger peptides*) are likely to materially affect their potency in vivo.”); EX1003, ¶184.

For example, PO's own publications, such as Wendt 2015, show that the shorter CNP variants, e.g. CNP27(K4,5,9R) (called "CNP27, K4R, K5R, K9R" in Wendt 2015) has markedly lower NEP resistance than longer CNP variants CNP-30, CNP-33, CNP-36–CNP-40, and Pro-Gly-CNP-37 (called "BMN-111" in Wendt 2015). EX1003, ¶185. This is shown in Wendt 2015's Table 1, reproduced below:

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
	kDa	nM	% 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	NT
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	60 $\pm$ 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	100 $\pm$ 20	102
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^{-6} 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 2WGC; HSA Ac P02768, PDB ID 1BM0).

EX1009, Table 1 (annotated); EX1003, ¶185. As shown above, the NEP resistance of CNP22 (2.4) and CNP27 (<5) is significantly lower than longer CNP variants

CNP30 to CNP 53 (ranging from 36 to 106). EX1009, Table 1 (annotated); EX1003, ¶185.

Second, each of the 12 PEGylated CNPs claimed (SEQ ID NOs: 54-65) represent a broad genus of peptides with different half-life and pharmacokinetics. EX1001, 67:1-40; EX1003, ¶¶186-187. The '106 patent discloses that PEG can “optionally have an alkylene group, (CH₂)_m, where m is an integer from 1 to 5.” EX1001, 19:14-16. Thus, each PEGylated peptide recited in claim 1 can have 0, 1, 2, 3, 4, or 5 CH₂ groups between the PEG polymer and the CNP peptide. EX1003, ¶186. 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, 24:51-59; EX1003, ¶186. 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. EX1003, ¶186. Additionally, the patent discloses that “[i]n various embodiments, the variant comprises a synthetic polymeric group [e.g., PEG] coupled to the variant through a hydrolysable linker,” thus the claimed PEGylated CNP variants can have PEG coupled to the CNP through a hydrolysable and a non-hydrolysable linkage. EX1001, 12:12-15; EX1003, ¶186. As exemplified

in Wendt 2015 by the varied degradation of PEGylated CNPs by NEP, this diverse group of PEGylated peptides would have varied half-life and pharmacokinetic profile. EX1009, Table 1; EX1003, ¶186.

Third, the CNP variants of claim 1 include at least two *inoperative* CNP variants: PEO24-CNP27(K4,5,9R); PEO12-CNP27(K4,5,9R). As Wendt 2015 acknowledges, PEO24-CNP27(K4,5,9R)³ “failed to provide a significant growth benefit in wild-type mice compared with the placebo control” in mice, leading PO to pursue other CNP variants for developing achondroplasia therapeutic. EX1009, 137, Table 1 (showing potency of 16 ± 2.8); EX1003, ¶187. Wendt 2015 also disclosed that PEO12-CNP27(K4,5,9R) “was the least pharmacologically active of the variants tested,” including PEO24-CNP27(K4,5,9R), “potentially due to poor tissue bioavailability associated with PEGylated proteins” and “performed similarly” to the failed PEO24-CNP27(K4,5,9R). EX1009, 137, Table 1 (showing potency of 7.8 ± 1.4); EX1003, ¶187. A POSA would not have known whether any of the other claimed PEGylated CNP variants would have had a therapeutic effect in

³ 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; EX1003, ¶185.

a subject (a term that encompasses myriad different animal species), as claimed.

EX1003, ¶¶183-187.

c. “skeletal dysplasia”

Claim 1 requires treating “skeletal dysplasia”—another term representing a broad genus. EX1003, ¶¶188-191. 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; EX1003, ¶188. Before July 9, 2021, at least 450 different skeletal dysplasias were known in the art, which in turn were caused by mutations in at least 437 different genes. EX1025, 2394; EX1007, 105; EX1003, ¶188. These genes coded a variety of proteins involved in causing skeletal dysplasia ranging from “tissue-specific proteins that are essential for the formation and maintenance of bone and cartilage” to “proteins that have a more ubiquitous role such as regulating gene transcription, cell division, or intracellular transport,” with “the skeletal roles [of many genes] not yet clear.” EX1025, 2417; EX1003, ¶188. The skeletal dysplasias were not linked by a single gene or molecular pathogenesis such that a single therapeutic (such as a CNP-based therapeutic) could (and would) not have been used to treat each of them. EX1025, 2417; EX1003, ¶188.

For example, some skeletal dysplasias were known to be characterized by bone *overgrowth* and these dysplasias could not (and would not) have been treated with a CNP variant, including any of the claimed CNP variants. EX1003, ¶190. For

example, the '106 patent includes skeletal dysplasias with an “NPR2 mutation” (i.e., mutation in the CNP receptor, NPR-B) as one of the claimed skeletal dysplasias. EX1001, 67:61-68:14. However, as Dr. Abuzzahab explains, “a gain-of-function mutation at NPR2” gene was known to cause an “overgrowth syndrome characterized by tall stature . . . similar to those previously reported in association with CNP/NPR2 overactivity.” EX1040, Abstract; EX1003, ¶190. Similarly, Marfan syndrome is another example of known skeletal dysplasia that was characterized by bone overgrowth. EX1025, 2410; EX1003, ¶190. As Dr. Abuzzahab explains, a POSA would have known that skeletal dysplasias with bone overgrowth syndromes could not (and would not) have been treatable with any of the claimed CNP variants. EX1003, ¶190. In fact, treatment with any of the claimed CNP variants (or any other CNP variant) would have *worsened* the disorder by further increasing the bone growth consistent with CNP’s role in increasing long-bone growth. *See* Section V; EX1005, 26 (stating that “exogenous C-type natriuretic peptide restores the impaired bone growth observed in mice with achondroplasia and increase long-bone growth in wild-type monkeys by inhibiting the FGFR3-mediated MAPK signaling pathway.”).

The broad genus of skeletal dysplasias includes skeletal dysplasias characterized by mutation in CNP receptor NPRB gene causing the receptor to lose function and these dysplasias could not (and would not) have been treated with a

CNP variant, including any of the claimed CNP variants. EX1003, ¶190. For example, the '106 patent specifically lists and claims *acromesomelic dysplasia* as a skeletal dysplasia. EX1001, 4:41-42, claim 9. However, POSAs knew that “CNP therapy is *not effective for acromesomelic dysplasia* type Maroteaux, which is caused by loss-of-function mutations in the GC-B gene,” the gene encoding CNP receptor (NPR-B). EX1038, 662, 664; EX1003, ¶190. Skeletal dysplasias have broad range of severity, including skeletal dysplasias that are incompatible with postnatal life. EX1037, 515; EX1003, ¶189. The term “skeletal dysplasia” encompasses a wide variety disorders, many of which were not even treatable with a CNP variant. EX1003, ¶¶188-191.

In sum, in view of at least the above-noted broad claim terms, claim 1 captures a massive and diverse genus of treatment methods. One cannot rely on the knowledge and efforts of a POSA to try to “fill the gaps in the specification” regarding which of the “many, many thousands” of possible methods should be selected for screening, and which in this case would have been impossible. *Idenix*, 941 F.3d at 1159.

2. Quantity of experimentation necessary and nature of the invention

The amount of experimentation necessary to practice the full scope of the claims would have been insurmountably high. EX1003, ¶¶192-197.

As discussed above, at least in view of the claim terms “subject,” “skeletal dysplasia,” and the recited “CNP variant[s],” the claim scope is enormous. Further claim 1 requires “*treating* skeletal dysplasia” by administering the CNP variant in an “*amount effective to treat*.” EX1001, 63:37-42; EX1003, ¶194. The ’106 patent states that for “effective” amount, “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; EX1003, ¶193. To devise and practice the full scope of the claimed method, a POSA would need to determine the “amount effective to treat” for more than 65 different CNP variants, for tens of thousands of different animal species, and for more than 450 different types of skeletal dysplasia. EX1003, ¶¶194-197. That is not only a large amount of experimentation, that is undue. *Amgen*, 598 U.S. at 614-15.

3. Amount of direction or guidance presented and presence or absence of working examples

The ’106 patent specification provides minimal guidance for the entire scope of claimed method. The specification provides no guidance for treating any skeletal dysplasia other than achondroplasia, despite the diverse pathophysiology and

severity of diseases in the genus, with some known to be untreatable with CNPs. EX1003, ¶¶198-199.

The specification also provides no guidance for treating *any mammal or non-mammal* about 0 month to about 2 years old, other than purportedly 0 month to 2 year olds humans. The specification contemplates broad dosing ranges for CNP variants, from 3 nmol/kg up to 300 nmol/kg, or 3 mg/kg to 1000 mg/kg. EX1001, 35:51, 35:66-36:4. While the specification provides examples of dosing for vosoritide in human children, such guidance would not have been instructive for determining the “amount effective to treat” for the full scope of the claimed CNP variants, which have wide variations in half-life and pharmacokinetic profiles. EX1003, ¶196. Beyond a single CNP peptide applied to a single disease, the specification provides no guidance for determining which dose in these ranges (which span two orders of magnitude) would be “an amount effective to treat” for the broad variety of the claimed CNP variants for treating hundreds of diverse skeletal dysplasias in thousands of subjects encompassed by the claims. EX1003, ¶199.

The specification only provides a single working example, narrowly drawn to treating achondroplasia using one particular CNP variant, vosoritide, at two doses, 15 µg/kg and 30 µg/kg, in human children with achondroplasia. EX1001, 39:25-50:16; EX1003, ¶198.

4. The state of the prior art and the predictability or unpredictability of the art

The general knowledge in the art also would not have enabled the '106 patent's scant disclosure. For example, as discussed above, the claims encompass using CNP variants that are PEGylated at an internal site. *See* Section XIII.A.1; EX1003, ¶186. Claim 1 also expressly recites "PEO24-CNP27(K4, 5, 9R)" (SEQ ID NO: 62), a CNP variant that "failed to provide a significant growth benefit in wild-type mice" and PEO12-CNP27(K4, 5, 9R) (SEQ ID NO: 30) that "performed similarly" to the failed PEO24-CNP27(K4, 5, 9R). EX1009, 137; EX1001, 67:20-30. In view of the prior art knowledge, a POSA would not have been able to practice the full scope of the CNP variants in the claimed method. EX1003, ¶200.

This unpredictability is exacerbated by the large number of CNP variants and tens of thousands of mammals and non-mammals covered by the claims, all with widely varying pharmacokinetic properties. *See* Section XIII.A.1.

5. The relative skill in the art

While the level of skill in the art is high (*see* Section IV), such skill and experience would not have been enough to overcome the massive scope of the claims, unpredictability in the field across tens of thousands of different animal species, the limited working examples and guidance in the specification, and the impossible amounts of experimentation required to practice the full scope of the claimed method. EX1003, ¶201.

6. Weighing the *Wands* factors

Weighing the *Wands* factors as a whole, there is no question that practicing the full scope of the claimed method would have required undue experimentation. EX1003, ¶202. The facts here are similar to those in *Amgen*, where the claimed “class of antibodies does not include just the 26 that Amgen has described by their amino acid sequences, but a ‘vast’ number of additional antibodies that it has not.” *Amgen*, 598 U.S. at 613. In view of the large breadth of the asserted claims, the limited disclosure in the specification (including a single working example), and the unpredictability of using a diverse genus of CNP variants across a diverse genus of skeletal dysplasia in a diverse genus of animals, the ’106 patent specification leaves POSAs to engage in “random trial-and-error discovery.” *Amgen*, 598 US at 615; EX1003, ¶202. A POSA reviewing the specification, with or without the prior art, could not have practiced the full scope of the claimed method without undue experimentation. EX1003, ¶202. Claim 1 is unpatentable for lack of enablement.

B. Claims 2-14

Claims 2-14 are also not enabled. Claims 2-8 and 11-12 encompass the same massive genera of “subject,” “skeletal dysplasia,” and “CNP variant” recited in claim 1, and are not enabled for the same reasons discussed above. *See* Section XIII.A; EX1003, ¶¶203-209. Claims 9-10 recite specific types of skeletal dysplasia, but fail to limit the massive genera of “subject” or “CNP variant” recited in claim 1.

EX1003, ¶204. Claims 13 and 14 recite smaller groups of CNP variants, but fail to limit the massive genera of “subject” or “skeletal dysplasia” recited in claim 1. EX1003, ¶205.

XV. GROUND 7: CLAIM 8 FAILS TO FURTHER LIMIT CLAIM 5

A dependent claim must “specify a further limitation of the subject matter claimed” in the claim from which it depends. 35 U.S.C. § 112(d). Claim 5 requires administering a composition of claim 1 at a dose of 30 µg/kg. EX1001, 67:53-54. Claim 8 depends from claim 5 and further requires that “the dosage *may be* decreased to 15 µg/kg.” *Id.*, 67:59-60. By using the word “may,” claim 8 does not necessarily further limit the scope of claim 5. EX1003, ¶¶207-209. A POSA practicing claim 8 can continue to administer a dose of 30 µg/kg as required by claim 5, or the artisan can optionally decrease the dose to 15 µg/kg when the subject turns 2 years old. Claim 8 thus fails to narrow the scope of claim 5. *Johnston*, 435 F.3d at 1384. A dependent claim is unpatentable if it “does not narrow the scope” of the claim from which it depends. *Pfizer Inc. v. Ranbaxy Labs.*, 457 F.3d 1284, 1291-92 (Fed. Cir. 2006). Claim 8 is unpatentable on this basis alone.

Even if claim 8 *required* administering a dose of 15 µg/kg, it is still unpatentable because claim 5 requires administering a *fixed dose* of 30 µg/kg and explicitly does not encompass the 15 µg/kg dose. “A dependent claim that contradicts, rather than narrows, the claim from which it depends is invalid.”

MultiLayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp., 831 F.3d 1350, 1362 (Fed. Cir. 2016) For this additional reason, claim 8 is unpatentable for failing to further limit claim 5.

XVI. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): The real parties-in-interest are ZYDUS LIFESCIENCES LIMITED, ZYDUS LIFESCIENCES GLOBAL FZE, and ZYDUS PHARMACEUTICALS (USA) INC.

Out of an abundance of caution, Petitioners certify that the following are also identified as real parties-in-interest, for purposes of compliance with 35 U.S.C. §312(a)(2):

Zydus Healthcare Limited
German Remedies Pharmaceuticals Private Limited
Zydus Wellness Limited
Zydus Wellness Products Limited
ZyVet Animal Health Inc.
Liva Nutritions Limited
Zydus Healthcare (USA) LLC
Sentyln Therapeutics Inc.
Zydus Animal Health and Investments Limited
Dialforhealth Unity Limited
Dialforhealth Greencross Limited
Viona Pharmaceuticals Inc.
Violio Healthcare Limited
Zynext Ventures USA LLC
Zynext Ventures PTE. LTD.
Zydus Pharmaceuticals Limited
Alidac Pharmaceuticals SA Pty. Ltd.
Biochem Pharmaceutical Private Limited
Script Management Services (Pty) Ltd.

Zydus Strategic Investments Limited
Zydus Wellness [BD] Pvt Ltd
Zydus VTEC Limited
Zydus Pharmaceuticals Mexico SA De. C.V.
LM Manufacturing India Private Limited
Zydus Pharmaceuticals Mexico Services Company SA De. C.V.
M/s. Recon Pharmaceuticals and Investments, a Partnership Firm
Zydus Worldwide DMCC
Zydus Medtech Private Limited
Zydus Wellness International DMCC
Naturell (India) Private Limited
Zydus Pharmaceuticals (Canada) Inc.
Zydus International Private Limited
Zydus Pharmaceuticals UK Limited
Zydus Lanka (Private) Limited
LM Manufacturing Limited
Zydus Nikkho Farmaceutica Ltda.
Medsolutions (Europe) Limited
Zydus Healthcare Philippines Inc.
LiqMeds Worldwide Limited
Zydus Ventures PTE. LTD.
LiqMeds Limited
Laboratorios Combix S.L.
LiqMeds Lifecare Limited
Zydus Netherlands B.V.
Naturell Inc.
Zydus France, SAS
Alidac Healthcare (Myanmar) Limited
Zydus Therapeutics Inc.
Zydus Healthcare S.A. (Pty) Ltd
Etna Biotech S.R.L.
Assertio Holdings, Inc.

Related Matters (37 C.F.R. § 42.8(b)(2)): Pending U.S. Patent Application No. 19/033,994 claims the benefit of the '106 patent.

BioMarin Pharmaceutical Inc. v. Zydus Lifesciences Limited et al., Civ. Action No. 1:26-cv-01005 (D.N.J.), Complaint filed February 2, 2026.

Ascendis Pharma A/S v. BioMarin Pharmaceutical Inc., PGR2026-00013, Petition filed November 24, 2025.

Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3)):

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Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to counsel at the above addresses. Petitioners consent to service by email at the addresses above.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.206(a). Concurrently filed herewith are a Power of Attorney and Exhibit List (Appendix A) under 37 C.F.R. §§ 42.10(b) and 42.63(e), respectively. The required fee is paid through Deposit Acct. No. 02-4800. The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 02-4800.

XVII. CONCLUSION

The Board should institute this PGR and cancel Claims 1-14.

Respectfully submitted,

Date: June 5, 2026

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APPENDIX A – EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 12,233,106 to Day et al., issued February 25, 2025
1002	Prosecution History of U.S. Patent No. 12,233,106
1003	Declaration of Dr. Mary Jennifer Abuzzahab, M.D.
1004	<i>Curriculum Vitae</i> of Dr. Mary Jennifer Abuzzahab, M.D.
1005	Savarirayan, Ravi, et al. “C-type natriuretic peptide analogue therapy in children with achondroplasia.” <i>New England Journal of Medicine</i> 381: 25-35 (2019).
1006	Pauli, Richard M. “Achondroplasia: a comprehensive clinical review.” <i>Orphanet Journal of Rare Diseases</i> 14: 1-49 (2019).
1007	Högler, Wolfgang, and Ward, Leanne M. “New developments in the management of achondroplasia.” <i>Wiener Medizinische Wochenschrift</i> 170: 104-111 (2020).
1008	US Patent No 9,907,834 to Bullens et al., issued March 6, 2018
1009	Wendt, Daniel J., et al. “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: 132-149 (2015).
1010	Baujat, Geneviève, et al. “Achondroplasia.” <i>Best Practice & Research Clinical Rheumatology</i> 22: 3-18 (2008).
1011	Ornitz, David M., and Marie, Pierre J. “FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease.” <i>Genes & Development</i> 16: 1446-1465 (2002).

Exhibit No.	Description
1012	Ornitz, David M., and Legeai-Mallet, L. “Achondroplasia: development, pathogenesis, and therapy.” <i>Developmental Dynamics</i> 246: 291-309 (2017).
1013	Wallis, Gillian A. “Bone growth: coordinating chondrocyte differentiation.” <i>Current Biology</i> 6: 1577-1580 (1996).
1014	Su, Nan, et al. “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>Clin Perinatol</i> 42: 301-319 (2015)
1016	Nguyen, Jie C., et al. “Imaging of pediatric growth plate disturbances.” <i>Radiographics</i> 37: 1791-1812 (2017).
1017	Yamanaka, Shigeki, et al. “Circulatory CNP rescues craniofacial hypoplasia in achondroplasia.” <i>Journal of Dental Research</i> 96: 1526-1534 (2017).
1018	Rimoin, David L., et al. “The Skeletal Dysplasias: Clinical–Molecular Correlations.” <i>Annals of the New York Academy of Sciences</i> 1117: 302-309 (2007).
1019	Krejci, Pavel, et al. “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: 5089-5100 (2005).
1020	Pejchalova, Katerina, et al. “C-natriuretic peptide: an important regulator of cartilage.” <i>Molecular Genetics and Metabolism</i> 92: 210-215 (2007).

Exhibit No.	Description
1021	Wu, Chengliang, et al. “Furin-mediated processing of Pro-C-type natriuretic peptide.” <i>Journal of Biological Chemistry</i> 278: 25847-25852 (2003).
1022	Meyer, Markus, et al. “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, Geert R., et al. “Nosology and classification of genetic skeletal disorders: 2019 revision.” <i>American Journal of Medical Genetics Part A</i> 179: 2393-2419 (2019)
1026	Breinholt, Vibeke Miller, et al. “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: 459-471 (2019).
1027	Merker, Andrea, et al. “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: 1723-1734 (2018).
1028	Reid, Cheryl S., et al. “Cervicomedullary compression in young patients with achondroplasia: value of comprehensive neurologic and respiratory evaluation.” <i>The Journal of Pediatrics</i> 110: 522-530 (1987).
1029	Hecht, Jacqueline T., et al. “Mortality in achondroplasia.” <i>American Journal of Human Genetics</i> 41: 454-464 (1987).

Exhibit No.	Description
1030	Simmons, Kristen, et al. “Mortality in babies with achondroplasia: revisited.” <i>Birth Defects Research Part A: Clinical and Molecular Teratology</i> 100: 247-249 (2014).
1031	Bartels, Cynthia F., et al. “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: 27-34 (2004).
1032	Chitty, L. S., et al. “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: 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, William A., et al. “Achondroplasia.” <i>The Lancet</i> 370: 162-172 (2007).
1036	Bianchi, M. L. “Hypophosphatasia: an overview of the disease and its treatment.” <i>Osteoporosis International</i> 26: 2743-2757 (2015).
1037	McInerney-Leo, Aileen M., et al. “Short-rib polydactyly and Jeune syndromes are caused by mutations in WDR60.” <i>The American Journal of Human Genetics</i> 93: 515-523 (2013).
1038	Yasoda, Akihiro, and Nakao, Kazuwa. “Translational research of C-type natriuretic peptide (CNP) into skeletal dysplasias.” <i>Endocrine journal</i> 57: 659-666 (2010).

Exhibit No.	Description
1039	Prickett, T. C., & Espiner, E. A. (2011). 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.
1040	Miura, Kohji, et al. “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: 156-163 (2013).
1041	European Patent 0769554 B1 to Tanaka et al., issued March 5, 2008
1042	Naski, Michael C., et al. “Repression of hedgehog signaling and BMP4 expression in growth plate cartilage by fibroblast growth factor receptor 3.” <i>Development</i> 125: 4977-4988 (1998).
1043	Bienaimé, Jean-Jacques “38 th Annual J.P. Morgan Healthcare Conference.” BioMarin. PowerPoint Presentation. January 2020.
1044	Minina, Eleonora, et al. “Interaction of FGF, Ihh/Pthlh, and BMP signaling integrates chondrocyte proliferation and hypertrophic differentiation.” <i>Developmental Cell</i> 3: 439-449 (2002).
1045	Oefner, Christian, et al. “Structure of human neutral endopeptidase (Neprilysin) complexed with phosphoramidon.” <i>Journal of Molecular Biology</i> 296: 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).

Exhibit No.	Description
1049	Watanabe, Yasuhiro, et al. “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: 47-51 (1997).
1050	Mora, Camilo, et al. “How many species are there on Earth and in the ocean?” <i>PLoS Biology</i> 9: e1001127 (2011).
1051	Shim, Kye Shik. “Pubertal growth and epiphyseal fusion.” <i>Annals of Pediatric Endocrinology & Metabolism</i> 20: 8-12 (2015).
1052	Excerpt from Nelson, D. L., and Cox, M. M. “Lehninger Principles of Biochemistry,” W. H. Freeman (2013)
1053	Long, Shinong, et al. “A novel method for the large-scale production of PG-CNP37, a C-type natriuretic peptide analogue.” <i>Journal of Biotechnology</i> 164: 196-201 (2012).
1054	Neumeyer, L., Merker, A., & Hagenäs, L. “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: 401-412 (2021).
1055	Hoover-Fong, Julie E., et al. “Achondroplasia Natural History Study (CLARITY): a multicenter retrospective cohort study of achondroplasia in the United States.” <i>Genetics in Medicine</i> 23: 1498-1505 (2021).
1056	<i>Intentionally left blank</i>
1057	<i>Intentionally left blank</i>
1058	Burdan, F., et al., “Morphology and physiology of the epiphyseal growth plate,” <i>Folia Histochemica Et Cytobiologica</i> 47:5-16 (2009)

Petition for Post-Grant Review of U.S. Patent No. 12,233,106

Exhibit No.	Description
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. “Explaining large scale patterns of vertebrate diversity.” <i>Biology Letters</i> 11: 1-13 (2015).
1062	Espiner, E. et al. “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., et al. “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).
1064	Petition for Post-Grant Review of U.S. Patent No. 12,233,106, <i>Ascendis USA, Inc. et al v. BioMarin Pharmaceutical Inc.</i> , PGR2026-00013, Paper 1.
1065	Notice of Decisions on Institution, <i>Ascendis USA, Inc. et al v. BioMarin Pharmaceutical Inc.</i> , PGR2026-00013, Paper 14.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. §42.24

The undersigned hereby certifies that the foregoing Petition totals 18,688 words, excluding the parts which are exempted by 37 C.F.R. §42.24(a)(1).

Date: June 5, 2026

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 12,233,106, EXHIBITS 1001-1023, 1025-1033, 1035-1055, 1058-1059, 1061-1065, and PETITIONERS' POWERS OF ATTORNEY** were served on this 5th day of June, 2026 via FedEx Priority Overnight on Patent Owner at the correspondence address of record for U.S. Patent No. 12,233,106 as follows:

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and courtesy copies are being served on counsel for Petitioner and Patent Owner in PGR2026-00013 via FedEx Priority Overnight

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