UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SUN PHARMACEUTICAL INDUSTRIES LTD.
Petitioner,

v.

AURINIA PHARMACEUTICALS INC.
Patent Owner

Case IPR2022-00617
Patent 10,286,036

PETITION FOR *INTER PARTES* REVIEW OF
UNITED STATES PATENT NO. 10,286,036

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1005	AURA-LV: Aurinia Urinary Protein Reduction Active – Lupus with Voclosporin (AURA) (AURA-LV), Clinical Study NCT02141672, Study Record Version 10, submitted June 30, 2015, https://clinicaltrials.gov/ct2/history/NCT02141672?A=10&B=10&C=merged#StudyPageTop (last accessed February 1, 2022) ("AURA-LV")
1006	Papp K. et al., "Efficacy of ISA247 in plaque psoriasis: a randomized, multicenter, double-blind, placebo-controlled phase III study," *Lancet* (2008) 371:1337-42 ("Papp")
1007	Ha et al., "Increased risk of everolimus-associated acute kidney injury in cancer patients with impaired kidney function," *BMC Cancer* (2014) 14:906 ("Ha")
1008	History of Changes for Study NCT02141672 (AURA-LV), comparison of May 15, 2014 (Version 1, A), and June 30, 2015 (Version 10, B)
1009	Comprehensive Clinical Nephrology, R.J. Johnson, J. Feehally, and J. Floege (Eds.), Elsevier Saunders (5th Edition, 2015) (excerpts)
1010	Parikh S.V. and Rovin B.H., "Current and emerging therapies for lupus nephritis," *J. Am. Soc. Nephrol.* (2016) 27:2929-2939
1011	U.S. Patent No. 7,332,472
1012	Ling S.Y. et al., "Pharmacokinetics of voclosporin in renal impairment and hepatic impairment," *J. Clin. Pharmacol.* (2013) 53(12):1303-1312
1013	Gheith O., Al-Otaibi T., and Mansour H., "Next-generation calcineurin inhibitors in development for the prevention of organ rejection," *Transpl. Res. Risk Manag.* (2014) 6:23-30
1014	Rovin B.H. et al., "A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis," *Kidney Int'l* (2019) 95:219-231

1015	Lupus Foundation of America: National Resource Center on Lupus, "What is Lupus Nephritis," https://www.lupus.org/resources/what-is-lupus-nephritis, last accessed Feb. 9, 2022
1016	Levey A.S. et al., "A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation," *Ann. Intern. Med.* (1999) 130:461-470
1017	Boele-Schutte E. and Gansevoort R.T., "Measured GFR: not a gold, but a gold-plated standard," *Nephrol. Dial. Transplant.* (2017) 32:ii180-ii184
1018	Chang D. R. et al., "The ratio and difference of urine protein-to-creatinine ratio and albumin-to-creatinine ratio facilitate risk prediction of all-cause mortality," *Sci. Rep.* (2021) 11:7851
1019	"A brief history on the estimation of Glomerular Filtration Rate," *Gentian Diagnostics*, Feb. 4, 2021, https://www.gentian.com/news/cystatin-c-glomerular-filtration-rate (last accessed Feb. 15, 2022)
1020	National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am. J. Kidney Dis.* (2002) 39:S1-S000 (suppl 1)
1021	Huizinga R.B. et al., "AURION Study: 24-week data of multi-garget therapy with voclosporin, MMF and steroids for active lupus nephritis," *LUPUS* (2017) 4(Suppl 1):A10
1022	Keane W.F., Eknoyan G., "Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation," *Am. J. Kidney Dis*. (1999) 33:1004–1010
1023	Almaani, S., Meara A., and Rovin B.H., "Update on Lupus Nephritis," *Clin. J. Am. Soc. Nephrol.* (2017) 12:825-835
1024	Li X. et al., "Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis," *Nephrol. Dial. Transplant.* (2012) 27:1467-1472
1025	Alamilla-Sanchez M.E. et al., "Mechanism of action and efficacy of immunosuppressors in lupus nephritis," *Int. J. Nephrol. Renov. Dis.* (2021) 14:441-458
1026	Huizinga R.B. et al., "AURION Study: 48-week data of multi-target therapy with voclosporin, MMF and steroids for active lupus nephritis," presented March 27, 2017, The 12th International Congress on Systemic Lupus Erythematosus (LUPUS 2017) & the 7th Asian Congress on Autoimmunity (ACA 2017)

1027	Aurinia Press Release, "Aurinia announces voclosporin meets 48-week remission endpoints, achieving highest complete remission rate of any global lupus nephritis study," March 1, 2017
1028	Label for Afinitor (everolimus) tablets for oral administration, Novartis, revised 07/2012
1029	Busque S. et al., "The PROMIS*E* study: A phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation," *Am. J. Transplant*. (2011) 11:2675-2684
1030	Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C. § 301), excerpt (Section 801)
1031	Aurinia Press Release, "Isotechnika merger with Aurinia to create leading nephrology company," February 5, 2017
1032	USPTO Assignment Record for U.S. Pat. No. 10,286,036
1033	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Patent and Exclusivity for N213716, voclosporin (Lupkynis) capsule 7.9mg
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I. INTRODUCTION

Sun Pharmaceutical Industries Ltd. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 of claims 1-13 of U.S. Patent No. 10,286,036 ("the '036 patent"; EX1001). Because the '036 patent claims a method of using a known active ingredient and monitoring a patient's progress using routine clinical tests, a reasonable likelihood exists that Petitioner will prevail with respect to at least one of the challenged claims.

The '036 patent issued on May 14, 2019, and is currently assigned to Aurinia Pharmaceuticals Inc. ("Patent Owner"). The '036 patent claims a dosing regimen for treating a proteinuric kidney disease, such as lupus nephritis, that involves administering a known calcineurin inhibitor, voclosporin, to a patient, monitoring the patient's renal function using routine clinical tests (estimated Glomerular Filtration Rate ("eGFR") or urinary protein to creatinine ratio ("UPCR")), and adjusting or stopping the dose of voclosporin in response to changes in eGFR. Decreases in eGFR are a known side-effect of treatment with voclosporin, and indicate worsening kidney function. Treating kidney disease with a calcineurin inhibitor ("CNI") like voclosporin and observing concomitant changes in eGFR was also known at the time of the invention. The '036 patent adds nothing new, and instead, attempts to claim a treatment regimen relying upon these well-known tests.

First, claims 1-11 of the '036 patent would have been obvious over the AURA-LV Clinical Trial Study Record (EX1005, hereafter "AURA-LV") in view of Papp (EX1006). AURA-LV is discussed in the '036 patent, (*see* EX1001 at 2:9-18), and involved testing the effects of low and high dose voclosporin on patients with lupus nephritis over 24 and 48 weeks while monitoring eGFR levels. *Id*. AURA-LV explicitly disclosed all of the claimed method steps but one. The remaining required step—decreasing or stopping treatment with voclosporin if a patient's eGFR declined more than 30%—was disclosed in Papp. *See* EX1006 at 1338-39. That step would have been obvious to a skilled artisan, who would have known that a decline in eGFR was a known side effect of treatment with a CNI like voclosporin, and if left unchecked, could lead to kidney failure. Indeed, such parameters were routinely monitored, and therapy adapted or withdrawn if they showed signs of worsening.

Second, claims 12-13 of the '036 patent add the obvious step of determining a patient's eGFR at a third point in time, and if the patient's eGFR has returned to a certain percentage of baseline levels, resuming dosage with voclosporin. It would have been obvious to a skilled artisan to restart therapy once a patient's eGFR values re-approached baseline values. Modulating therapy in this way when a patient's kidney function was at risk was well-known to those of skill in the art, and was expressly disclosed in Ha. *See* EX1007 at 2, 4. In Ha, kidney function in

the form of eGFR was monitored in patients receiving an immunosuppressant, and treatment was reduced or stopped when kidney function worsened. *Id*. at 4. After kidney function recovered, treatment was resumed. *Id*. As Petitioner's expert witness, Dr. Jaimes, explains, such modulation of therapy was routine at the time of the invention. EX1003 at ¶¶ 29, 85, 123.

Thus, when viewed in the context of the state of the art at the time of filing, the '036 patent claims represent no more than "a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures." *BioMarin Pharms. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, IPR2013-00534, Paper No. 81 at 13-14 (P.T.A.B. Feb. 23, 2015). Accordingly, claims 1-13 are unpatentable under 35 U.S.C. § 103 as obvious. Petitioner therefore respectfully requests that the Board institute IPR and cancel claims 1-13.

II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '036 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

B. Challenge Under 37 C.F.R. § 42.104(b) and Relief Requested

Petitioner requests an IPR of claims 1-13 of the '036 patent on the below statutory grounds and requests that each claim be found unpatentable. Petitioner

explains how these claims are unpatentable under each ground, supported by the Declaration of Dr. Edgar Jaimes (Ex. 1003).

Ground	'036 Patent Claims	Basis for Rejection
Ground 1	1-11	§ 103 over AURA-LV in view of Papp
Ground 2	12-13	§ 103 over AURA-LV in view of Papp and Ha

AURA-LV (EX1005), Papp (EX1006), and Ha (EX1007) qualify as prior art under post-America Invents Act (AIA) 35 U.S.C § 102(a)(1) and § 102(b) because they were made available to the public more than one year before the effective filing date of the claimed invention (May 12, 2017).

C. Claim Construction

A claim subject to IPR "shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b).

Here, because the asserted prior art references expressly disclose and otherwise render obvious the language used in the claims of the '036 patent, no construction is necessary for the claim terms, as the asserted prior art teaches the limitation regardless of how the claim terms are construed. *See Vivid Techs., Inc.*

v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.").

Still, petitioner notes that the preamble phrase "[a] pharmacodynamic method to treat a proteinuric kidney disease" in claim 1 is not limiting. "[A]s a general rule preamble language is not treated as limiting." *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1347 (Fed. Cir. 2012). Further, a preamble is "not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Braintree Lab'ys, Inc. v. Novel Lab'ys, Inc.*, 749 F.3d 1349, 1357 (Fed. Cir. 2014) (internal quotations omitted). Here, the patentee defined a structurally complete invention—a method of treatment—in the claim body, and the preamble only recites the intended function of treating a proteinuric kidney disease. *See* EX1001 at claim 1.

Repetition of a "pharmacodynamic method" within the claim body does not transform them from non-limiting preamble language into limitations. Reference to the "pharmacodynamic method" within the claim body is simply a reiteration of the preamble, ("said pharmacodynamic method ***further comprising***"), or a "preamble within a preamble." *See, e.g., Microprocessor Enhancement Corp. v. Tex. Instruments Inc.*, 520 F.3d 1367, 1374 (Fed. Cir. 2008); *HTC Corp. v. IPCom*

GmbH & Co., KG, 667 F.3d 1270, 1277-78 (Fed. Cir. 2012). Such a "preamble within a preamble" is not limiting if it serves "as a contextual label for the body of the claim that followed rather than being essential to understanding the invention," as is the case here. *Simpson Strong-Tie Co., Inc. v. Oz-Post Int'l, LLC*, No. 3:18-CV-01188-WHO, 2020 WL 3187950, at *3 (N.D. Cal. June 15, 2020). Here, the body of the claim recites the steps of the "pharmacodynamic method"; thus, it carries no independent patentable weight. *See, e.g., Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375–76 (Fed. Cir. 2001) (finding preamble to a method of treatment non-limiting when it "does not result in a manipulative difference in the steps of the claim" and "does not change those amounts or otherwise limit the claim.").

Should Patent Owner contend that "method to treat a proteinuric kidney disease" is limiting and that "method to treat" should be construed to require producing a therapeutic effect in a patient, Petitioner disagrees. Not every patient described in the '036 patent experienced a therapeutic effect from the method of treatment. *See* EX1001 at 9:3-40 (tables showing less than 100% patients achieving a partial response to treatment). Moreover, the recited method steps "are performed the same way regardless whether or not the patient experiences a [therapeutic effect]." *Bristol-Myers Squibb*, 246 F.3d at 1375. Therefore, neither the claim language nor the description of the claimed invention supports construing

the "method to treat" portion of the preamble to require producing a therapeutic effect in a patient. Thus, if construed at all, the phrase should be construed as a "method intended to benefit a patient." *See, e.g., Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 9 at 7-10 (P.T.A.B. Sept. 22, 2016).

III. BACKGROUND

A. Proteinuric Kidney Disease and Lupus Nephritis

Proteinuric kidney diseases are a group of disorders associated with significant losses of protein in the urine (called "proteinuria"). *See* EX1009 at 14, 41; EX1001 at 1:30-34; EX1003 at ¶ 19. While these disorders cover a broad spectrum, (*see* EX1001 at 2:54-62), the '036 patent focuses on lupus nephritis. *See* EX1001 at 1:15-16, 1:20-2:26.

Lupus nephritis is a complication that can arise in patients who suffer from the autoimmune disease lupus. EX1009 at 303; EX1003 at ¶ 34. Injury to the kidney in the form of lupus nephritis is common in lupus patients; over 40% of lupus patients will develop lupus nephritis at some point in their lives. EX1009 at 303; EX1001 at 1:22-25; EX1003 at ¶ 34. In its early stages, lupus nephritis can go unnoticed, but if left untreated, symptoms can worsen and lead to kidney damage and ultimately, kidney failure. EX1015 at 1; EX1009 at 309-310; EX1001 at 1:25-30; EX1003 at ¶ 35. Permanent kidney damage, referred to as chronic kidney disease (CKD), can result in kidney failure, also called end-stage renal

disease (ESRD), generally requiring either dialysis or a kidney transplant. EX1009 at 942, 947; EX1003 at ¶ 35.

B. Monitoring Kidney Function During Disease Progression

Healthy kidneys function by filtering toxins out of the bloodstream and removing them by excreting urine. EX1009 at 14; EX1003 at ¶ 22. One measure of kidney health is the "estimated Glomerular Filtration Rate," or "eGFR." EX1009 at 34-35; EX1020 at 14; EX1003 at ¶ 22. eGFR is part of basic and comprehensive metabolic panels performed in routine blood tests, and is used to help detect kidney disease before any overt symptoms may be present. *See* EX1009 at 37, 942-944; EX1003 at ¶ 23. In a healthy young adult, eGFR is approximately 120 mL/min/1.73 m^2, and declines normally with age or with worsening kidney function caused by disease or injury. *See* EX1003 at ¶ 25.

To determine eGFR, a medical provider uses a specific formula that factors in a patient's creatinine level in the bloodstream, their age, sex, height, weight, race and/or ethnicity. EX1003 at ¶ 26. While healthy kidneys will filter all of the creatinine out of the bloodstream (excreting it in urine), diseased or impaired kidneys filter creatinine less effectively, causing it to build up in the blood. EX1009 at 31-32; EX1020 at 86; EX1003 at ¶ 27. Elevated creatinine in a patient's blood can indicate kidney disease or damage, and for that reason the creatinine level forms the main basis for the eGFR calculation. *See* EX1009 at 34;

EX1020 at 85; EX1003 at ¶ 27. Once eGFR levels drop below 60 mL/min/1.73 m^2, permanent damage has generally occurred, and additional symptoms may arise as waste buildup due to incomplete clearance causes complications. EX1009 at 942-947; EX1001 at 6:6-34; EX1003 at ¶ 28. Thus, as Dr. Jaimes explains, in addition to being an indicator of kidney function, improvement in eGFR is a key target outcome, and eGFR is therefore carefully monitored. EX1003 at ¶ 24.

In addition to filtering toxins like creatinine, healthy kidneys also function as a barrier that prevents the filtering of proteins into the urine. EX1009 at 14; EX1020 at 14; EX1003 at ¶ 30. Diseased or damaged kidneys may not process proteins as effectively, causing detectible amounts of proteins to be present in the urine. EX1009 at 14, 41; EX1020 at 14-15; EX1003 at ¶ 30. Protein in the urine, referred to as proteinuria, can be used to calculate another clinical test parameter for kidney function—the urinary protein to creatinine ratio, or UPCR, which compares the amount of protein found in a patient's urine against the amount of creatinine. EX1003 at ¶ 31. Creatinine is normally released into the urine at a constant rate, and thus the ratio of the two measurements can be used to detect changes in the amount of protein excreted. EX1009 at 31-32, 41-42; EX1003 at ¶ 32.

Neither eGFR or UPCR is new; both have been in standard clinical practice for decades. For example, glomerular filtration rate, by some metric or another,

has been used to assess kidney function dating back to the 1970s. *See* EX1019 at 2-3; EX1003 at ¶ 33. The current gold standard for eGFR, the CKD-EPI equation, was established by the National Institutes of Diabetes, Digestive and Kidney Disease in 2009, and thus was in routine use at the time the '036 patent was filed. *See* EX1009 at 35; EX1017 at ii183; EX1003 at ¶ 33. Likewise, UPCR has been in widespread use since at least the 1990s, and was also in routine use at the time the '036 patent was filed. EX1003 at ¶ 33. Notably, both parameters were also used at that time to assess kidney function in patients with proteinuric kidney disease. *Id*.

C. Evolution of Lupus Nephritis Treatment and the Discovery of Voclosporin

Treatment of lupus nephritis has changed significantly in the past decades. In the 1950s, lupus nephritis had a survival rate of only 17% at five years. EX1010 at 2929. The introduction of corticosteroids and the subsequent introduction of cytotoxic agents in the 1970s increased the survival rate to 80% at five years. *Id*.; EX1003 at ¶ 37. Prior to the introduction of voclosporin and other alternative therapies, such as cyclosporine, tacrolimus, rituximab (Rituxan®), or belimumab (Benlysta™), the standard of care was high-dose corticosteroids given with an immunosuppressive agent such as mycophenolate mofetil (MMF) or cyclophosphamide. *See* EX1009 at 310-311; EX1010 at 2929; EX1001 at 1:38-40; EX1003 at ¶ 37.

Treatment of lupus nephritis generally occurs in two phases. In the initial

treatment phase, called induction, the goal is to rapidly attenuate the renal inflammation so that the kidney can begin to heal. EX1010 at 2929; EX1009 at 310-312; EX1003 at ¶ 38. Because lupus nephritis often relapses, it requires ongoing treatment to limit disease flare-ups, a second phase of treatment known as maintenance therapy. EX1010 at 2930; EX1009 at 309, 312-313; EX1003 at ¶ 38.

Clinicians in the 2000s and 2010s continued to pursue new medicines and seek improved therapeutic regimens, casting a wide net of potential drug options. *See, e.g.*, EX1010 at 2932-35; EX1003 at ¶ 39.

One promising category of small molecule drugs was calcineurin inhibitors ("CNIs"), which act by preventing the release of certain pro-inflammatory cytokines. EX1010 at 2935; EX1003 at ¶ 40. CNIs tacrolimus and cyclosporine, paired with the standard of care corticosteroids and MMF, were tested with favorable initial results. EX1010 at 2935; EX1009 at 310-312; EX1024 at 1469; EX1003 at ¶ 40. CNIs' well-known side effect of nephrotoxicity, however, generally restrict their availability for long-term use in treating kidney disease. *See* EX1006 at 1337; EX1009 at 888; EX1011 at 4:28-48, 5:34-38; EX1003 at ¶ 41. While the exact mechanism by which CNIs cause renal injury is not completely understood, it was known that reducing the dose of CNIs would lead to improved renal function. EX1011 at 4:46-48; EX1003 at ¶ 41.

Analogs of the CNI cyclosporine were investigated, and an analog called

ISA247 was found to exhibit a combination of enhanced potency and reduced toxicity over the naturally occurring cyclosporines. *See* EX1011 at 4:51-63; EX1003 at ¶ 42. ISA247, which came to be known as voclosporin, differs from cyclosporine by adding a single carbon extension to the 1-amino acid residue, as shown below:

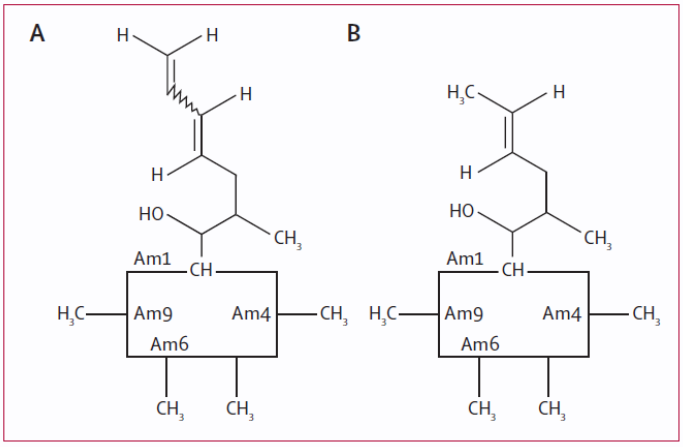

Figure 1: Comparison of the structures of ISA247 (A) and ciclosporin (B)

EX1006 at 1338; *see also* EX1011 at 4:54-59, 6:1-39; EX1012 at 1. This modification allowed voclosporin to bind more tightly to calcineurin than cyclosporine does, resulting in more complete inhibition and a nearly 4-fold increase in immunosuppressive effect. EX1006 at 1337; EX1012 at 1; EX1013 at 24. Additionally, the metabolism of voclosporin results in fewer metabolites than cyclosporine, as well as faster elimination of the metabolites that are produced, leading to a reduction (but not elimination) of side effects and an overall improved safety profile. EX1006 at 1337; EX1012 at 1; EX1013 at 24; EX1003 at ¶ 42. Thus, voclosporin held promise as an improved CNI and overall

immunosuppression agent.

Voclosporin was subsequently studied in numerous clinical trials as a treatment for a wide variety of autoimmune conditions, including plaque psoriasis, (EX1006; EX1013 at 25), prevention of kidney transplant rejection, (*see* EX1012; EX1013; EX1029), uveoretinitis, (EX1013), and, critically, lupus nephritis, (*see* EX1005; EX1010 at 2933; EX1012; EX1013 at 23; EX1021 at A10). *See also* EX1011 at 23:25-24:22 (listing indications of interest for voclosporin and its isomers); EX1003 at ¶ 43. Thus, prior to the effective filing date of the '036 patent, clinicians had used voclosporin in clinical trials to successfully treat lupus nephritis, as well as many other diseases.

IV. SUMMARY OF THE '036 PATENT

The '036 patent is entitled "Protocol for Treatment of Lupus Nephritis." EX1001. It was filed in the United States on December 7, 2017, and claims priority to two provisional applications, U.S. Pat. App. No. 62/541,612, filed on August 4, 2017, and U.S. Pat. App. No. 62/505,734, filed on May 12, 2017 (the effective filing date of the '036 patent). The '036 patent is drawn to method claims, and issued after rejections over an earlier version of the AURA-LV study design, (*see* EX1008), and another prior art reference not asserted here, Lorenz.

A. The '036 Patent Does Not Claim the Compound Voclosporin

The voclosporin compound itself was claimed in U.S. Pat. No. 7,332,472,

which has an effective filing date of October 19, 2001. EX1011. The '472 patent was assigned to Patent Owner in October 2013 following Patent Owner's merger with the original assignee, Isotechnika Pharma Inc. *See* EX1031; EX1032. Apart from the '036 patent, the '472 patent is the only other Orange Book-listed patent for Patent Owner's marketed voclosporin drug, Lupkynis™, and is set to expire on October 17, 2022. EX1033. The '036 patent, which does not expire until 2037, provides fifteen additional years of patent protection to Patent Owner's voclosporin product. *Id*.

B. The '036 Patent Claims

The '036 patent includes thirteen claims, each of which covers a method for treating kidney disease with voclosporin while monitoring the patient for a known side effect—a reduction in the patient's eGFR—and decreasing or stopping voclosporin if the patient's eGFR decreases below a certain level. Claim 1, the only independent claim of the '036 patent, reads as follows:

> 1. A pharmacodynamic method to treat a proteinuric kidney disease which method comprises administering to a subject diagnosed with said disease a predetermined daily dosage of an effective amounts[sic] of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:
>
> (a) assessing the estimated Glomerular Filtration Rate (eGFR) of said subject at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73 m^2 between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject;

(ii) if the eGFR of said subject decreases by less than said target % between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

EX1001 at claim 1. The remaining claims of the '036 patent all depend directly or indirectly from claim 1.

C. The '036 Patent Specification

The background section of the '036 patent first describes a Phase I study, in which patients with lupus nephritis were dosed with 23.7 mg of voclosporin twice daily in combination with MMF and a corticosteroid over 24 weeks. EX1001 at 1:59-65; *see also* EX1021 at A10. The study specified that entry criteria included determination of a UPCR of ≥ 1.0 mg/mg or ≥ 1.5 mg/mg, depending on the results of a renal biopsy, as well as an eGFR of ≥ 45 mol/mn/1.73 m^2. EX1001 at 1:65-2:3; EX1021 at A10. The results of that study showed that 70% of subjects achieved complete response at 24 weeks, and indicated that renal function (i.e. eGFR) remained stable. EX1021 at A10; *see also* EX1001 at 2:3-5. Results after 48 weeks showed similar findings. *See* EX1026 at 15, 20.

The '036 patent goes on to describe a Phase II study, AURA-LV, which

tested the twice daily 23.7 mg of voclosporin dose, as well as a higher dose of 39.5 mg twice daily. EX1001 at 2:9-14. The patent describes successful complete or partial remission results, (*id*. at 2:14-18), which were published in a news release on March 1, 2017. *Id*. at 2:9-10; *see also* EX1027.

Turning to the disclosure of the invention as claimed, Example 1 of the '036 patent is entitled "48 Week Study of LN Treatment." EX1001 at 8:1-4. This example discloses results obtained during the AURA-LV study by segregating subjects into patients who experienced significant eGFR reduction (and had their voclosporin dosage reduced) and those who did not (and maintained their voclosporin dosage). EX1001 at 8:41-64. Tables 2 and 3 disclose the percentages of patients who experienced complete remission (CR) or partial remission (PR) after 24 weeks and 48 weeks, respectively. *Id*. at 9:4-40. The specification notes that complete remission rates were not affected by the difference in dosing regimens at 24 weeks. *Id*. at 9:50-55. Likewise, the percentage of patients with partial remission at 24 weeks was also "roughly the same." *Id*. Similar results were observed at 48 weeks. *Id*. at 9:55-58.

D. Prosecution History

During prosecution of the application that resulted in the '036 patent, the Examiner rejected the claims twice as obvious over the combination of AURA-LV, (EX1005), and a journal article by Lorenz, not asserted here. *See* EX1002 at 62-

64, 107-115. The claims were allowed only after an expert declaration and disclosure of allegedly unexpected results. *See id*. at 142-149, 166-184, 231-236.

The Examiner first issued a non-final rejection, finding that AURA-LV disclosed treating patients with lupus nephritis with voclosporin using the claimed dosage amounts. *See id*. at 62-63. The Examiner further found that AURA-LV taught measuring eGFR and UPCR as primary and secondary outcomes, as well as at baseline. *Id*. at 63. While the Examiner indicated that AURA-LV "is silent to the specific dosing protocol and adjusting the dose based on eGFR being within a certain percentage of a desired range," he found that AURA-LV "teaches the desired[sic] to improve eGFR or keep it at a level that does not decrease more than 20%," thus providing motivation for a person of skill in the art to optimize dosage in response to changing eGFR levels. *Id*. This motivation was further supplemented by Lorenz's disclosures of "altering dosages of the therapeutic based in[sic] indicators of response including eGFR." *Id*.

In response, the applicant attempted to distinguish Lorenz as "relat[ing] to a different drug" and protocol and alleged that certain limitations were absent—namely, adjusting the treatment based on eGFR. *Id*. at 83.

The Examiner disagreed, and issued a final rejection. *See id*. at 107-115. Regarding the dosing protocol parameters of adjusting or maintaining the dosage based on eGFR, the Examiner argued that "[i]t would be obvious at the time of the

invention to optimize the dosing of the voclosporin based on eGFR and changes of eGFR following treatment and treatment duration…given that eGFR is a known indicator of response to a drug as taught by [Lorenz]." *Id*. at 113.

In response to the final rejection, the applicant requested an interview with the Examiner to discuss a series of documents that applicant alleged showed unexpected results supportive of non-obviousness—namely, additional results from the AURA-LV study not found in the specification, and a supporting expert declaration from Dr. James Tumlin, a scientific adviser to applicant and one of the investigators on AURA-LV. *See id*. at 141-184. Dr. Tumlin argued that it was "clinically and scientifically counterintuitive" that the "subjects in the cohort that had reduced dosage overall (i.e. underwent dose reduction due to decrease in eGFR) surprisingly showed better efficacy at both 24 weeks and 48 weeks in both partial response (PR) and complete response (CR) than those who were given an overall higher dose." *Id*. at 182.

The Examiner thereafter allowed the claims, finding the declaration "sufficient to overcome the rejection," and noting that the applicant had shown "unexpected results with regards to greater efficacy in subjects where the dosage was adjusted individually based on eGFR," and in particular found the fact that "patients wherein the dosage was lowered due to lower eGFR actually had greater therapeutic outcome then patients wherein the dosage was not lowered" was

"unexpected and surprising because these subjects were less able to tolerate the drug and less receptive to the treatment." *Id*. at 233.

The Examiner erred in allowing claims 1-13 of the '036 patent. For the reasons discussed in detail below in Section V(D)(1), the Examiner's decision to credit the testimony of applicant's declarant and evidence of supposed unexpected results misapprehended the full nature of these claims, which are directed to a protocol for treatment that involves, as an ***alternative*** to the dosage reduction which led to the alleged unexpected results, ***cessation*** of treatment altogether. *See, e.g*., EX1001 at claim 1 ("if the eGFR of said subject decreases by more than a target % …reducing the daily dosage…***or stopping the administering of voclosporin to said subject***…") (emphasis added). Setting aside the question of whether the dose reduction step was obvious, the inclusion of a treatment termination step expands the claim to encompass disclosures in the prior art, and necessarily renders the claims unpatentable. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328, n.4 (Fed. Cir. 2008), ("[c]laims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter."). Papp, a reference the Examiner did not consider, disclosed this limitation. *See* EX1006 at 1338-39, 1341; EX1001 at "References Cited".

V. CLAIMS 1-13 OF THE '036 PATENT ARE UNPATENTABLE

Regarding obviousness, four factors are analyzed below: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007).

A. Level of Skill in the Art

A person of ordinary skill in the art would be a physician with a background in either nephrology or rheumatology, who at the time of the invention would have had at least three years of experience diagnosing and treating patients with proteinuric kidney diseases, and would also have experience conducting clinical trials and/or reviewing and understanding the results of those trials. EX1003 at ¶ 69.

B. Ground 1: Claims 1-11 Would Have Been Obvious Over AURA-LV in view of Papp

Independent claim 1 and dependent claims 2-11 of the '036 patent would have been obvious over AURA-LV (EX1005) in view of Papp (EX1006).

1. The Prior Art

(a) AURA-LV

AURA-LV is the Study Record for the Phase 2 Study NCT02141672, or the "Aurinia Urinary Protein Reduction Active – Lupus with Voclosporin" study sponsored by Patent Owner and first published in the ClinicalTrials.gov database of the National Library of Medicine on May 15, 2014. *See* EX1005 at 1. The study investigators submitted a series of revisions incorporating additional changes to the study through April 26, 2021. *Id*. The version relied upon here as prior art is version 10, submitted on June 30, 2015, more than one year before the May 12, 2017 claimed filing date of the '036 patent. *Id*. This version was archived by the Internet Archive on October 2, 2015 (as authenticated by the affidavit of N. Frank-White, EX1034). *See Advanced Micro Devices, Inc., v. Aquila Innovations, Inc.*, IPR2019-01526, Paper 13 at 53-57 (P.T.A.B. Mar. 13, 2020) (crediting Internet Archive affidavit as evidence of public accessibility). Additionally, as Dr. Jaimes explains, all clinical trials in the United States are required to be made public on the clinicaltrials.gov website, both now and in 2017. EX1003 at ¶ 53; *see also* EX1034 at 11-14. Further, Dr. Jaimes utilized this website, as did his colleagues and patients, to access clinical trial information. *Id*. Indeed, in 2007 Congress mandated that the clinical trials registry be expanded and that it be "ensure[d] that the registry data bank is made publicly available through the Internet." EX1030 at

6; *see also id.* at 7-8 (required information); *see also id.* at 11 (explaining goal "to enhance patient access to and understanding of the results of clinical trials"). Information on a clinical trial must generally be reported within twenty-one days of enrollment of the first patient. *See id*. at 8-9. Information will then be published on the website within thirty days. *Id*. at 9. Thus, the AURA-LV study record was made publicly available and accessible more than a year before the effective filing date of the '036 patent and is prior art.

AURA-LV describes voclosporin as a "next generation CNI intended for use in the prevention of organ graft rejection and for the treatment of autoimmune diseases." *Id*. at 2. AURA-LV's goal was "to investigate whether voclosporin added to the standard of care treatment in active [lupus nephritis] is able to reduce disease activity, as measured by a reduction in proteinuria." *Id*. To qualify at the outset, patients had to have a "UPCR of ≥ 1.5 mg/mg assessed in a first morning void urine specimen," and an eGFR of >45 mL/min/1.73 m^2. *Id*. at 5.

Patients were divided into three arms of the study: low dose voclosporin (23.7 mg BID (i.e. twice daily), in three 7.9 mg capsules), high dose voclosporin (39.5 mg BID, in five 7.9 mg capsules), and placebo. *Id*. at 3. All patients were also treated with "a background of MMF and corticosteroids," the standard of care therapy. EX1005 at 4; EX1003 at ¶ 55.

Study efficacy was assessed "by the ability of the drug combination to

reduce the level of proteinuria while demonstrating an acceptable safety profile." *Id*. Specifically, the study defined complete remission as a confirmed UPCR of ≤ 0.5 mg/mg and an eGFR of ≥ 60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥ 20% at 24 weeks. *Id*. The study defined partial remission by 50% reduction in UPCR from baseline at weeks 24 and 48. *Id*. The study also included additional secondary outcome measures, such as the "[c]hange from baseline in serum creatinine, urine protein, serum albumin, eGFR at each visit measured" over a 50 week period. *Id*. at 3-4.

(b) **Papp**

Papp is an article entitled "Efficacy of ISA247 in plaque psoriasis: a randomized, multicenter, double-blind, placebo-controlled phase III study," published on April 19, 2008 in The Lancet. EX1006. As discussed above in Section III(C), "ISA247" is voclosporin. *See, e.g.*, EX1013 at 24 ("As a result of the continuous search for immunosuppressive agents with better efficacy and safety profiles, CsA derivative ISA247 (voclosporin; VCS) was successfully created."). Papp describes voclosporin as "a novel calcineurin inhibitor intended for the treatment of autoimmune diseases, such as psoriasis and uveitis, and prevention of organ transplant rejection." EX1006 at 1337. Papp explains that "[t]he use of systemic calcineurin inhibitors for the treatment of patients with psoriasis is limited by toxicity, particularly nephrotoxicity," and thus voclosporin

was desirable to test because it "was more potent and had a more favorable side-effect profile" in animal models." *Id*.

Papp describes the results of a Phase 3 study testing voclosporin for use in treating plaque psoriasis, an autoimmune disease that primarily affects the skin. To qualify for the study, patients had to have "a glomerular filtration rate (GFR) greater than 60 mL/min, and less than 30% change in the GFR between screening and randomisation." *Id*.

Plaque psoriasis patients were treated with either placebo or one of three dosages of voclosporin (0.2 mg/kg, 0.3 mg/kg, or 0.4 mg/kg) taken orally twice a day for twelve weeks. EX1006 at 1338. After twelve weeks, patients taking voclosporin remained in their treatment groups, while patients receiving the placebo switched to the 0.3 mg/kg voclosporin treatment group for the remaining twelve weeks of the study. *Id*.

Because nephrotoxicity was a known concern with CNIs, during the study, "[s]tandard clinical and laboratory tests were done every 4 weeks," and "[r]enal function was assessed with calculated GFR to identify any potential nephrotoxicity." *Id*. at 1338-1339. Critically, Papp explains that "[i]f a patient had a 30% or more…reduction in baseline GFR, a second GFR was obtained," and if the second GFR measurement was still reduced by at least 30%, "the patient was withdrawn from the trial." *Id*. at 1339. Indeed, reduced GFR "was the most

frequently reported adverse event that resulted in discontinuation." *Id*. at 1340-1341; *see also id.* at 1340 (Table 4). Thus, a subset of patients who began the study taking voclosporin had their treatment withdrawn, or stopped, following a reduction in baseline GFR of at least 30%. *Id*.; EX1003 at ¶ 61.

The results published in Papp showed that at 12 weeks, voclosporin improved plaque psoriasis in patients, and the patients retained this improvement during the following 12 weeks. *See* EX1006 at 1341. Papp notes that "pharmacokinetic data show a strong correlation between response and drug concentrations, raising the potential for precise titration of dosing in clinical practice," and concludes that voclosporin "could provide effective immunosuppression without many of the dose-limiting side-effects associated with other calcineurin inhibitors" due to its "improved safety profile" and "increased potency." *Id*. at 1342.

(c) **The Combination of AURA-LV and Papp**

A person of ordinary skill in the art would have been motivated to combine AURA-LV and Papp because AURA-LV taught that voclosporin was "a next generation CNI intended for use in the prevention of organ graft rejection and for the treatment of autoimmune diseases." EX1005 at 4. Papp was an earlier study that disclosed using voclosporin for treatment of one such autoimmune disease—plaque psoriasis. EX1006 at 1337. Thus, a person of ordinary skill in the art

seeking to effectively treat disease with voclosporin would have looked to Papp as an example of a previous clinical trial using voclosporin, and learned from Papp that the eGFR of patients treated with voclosporin should be monitored and voclosporin withdrawn if the patient's eGFR dropped by 30% or more from his or her baseline. EX1003 at ¶ 74.

A person of ordinary skill in the art seeking to use voclosporin as a treatment for a proteinuric kidney disease would have looked to Papp for the additional reason that Papp was a study funded by Isotechnika Inc., the company who developed and patented voclosporin. *See* EX1006 at 1337; EX1011 at 1 (showing Isotechnika Inc. as the assignee of the '472 patent claiming voclosporin); *id.* at 23:36-24:23 (indications for voclosporin including both glomerulonephritis (24:8) and plaque psoriasis (23:67)); *see also* EX1003 at ¶ 75.

Both AURA-LV and Papp each independently disclose the majority of the limitations of claims 1-11. Considered in combination, they render all of the limitations of those claims obvious, as will be discussed below. At a high level, AURA-LV describes a study protocol in which patients with lupus nephritis were treated with voclosporin over 48 weeks, while their renal function was monitored for changes in eGFR and UPCR, parameters required to achieve complete remission. EX1005 at 2-4; EX1003 at ¶ 70. Papp describes a similar study in plaque psoriasis patients, where eGFR was also closely monitored. What Papp

specifically adds to the combination that is not express in AURA-LV is that if a patient's eGFR fell by 30% or more compared to baseline, treatment with voclosporin was stopped. EX1006 at 1338-1339; EX1003 at ¶ 70. It would have been obvious to a person of ordinary skill in the art, based upon Papp as well as her own knowledge, that a reduction of eGFR of 30% or more indicates a significant worsening of kidney function and puts the patient at risk to develop permanent kidney damage. EX1003 at ¶ 70. Thus, it would have been obvious to a person of ordinary skill in the art to either reduce or discontinue a patient's treatment with voclosporin following such a decrease in eGFR. *Id*.

2. Claim 1

(a) **"A pharmacodynamic method to treat a proteinuric kidney disease…"**

To the extent that the preamble is found to be limiting, AURA-LV discloses a "pharmacodynamic method to treat a proteinuric kidney disease" through its clinical trial protocol for treating patients diagnosed with lupus nephritis. *See* EX1005 at 4 (describing goal of study "[t]o assess the efficacy of 2 doses of voclosporin compared to placebo in achieving complete remission after 24 weeks of therapy subjects with active lupus nephritis"). Lupus nephritis is a "proteinuric kidney disease." EX1003 at ¶ 72; EX1001 at 1:1-2, 1:22-23, 2:30-32. AURA-LV discloses a pharmacodynamic method of treating lupus nephritis by disclosing monitoring the eGFR of patients and continuing treatment with voclosporin.

Papp also discloses a "pharmacodynamic method to treat a proteinuric kidney disease." Papp teaches a method of treatment wherein renal function was tested every four weeks and "[i]f a patient had a 30% or more…reduction in baseline GFR" that persisted over two readings, "the patient was withdrawn from the trial." EX1006 at 1339. Eight such patients were withdrawn from the trial on this basis. *See id*. at 1340-1341. Thus, continued treatment of the patients in Papp with voclosporin depended on their retention of baseline renal function. EX1003 at ¶ 73.

(b) **Thus, AURA-LV and Papp, alone or together, disclose a "pharmacodynamic method for treating proteinuric kidney disease." "…which method comprises administering to a subject diagnosed with said disease a predetermined daily dosage of an effective amounts of voclosporin…"**

AURA-LV discloses "administering to a subject diagnosed with [proteinuric kidney disease] a predetermined daily dosage of an effective amounts[sic] of voclosporin." First, the inclusion criteria for the AURA-LV study required a "[k]idney biopsy within 6 months prior to Screening (Visit 1) with a histologic diagnosis of lupus nephritis" and "[l]aboratory evidence of active nephritis at screening[.]" EX1005 at 7. Thus, AURA-LV discloses treatment of subjects diagnosed with lupus nephritis. EX1003 at ¶ 77.

Second, AURA-LV discloses administering to these subjects "a

predetermined daily dosage" of 23.7 mg BID (i.e. twice daily) or 39.5 mg BID voclosporin. *Id*. at 5. As a Phase II study, AURA-LV would have necessarily followed Phase I studies and preclinical studies using voclosporin, and the study sponsor and principal investigators would have selected the dosages of voclosporin they expected most likely to be effective. EX1003 at ¶ 78. Moreover, studies of voclosporin for other indications showed successful treatment using similar dosages. For example, Papp used dosages of 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg voclosporin twice daily, with patients ranging in weight from 49-140 kg. *See* EX1006 at 1339 (Table 1). Papp demonstrated that all three dosages effectively treated plaque psoriasis. *See id*. at 1340 (Table 3 showing statistically significant p values at each dosage at 12 weeks). These dosages translate to a range of 9.8-56 mg voclosporin, as shown below:

Papp Dose (mg/kg)	***Dose for 49 kg patient (mg)***	***Dose for 140 kg patient (mg)***
0.2	9.8	28
0.3	14.7	42
0.4	19.6	56

Thus, both voclosporin dosages disclosed in the AURA-LV study protocol (23.7 mg and 39.5 mg) fall well within the effective range disclosed in Papp. EX1005 at 5; EX1006 at 1339; EX1003 at ¶ 79.

Additionally, the original voclosporin patent taught that "[d]osage levels of the order from about 0.05 mg to about 50 mg per kilogram of body weight per

day," were useful in treating the indications listed in the patent, which included glomerulonephritis. EX1011 at 26:34-36; *see also id.* at 23:36-24:23; EX1003 at ¶ 80.

(c) **"…over a projected treatment period of at least 24 weeks…"**

In the AURA-LV study, patients received treatment with voclosporin for a period of 48 weeks, with the primary outcome measured at 24 weeks. *See* EX1005 at 5; EX1003 at ¶ 81. Similarly, in Papp, patients not on placebo received treatment with voclosporin for a total period of 24 weeks. EX1006 at 1338; *see also id*. at 1340 (Table 3); EX1003 at ¶ 81.

(d) **[said pharmacodynamic method further comprising:] "(a) assessing the estimated Glomerular Filtration Rate (eGFR) of said subject at at least a first time point and a second time point on different days of said treatment period, and"**

In the AURA-LV study, the eGFR of potential subjects was measured at a first time point prior to study initiation to confirm that each participant in the clinical trial had an eGFR of > 45 mL/min/1.73 m^2. EX1005 at 7-8. Any subject with an eGFR ≤ 45 mL/min/1.73m^2 was excluded from the study. *Id*.; EX1003 at ¶ 82. Each subject enrolled in the AURA-LV study then had his or her eGFR measured at a second time point, namely on each visit for 50 weeks, and change from the baseline value was assessed. *See* EX1005 at 7-8; EX1003 at ¶ 82.

Indeed, eGFR change from baseline was identified as a secondary outcome measure of the study. *See* EX1005 at 5-7.

Similarly, in Papp, the eGFR of potential subjects was measured at a first time point prior to study initiation to confirm that each participant in the clinical trial had an eGFR of > 60 mL/min. EX1006 at 1337. "[S]afety analysis" was performed using "[s]tandard clinical and laboratory tests" every four weeks. *Id*. at 1338. As part of the safety analysis, "[r]enal function was assessed with calculated GFR to identify any potential nephrotoxicity." *Id*. at 1338-1339. Thus, eGFR was measured at secondary time points throughout the course of the study. *Id*.; EX1003 at ¶ 83.

Both AURA-LV and Papp therefore disclose "assessing the [eGFR] of said subject at at least a first time point and a second time point on different days of said treatment period[.]" EX1001 at claim 1; EX1003 at ¶¶ 82-83.

(e) **"(b)(i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73 m^2 between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject"**

As noted above, patients enrolled in Papp began the study with an eGFR greater than 60 mL/min, thus beginning with a "predetermined value in the range of 50-90 mL/min/1.73 m^2" as required by the claims. EX1006 at 1337; EX1001 at

claim 1. Papp explains that over the course of the study, "[i]f a patient had a 30% or more (defined as mild to moderate) reduction in baseline GFR, a second GFR was obtained," and "[i]f the second GFR was reduced by at least 30% compared with baseline, the patient was withdrawn from the trial." EX1006 at 1339. Thus, "if the eGFR of said subject decreases by more than a target % in the range of 20-45%"—here, 30%—"between said first and second time points," investigators would "stop[] the administering of voclosporin to said subject," as required by the claims. *Id.*; EX1001 at claim 1. Papp therefore discloses this limitation. EX1003 at ¶ 84.

Where the prior art discloses one of the two claimed alternatives, the claim is invalid. *See Brown v. 3M*, 265 F.3d 1349, 1352 (Fed. Cir. 2001) (finding claim anticipated where prior art disclosed one of two alternatives claimed); *In re Theresa*, 720 F. App'x 634, 637 (Fed. Cir. 2018) (finding claim rendered obvious where prior art disclosed one of two alternatives claimed). Additionally, even if reducing the voclosporin treatment was nonobvious—it is not, as explained below—that would not rescue the claim from invalidity. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008), ("[c]laims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter.") (quoting *In re Lintner*, 458 F.2d 1013, 1015 (C.C.P.A. 1972), *abrogated on other grounds*).

Even setting Papp aside, it would have obvious to a person of ordinary skill in the art treating a patient with a calcineurin inhibitor like voclosporin to monitor the patient's renal function through eGFR. *See* EX1007 at 2, 4; EX1012 at 1304; EX1003 at ¶¶ 22-29, 41-44, 85. It was well known at the time of the invention that calcineurin inhibitors such as voclosporin could cause nephrotoxicity and impaired renal function. *See id*.; EX1006 at 1337; EX1011 at 4:28-48, 5:34-38. Because prolonged renal impairment could lead to permanent damage and progressively worsening CKD, a person of ordinary skill would have found it obvious closely monitor renal function when treating a patient with a calcineurin inhibitor, and, upon observing a 20-45% drop in eGFR, would have either reduced the dosage of the calcineurin inhibitor or stopped treatment. EX1003 at ¶ 85; *see also* EX1007 at 2, 4 (reducing or withdrawing treatment with a calcineurin inhibitor following a decrease of more than 25% eGFR). As Dr. Jaimes explains, upon observing a decline in eGFR, a skilled artisan would often reduce or temporarily stop treatment, to allow kidney function to recover. EX1003 at ¶ 85.

Additionally AURA-LV discloses that voclosporin was dosed in individual 7.9 mg capsules. *See* EX1005 at 5 (low dose voclosporin placebo, designed to mimic the 23.7 mg dose of voclosporin, was provided to the patient in 3 capsules, thus each capsule contained 7.9 mg (i.e. 23.7 ÷ 3 = 7.9)); EX1003 at ¶ 86. Therefore, it would have been obvious to reduce a patient's dosage in 7.9 mg

increments—i.e., taking one less pill at a time. EX1003 at ¶ 86.

(f) **"(ii) if the eGFR of said subject decreases by less than said target % between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject"**

In Papp, if a patient's GFR did not decrease by at least 30% compared with baseline, the patient remained in the trial and continued to receive "the same predetermined daily dosage of voclosporin"—either 0.2 mg/kg, 0.3 mg/kg, or 0.4 mg/kg voclosporin. *See* EX1006 at 1338-1339; EX1003 at ¶ 87. Moreover, it would have been obvious to a person of ordinary skill in the art treating a patient with voclosporin who experienced either no reduction in eGFR or only a mild reduction in eGFR (i.e. less than a 20-45% reduction) that the voclosporin was not harming renal function, and would therefore have had no reason to reduce or discontinue treatment with voclosporin. EX1003 at ¶ 87.

3. Claim 2: The method of claim 1 wherein the first time point is immediately preceding administering voclosporin

As described above, in the AURA-LV study the eGFR of potential subjects was measured prior to study initiation, and more specifically, at screening time. *See* EX1005 at 7-8. Screening time typically occurs within days or weeks before enrollment. EX1003 at ¶ 89. Likewise, in the Papp study, the eGFR of potential subjects is not only taken at screening, but is again taken before randomization into

one of the arms of the study. *See* EX1006 at 1337 (ensuring patients had "less than 30% change in the GFR between screening and randomisation."). Randomization typically occurs either the same day or a few days before treatment initiation. EX1003 at ¶ 89. Thus, in both AURA-LV and Papp, the first time point at which eGFR is measured is "immediately preceding administering voclosporin," as required by claim 2. EX1001 at claim 2; EX1003 at ¶ 89. Moreover, it would have been obvious to a person of skill in the art to measure a patient's eGFR immediately before administering voclosporin, to ensure that the patient's kidneys were functional enough to endure therapy. EX1003 at ¶ 90. Indeed, running a metabolic panel and assessing kidney function would have been common practice before starting any sort of medication which was known to potentially affect renal function. *Id*.; *see also* EX1009 at 886, 888; EX1020 at 81-82; EX1021 at A10; EX1012 at 1304.

4. Claim 3: The method of claim 1 wherein the predetermined value is approximately 60 ml/min/1.73 m^2

As discussed above, in Papp subjects were only enrolled in the study if they had an eGFR of > 60 mL/min at screening. EX1006 at 1337. Thus, the predetermined minimum eGFR value for all subjects in Papp was 60 mL/min, as required by claim 3. *Id*.; EX1001 at claim 3; EX1003 at ¶ 93.

Additionally, 60 mL/min/1.73m^2 was also the primary outcome measure for

AURA-LV, (*see* EX1005 at 5), and is generally considered the standard lower end of the "normal" eGFR range. EX1003 at ¶¶ 92-93; EX1009 at 35; EX1020 at 98.

5. Claim 4: The method of claim 1 wherein the target % is approximately 30%

Similarly, as discussed above, in Papp "[i]f a patient had a 30% or more…reduction in baseline GFR" maintained through a second measurement, "the patient was withdrawn from the trial." EX1006 at 1339; *see also* EX1005 at 5 (patients achieved complete remission when they have "no confirmed decrease from baseline in eGFR of ≥ 20%"). Thus, Papp and AURA-LV disclose a target % of "approximately 30%" as required by claim 4. EX1001 at claim 4; EX1003 at ¶ 95.

6. Claim 5:

(a) **The method of claim 1 includes identifying said subject as appropriate for said method prior to conducting said method on said subject by: (a) determining that the urine protein creatinine ratio (UPCR) of said subject is > 1 mg/mg as measured by first morning void or 24 hour urine; and**

In AURA-LV, each patient's UPCR was evaluated prior to treatment to determine whether he or she met the inclusion criteria for the clinical trial. EX1005 at 7-8. Specifically, eligibility required:

Laboratory evidence of active nephritis at screening, defined as:

- Class III, IV-S or IV-G: Confirmed proteinuria ≥1,500 mg/24

hours when assessed by 24 hour urine collection, ***defined by a UPCR of ≥1.5 mg/mg assessed in a first morning void urine specimen*** (2 samples).

- Class V (alone or in combination with Class III or IV): Confirmed proteinuria ≥2,000 mg/24 hours when assessed by 24 hour urine collection, ***defined by a UPCR of ≥2 mg/mg assessed in a first morning void urine specimen*** (2 samples).

Id. (emphasis added). Thus, a patient only qualified for the trial if his or her UPCR was equal to or greater than 1.5 mg/mg, as assessed in a first morning void urine specimen. *Id*.; EX1003 at ¶ 97.

These entry criteria are also standard entry criteria routinely used in clinical trials for proteinuric kidney diseases like lupus nephritis. EX1003 at ¶ 98; EX1021 at A10; EX1001 at 1:65-2:3. Thus, this claim limitation adds nothing new.

(b) **(b) determining said subject has an eGFR as measured by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPl) of >45 ml/min/1.73 m^2**

Similarly, as discussed above, in the AURA-LV study, in addition to using UPCR as eligibility criteria, eGFR was also employed. EX1005 at 7-8. The eGFR of potential subjects was measured at a first time point prior to study initiation to confirm that each participant in the clinical trial had an eGFR of > 45 mL/min/1.73 m^2. *Id*. eGFR was "calculated by the Chronic Kidney Disease Epidemiology

Collaboration equation," as required by claim 5. *Id*. If the patient had a calculated eGFR of ≤ 45 mL/min/1.73 m^2, the patient was excluded. *Id*.; EX1003 at ¶ 100.

Likewise, in Papp, the eGFR of potential subjects was measured before enrollment in the trial to confirm that each participant in the clinical trial had an eGFR of > 60 mL/min. EX1006 at 1337. Papp cites to EX1016, indicating that the Papp investigators utilized the MDRD equation for calculating eGFR. *See* EX1006 at 1338 (citing EX1016). A person of ordinary skill in 2017 would have known that the MDRD equation had been replaced by the CKD-EPI equation as the standard for calculating eGFR. *See* EX1009 at 35; EX1017 at ii183; EX1003 at ¶ 101. The CKD-EPI equation was established in 2009, and was found to be more accurate than MDRD, particularly at GFR levels > 60 mL/min. EX1009 at 35; EX1003 at ¶ 101.

Thus, both AURA-LV and Papp disclose "determining said subject has an eGFR as measured by [CKD-EPI equation] of >45 mL/min/1.73 m^2," as required by claim 5. EX1001 at claim 5; EX1003 at ¶ 102.

(c) **wherein if (a) and (b) are met, said subject is identified as appropriate for said method**

As discussed above, in AURA-LV, eligible patients were identified as appropriate for the disclosed method only if they met ***both*** the requirement for UPCR > 1.5 mg/mg as measured by first morning void, (*see* EX1005 at 7-8 ("Inclusion Criteria")), ***and*** the requirement for an eGFR as measured by the CKD-

EPI equation of > 45 mL/min/1.73 m^2, (*see id*. at 8 ("Exclusion Criteria")), thus rendering all of the limitations of claim 5 obvious. EX1003 at ¶ 104.

7. Claim 6: The method of claim 1 wherein said predetermined daily dosage is 39.5. mg voclosporin BID, 31.6 mg voclosporin BID, 23.7 mg voclosporin BID, 15.8 mg voclosporin BID or 7.9 mg voclosporin BID

AURA-LV discloses administering to its clinical trial subjects "a predetermined daily dosage" of either 23.7 mg BID or 39.5 mg BID voclosporin. EX1005 at 5. Moreover, as discussed above, AURA-LV discloses that voclosporin was dosed in 7.9 mg capsules, (*see id*.), and each dosage in claim 6 is a multiple of 7.9 mg. It would therefore have been obvious to a person of ordinary skill in the art to provide voclosporin to patients in 7.9 mg increments (i.e., 7.9 mg, 15.8 mg, 23.7 mg, 31.6 mg, or 39.5 mg voclosporin). EX1003 at ¶ 106.

Likewise, as discussed above, Papp also discusses administering a range of doses of voclosporin from 9.8-56 mg, which encompasses all but one of the dosages in claim 6. *See* Section V(B)(2)(b), *supra*; *see also* EX1006 at 1339; EX1003 at ¶ 107.

8. Claim 7: The method of claim 1 wherein said method further includes evaluating said subject for renal function at a time point after the end of said treatment period by assessing eGFR

In the AURA-LV study, the eGFR of patients enrolled in the clinical trial was assessed throughout the study, including at week 48 (the last week of the

treatment period) and at week 50 (two weeks after the treatment period). *See* EX1005 at 7 ("time frame" of "[c]hange from baseline in…eGFR at each visit measured" is "50 weeks"). Likewise, Papp also indicates that eGFR was measured at the end of the treatment period, stating that "most reductions [in eGFR] were transient and resolved by the end of the study[.]" EX1006 at 1340. Thus, AURA-LV and Papp render this claim limitation obvious. EX1003 at ¶ 109. Moreover, continual monitoring of eGFR was standard practice in treating patients with proteinuria, which is generally a chronic condition. *Id*. at ¶ 110.

9. Claim 8: The method of claim 7 wherein said method further includes evaluating said subject for maintaining renal function by assessing protein/creatinine ratio (UPCR) at a time point after the end of said treatment period

In the AURA-LV study, the UPCR of patients enrolled in the clinical trial was assessed to determine whether the patient reached complete remission—a primary outcome measure (at week 24) and a secondary outcome measure (at week 48) of the trial. *See* EX1005 at 5. Specifically, complete remission required "[c]onfirmed protein/creatinine ratio of ≤ 0.5 mg/mg[.]" *Id*. Thus, AURA-LV discloses this claim limitation. EX1003 at ¶ 112. Moreover, continual monitoring of UPCR was standard practice in treating patients with proteinuria, which is generally a chronic condition. *Id*. at ¶ 113.

10. Claim 9: The method of claim 1 wherein said method further includes administering to said subject an effective amount of mycophenolate mofetil (MMF)

Claim 10: The method of claim 1 which further includes administering to said subject an effective amount of a corticosteroid

In the AURA-LV study, patients treated with voclosporin were maintained "on a background of ***MMF*** and ***corticosteroids***." EX1005 at 4 (emphasis added). Therefore, AURA-LV discloses a method of treatment that included "administering to said subject an effective amount of mycophenolate mofetil (MMF)," as required by claim 9 and "administering to said subject an effective amount of a corticosteroid," as required by claim 10. EX1003 at ¶ 115.

Likewise, a person of ordinary skill in the art reading Papp and looking to apply Papp's teachings to a method for treating patients with proteinuric kidney disease such as lupus nephritis would have found it obvious to administer MMF and corticosteroids in light of the known standard of care therapy for such patients, and the fact that a background treatment with MMF and corticosteroids was generally continued while treating these patients with an additional drug such as an immunosuppressant. EX1003 at ¶ 116.

11. Claim 11: The method of claim 1 wherein said treatment period is at least 48 weeks

In the AURA-LV study, patients received treatment with voclosporin for a period of 48 weeks, thus disclosing the limitation of claim 11. *See* EX1005 at 5;

EX1003 at ¶ 118.

C. Ground 2: Claims 12-13 Are Obvious Over AURA-LV in view of Papp and Ha

Dependent claims 12 and 13 depend from claim 1 and would have both been obvious to a person of ordinary skill in the art over AURA-LV (EX1005) in view of Papp (EX1006) and Ha (EX1007).

1. The Prior Art

(a) Ha

Ha is an article entitled "Increased risk of everolimus-associated acute kidney injury in cancer patients with impaired kidney function," published on December 3, 2014.[1] EX1007. Ha describes using the immunosuppressant everolimus to treat patients with cancer, primarily renal cell cancer (i.e. kidney cancer). *Id*. at 2. Ha explains that "[e]verolimus is familiar to nephrologists as an alternative immunosuppressant to calcineurin inhibitors after kidney transplantation, with the advantage of lack of nephrotoxicity," though "renal adverse effects have been reported." *Id*. at 5. While the nephrotoxicity of everolimus had been observed at the time of Ha's analysis, it was not well studied. *See* EX1007 at 2 (noting that "[i]ncreased serum creatinine level was one of the

[1] *See* https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-14-906 (last accessed Jan. 26, 2022).

frequently reported laboratory abnormalities…observed in a phase 3 trial of everolimus for metastatic renal cell cancer."). Thus, Ha sought to perform a retrospective analysis of kidney function in patients who had been treated with everolimus. *Id*.

The 110 patients identified for analysis "[g]enerally…received 10 mg of everolimus once daily," but "the dose and schedule could be modified according to toxicity and tolerability." *Id*. Patients with an eGFR lower than 15 mL/min/1.73 m^2 were excluded from the study. *Id*. Most patients "were followed every 4 weeks" and monitored through standard laboratory testing, including creatinine testing and eGFR calculation. *Id*. The duration of treatment varied, with a median duration of 20 weeks (interquartile range from 12 to 36 weeks). *Id*. at 3; *see also* EX1003 at ¶ 64.

Ha explains that the primary outcome targeted for the analysis was development of acute kidney injury (AKI), which is a sudden episode of kidney failure or kidney damage that happens within a few hours or a few days. EX1003 at ¶ 65. Patients experiencing worsening kidney function were classified into three categories based on changes in eGFR:

> [P]atients were classified in the "risk" category if serum creatinine increased 1.5-fold or eGFR decreased >25%, in the "injury" category if serum creatinine increased 2-fold or eGFR decreased >50%, and in

> the "failure" category if serum creatinine increased 3-fold or eGFR decreased >75%.

EX1007 at 2. Recovery from AKI "was defined as the return to a serum creatinine within 1.2-fold of the baseline value." *Id*. Serum creatinine is the primary component in calculating eGFR. EX1003 at ¶ 65; *see also* Section III(B), *supra*.

At baseline, 89% of patients suffering from renal cell carcinoma in Ha had decreased renal function (i.e. eGFR < 90 mL/min/1.73 m^2), with an average eGFR of 63 mL/min/1.73 m^2. EX1007 at 3. Of these patients, 28% had proteinuria at baseline. *Id*. Ha's analysis found that 14 patients (16.2%) from the renal cell carcinoma group experienced everolimus-associated AKI, meaning they were classified into the "risk," "injury," or "failure" categories identified above. Ten patients were classified in the "risk" category (eGFR decreased >25%), three in the "injury" category (eGFR decreased >50%), and one in the "failure" category (eGFR decreased >75%). *See id*. at 3, 4, 6. The table below shows the treatment modulation and outcome for each category of patients in Ha:

# Patients	Dose Modulation	Outcome
AKI-Risk Category (eGFR decreased > 25%)		
5	Dose reduced to 5 mg per day	No further renal deterioration
1	Withheld medication for one week, resumed at same dose	No further renal deterioration
1	Withheld medication one month, resumed at same dose	No further renal deterioration
3	Discontinued treatment	No further renal deterioration
AKI-Injury Category (eGFR decreased >50%)		
1	Withheld medication for 2 weeks, resumed at 50% dose	Kidney function recovered
1	Dose reduced to 50%	Kidney function recovered
1	Discontinued treatment	Kidney function recovered
AKI-Failure Category (eGFR decreased >75%)		
1	Discontinued treatment "eventually"	Kidney function recovered

EX1007 at 4. Thus, multiple patients in Ha's analysis were subject to dosage reduction, withdrawal of therapy, and/or resumption of therapy, based on kidney function (i.e. eGFR). *Id*.

Ha concluded that "clinicians should be cautious about potential nephrotoxicity when prescribing everolimus to patients with decreased kidney function," noting that in these patients "serial measurements of serum creatinine are needed." *Id*. at 6. Critically, Ha explained that treatment "could be continued at a reduced dose or after a short-term off period even in patients with AKI without renal deterioration," and that "[t]herefore, the treatment decision should be made using a multidisciplinary approach that includes the assessment of the oncological

benefit of everolimus and other therapeutic options for cancer in each individual." *Id*.

(b) **The Combination of AURA-LV, Papp, and Ha**

A person of ordinary skill in the art seeking to treat a proteinuric kidney disease would have been motivated to combine the disclosures in Ha with AURA-LV and Papp because in designing a dosing regimen with voclosporin, a comparatively new calcineurin inhibitor, she would have sought out literature on calcineurin inhibitors and alternatives to calcineurin inhibitors commonly used at the time. EX1003 at ¶ 124. Everolimus was approved by FDA in 2009, (*see* EX1028 at 1), and was in routine use at the time to treat renal cell cancer, (EX1003 at ¶ 124). *See also* EX1007 at 2 ("At the Samsung Medical Center, advanced RCC or hepatocellular carcinoma (HCC) that failed VEGFR-TKI treatment was an indication for everolimus treatment."). Ha explains that "[e]verolimus is familiar to nephrologists as an alternative immunosuppressant to calcineurin inhibitors after kidney transplantation, with the advantage of lack of nephrotoxicity." EX1007 at 5. Thus, a person of ordinary skill in the art would have known that everolimus was an alternative to calcineurin inhibitors like voclosporin, and, like voclosporin, was thought to have less nephrotoxicity. *See* EX1003 at ¶ 125. She therefore would have been familiar with Ha, and sought to incorporate Ha's disclosures on modulating therapy with the known methods of treatment using voclosporin that

were disclosed in AURA-LV and Papp.

For the reasons discussed above, claim 1 is rendered obvious by the combination of AURA-LV and Papp. *See* Section V(B)(2), *supra*. Claims 12 and 13 simply add the obvious step of checking a patient's eGFR at a third point in time and, if the patient's renal function has recovered by a target percentage, resuming treatment with voclosporin. *See* EX1001 at claims 12-13. This limitation is expressly disclosed in Ha. *See* EX1007 at 2, 4. Ha reflects the typical therapeutic practice at the time of the invention to monitor a patient's eGFR when prescribing a treatment known to affect kidney function and to reduce or withdraw treatment upon decline. *See* EX1003 at ¶ 119. Ha also reflects what skilled artisans routinely did in practice, resuming treatment when kidney function improves. *Id*.; EX1007 at 2, 4.

2. Claim 12: The method of claim 1 which further includes determining the eGFR of said subject at a third time point and if the eGFR is determined at said third time point to differ from the eGFR determined at said first time point by less than said target %, resuming administering said predetermined daily dosage of voclosporin

Ha discloses determining the eGFR of patients at a third time point—here, every four weeks during the treatment period. *See* EX1007 at 2. Based on the relative change in eGFR, the patient is categorized as either at "risk" (eGFR decreases by >25%), having "injury" (eGFR decreases by >50%), or having

"failure" (eGFR decreases by >75%). *Id*. In both the "risk" and "injury" categories, Ha discloses that in certain patients whose medication was withheld due to their decrease in eGFR, treatment with an immunosuppressant was resumed following recovery of kidney function. *Id*. Moreover, Ha found it "noteworthy that everolimus treatment was continued or resumed in most patients with AKI without renal deterioration," stating that "[t]his finding has important clinical significance when considering that the drug is indicated for patients with few therapeutic options[.]" *Id*. at 6.

As Dr. Jaimes explains, Ha reflects the reality of treating patients when impaired kidney function is expected or possible. EX1003 at ¶ 122. Rather than maintain a patient on a constant dosage, as a physician following a clinical study protocol would generally be required to do, in normal practice a physician would monitor a patient's kidney function on a regular basis, and reduce or withdraw therapy on an as-needed basis. *Id*. at ¶ 123. Moreover, Ha reflects that physicians will not hesitate to withdraw and restart therapy, depending on a patient's needs and the therapy in question. *Id*.

Reading Ha, a person of ordinary skill in the art would have appreciated the importance of carefully monitoring renal function, even though less nephrotoxicity was expected. *Id*.; *see also* EX1007 at 6 (noting that "clinicians should be cautious about potential nephrotoxicity when prescribing everolimus to patients with

decreased kidney function," and that "serial measurements of serum creatinine are needed" in these patients). Critically, Ha disclosed that the "dose and schedule [of a calcineurin inhibitor] could be modified according to toxicity and tolerability," (EX1007 at 2), meaning withdrawing and resuming treatment as needed according to kidney function, (EX1003 at ¶ 125). Accordingly, a person of ordinary skill seeking to use a calcineurin inhibitor like voclosporin to treat a proteinuric kidney disease would therefore have applied that teaching to the treatment protocols described in AURA-LV and Papp to arrive at claim 12. *See* EX1003 at ¶ 125.

3. Claim 13: The method of claim 12 wherein the target % is approximately 30%

Ha discloses that at baseline, patients with renal cell carcinoma had an average eGFR of 63 mL/min/1.73 m^2. EX1007 at 3. Over the course of treatment with the calcineurin inhibitor everolimus, 14 patients (16.2%) were diagnosed with everolimus-associated AKI, and treatment was reduced or withdrawn. *Id*. at 4. Several patients whose treatment was withdrawn recovered. *Id*. Ha specifically defined "recovery" as "the return to a serum creatinine within 1.2-fold of the baseline value." *Id*. at 2. It would have been obvious to a person of ordinary skill in the art reading Ha that a return to a serum creatinine within 1.2-fold of the baseline value is equivalent to "approximately 30%." EX1003 at ¶ 127. As Dr. Jaimes explains, because of the mathematical relationship between serum creatinine and eGFR, a return to a serum creatinine within 1.2-fold of the baseline

value corresponds to a 20% change in eGFR, which is equivalent to "less than approximately 30%" eGFR as required by the claim. *See* EX1003 at ¶ 127.

Moreover, Papp, which specifically dealt with treating patients with voclosporin, disclosed withdrawing patients from the clinical trial if they experienced a consistent 30% eGFR reduction. *See* EX1006 at 1338-39. Thus, it would have been obvious to a person of ordinary skill in the art that the reverse situation—a 30% ***increase*** in eGFR from baseline—indicated that a patient was ready to resume treatment. EX1003 at ¶ 128. Therefore, it would have been obvious to a person of ordinary skill in the art seeking to use voclosporin to treat a proteinuric kidney disease to resume treatment with voclosporin if a patient's eGFR levels differed from baseline by approximately 30%. *Id*.

D. No Objective Evidence of Nonobviousness

Objective evidence of nonobviousness cannot defeat a strong case of obviousness based upon the prior art references themselves. *See ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1375 (Fed. Cir. 2018). Here, the strong evidence of obviousness shown above outweighs any objective evidence that Patent Owner may present. The fact that voclosporin could be used to successfully treat proteinuric kidney disease was known in the art from both AURA-LV and Papp, as was the fact that the dose of voclosporin should be reduced or stopped if a patient's eGFR levels fell. Although Patent Owner submitted alleged evidence of

unexpected results during prosecution, the Examiner erred in failing to evaluate the credibility of this evidence, as well as whether it was commensurate with the scope of the claims. Because this evidence was weak and did not apply to the full scope of the claims, it does not support a finding of nonobviousness. No evidence supports any other objective indicia of nonobviousness here either.

1. Unexpected Results

As discussed above in Section IV(D), during prosecution Patent Owner secured allowance of the claims of the '036 patent by asserting that it was unexpected that patients who switched to a reduced amount of voclosporin due to decreased eGFR demonstrated better efficacy at both time points and on both outcome measures (partial response and complete response). *See* EX1002 at 144-145. Patent Owner supported this assertion with additional clinical trial results and an expert declaration. *See id*. at 166-184. This evidence fails to support a finding of nonobviousness because (i) the unexpected results are not shown for the full scope of the claims; (ii) the data supporting the alleged unexpected results are not credible or significant, and (iii) the patent's disclosures are inconsistent with an finding of significant unexpected results.

(a) Unexpected results are not shown for the full scope of the claimed invention

The unexpected results the applicant alleged during prosecution are not attributable to the full scope of the claimed invention. Independent claim 1

requires one of two alternative conditions to be met. Upon finding that eGFR decreases by more than a target percentage, the claims require ***either*** reducing the daily dosage of voclosporin ***or*** stopping administration of voclosporin altogether. *See* EX1001 at claim 1. The "unexpected results" that the applicant relied on during prosecution, however, were only attributable to the first alternative of ***reducing*** the daily dosage of voclosporin. *See* EX1002 at 145 (alleging the "results are unexpected and surprising because it would not be predicted that patients who tolerate the drug well and do not require a dose reduction would fare worse than those who do not tolerate it well and must be subject to dose reduction.") (emphasis in original); *see also id.* at 183 (applicant's declarant stating that "[t]his type of 'goldilocks porridge' finding, that a lower dose provides the maximal clinical effect without risking complications associated with higher doses, is in my professional opinion indeed truly novel and unexpected."). Thus, the focus of the unexpected results was entirely on the outcomes of patients who underwent dose reduction. *Id*.

Neither the applicant nor the applicant's declarant alleged that the same unexpected result occurred when voclosporin treatment was ***stopped***, as contemplated by the second part of the claim language. No evidence in the patent or in the applicant's submission during prosecution supports such a finding. *See generally*, EX1002 at 141-184.

It is "the established rule that objective 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); *MeadWestVaco Corp. v. Rexam Beauty and Closures, Inc.*, 731 F.3d 1258, 1264–65 (Fed. Cir. 2013); *In re Peterson*, 315 F.3d 1325, 1330-31 (Fed. Cir. 2003). "Establishing that one (or a small number of) species gives unexpected results is inadequate proof[.]" *In re Greenfield*, 571 F.2d 1185, 1189 (C.C.P.A. 1978); *see also E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1012 (Fed. Cir. 2018) (disclosure of unexpected results for "only a single pressure" in a claimed range was "not commensurate with the scope of the claims.").

Here, the inquiry is straightforward: the claims encompass two alternative methods—reducing the dose or stopping treatment. The unexpected results alleged by the applicant during prosecution, however, are only alleged for the first method of dose reduction. *See, e.g.*, EX1002 at 145. Therefore, because the alleged unexpected results are not applicable or commensurate with the full scope of the claims—i.e., to stopping treatment, the second of the two claimed methods—they simply cannot support a finding of non-obviousness. *Allergan*, 754 F.3d at 965.

Moreover, the unexpected results observed are not commensurate with the full scope of the claims because the claims are directed to a method to treat "a proteinuric kidney disease," and the unexpected results are shown only for treating

lupus nephritis. As the '036 patent itself acknowledges, a wide variety of proteinuric kidney diseases exists apart from lupus nephritis. *See* EX1001 at 2:54-62 (listing thirteen additional diseases). Patent Owner presented no evidence during prosecution that the allegedly unexpected results observed when treating lupus nephritis patients would be observed when treating any other proteinuric kidney disease, let alone the full scope of proteinuric kidney diseases contemplated by the patent. For this additional reason, the unexpected results presented to the Examiner cannot support a finding of non-obviousness. *Allergan*, 754 F.3d at 965.

(b) **The supplemental data submitted to the Patent Office lack credibility**

Second, the data alleged to support a finding of unexpected results are not reliable or significant. *See* EX1003 at ¶¶ 130-140. As an initial matter, the '036 patent does not present the data on statistical significance, nor does the patent contain any indication that this particular result is significant or surprising. *See, e.g.*, EX1001 at 9:3-58; EX1003 at ¶ 133. Instead, the Examiner's finding of unexpected results is premised entirely on additional information submitted by the applicant. *See* EX1002 at 233; *see also* Section IV(D), *supra*.

None of that additional information, however, provides the statistical significance that was lacking in the patent itself. EX1003 at ¶ 134. Moreover, as described in more detail by Dr. Jaimes, the information presented by the applicant altered the data to magnify certain results in a way that was favorable to its

arguments. EX1003 at ¶ 134.

More importantly, the applicant omitted from its charts the responses observed in the placebo arm of the trial, which is critical to understanding the significance (or lack thereof) of the different response rates observed. *See* EX1002 at 168-169, 172-173. As Dr. Jaimes explains, when all of the data is viewed together, the differences presented to the Examiner by Applicants are superficial and meaningless. *See* EX1003 at ¶¶ 135-136.

Such unreliable data cannot support a finding of unexpected results to overcome obviousness. *See, e.g., Senju Pharm. Co. v. Lupin Ltd*., 780 F.3d 1337, 1352-53 (Fed. Cir. 2015) (affirming finding of no unexpected results where "studies were not statistically significant" and the "numbers in the raw data appellants rely on for evidence of unexpected success occurred in studies where all of the numbers (including control values) widely varied, with large, unexplained error bars"); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) (affirming obviousness finding where the results presented "did not rise to the level of statistical significance," and "were inconsistent, not shown to be reproducible, and did not include comparative data vis-à-vis placebos…necessary to demonstrate unexpected or synergistic effects.").

Additionally, the nature of the unexpected result here (to the extent one exists at all) amounts to nothing more than a difference in degree, rather than a

difference in kind. In *Galderma Laboratories L.P. v. Tolmar, Inc.*, the Federal Circuit found that "where an increase by a percentage is expected but not found, that result is also likely only a difference in degree." 737 F.3d 731, 739 (Fed. Cir. 2013). There, the expected result was an increase in the prevalence of side effects. *Id*. The Court found that "[t]he failure of that percent increase to materialize, though unexpected, constitutes only a difference in degree from the prior art results," and it did "not constitute an unexpected result that is probative of nonobviousness." *Id*. Just so here, where the expected result was an increase in efficacy with higher or sustained voclosporin dosages. *See* EX1002 at 147 ("[I]t is expected, as would be the case for most drugs, that efficacy is enhanced by increasing dosage of the active agent in the drug."); *see also id.* at 182 (Dr. Tumlin explaining that "typical clinical studies attempt to find a maximum tolerated dose on the generally accepted premise that higher doses are more efficacious[.]"). The failure of the higher voclosporin dosage to provide increased efficacy, even if unexpected, is only a difference in degree, and not probative of nonobviousness. *Galderma*, 737 F.3d at 739.

(c) **The patent's disclosures are inconsistent with the later-alleged evidence of unexpected results**

Third, the existence and relative importance of any unexpected results is belied by the '036 patent itself. Apart from disclosing that a lower dosage "appeared" to be "even more effective" than a higher dosage, (*see* EX1001 at 2:16-

18), and noting that "[l]ow dosages may show superior results," the patent otherwise does not emphasize or highlight that patients who underwent a dose reduction had more favorable outcomes than patients for whom no dose reduction was needed. EX1003 at ¶ 137. Rather, citing to the same data relied upon by the applicant during prosecution, the patent concludes that after 24 weeks "[t]he percentage of patients with complete response ***was not affected*** in either dosage groups by the pharmacodynamic dosage and the percentage with partial response was also ***roughly the same***, although with the high dose group, the percentage with partial reduction improved." EX1001 at 9:50-55 (emphasis added). Likewise, after 48 weeks, "similar results" were shown, and "[a]gain, ***no drastic effect*** on the overall response was exhibited." *Id*. at 9:55-58 (emphasis added).[2]

This conclusion stands in stark contrast to applicant's declarant's conclusion during prosecution that it was a "surprising and unexpected" finding that "the subjects in the cohort that had reduced dosage overall…surprisingly showed better efficacy at both 24 weeks and 48 weeks in both partial response (PR) and complete

[2] In addition to not being emphasized in the patent, the applicant's proffered unexpected results were absent from both the press release announcing the study results, (*see* EX1027), and the peer-reviewed journal article which published the results of the AURA-LV clinical trial, (*see* EX1014). EX1003 at ¶ 139.

response (CR) than those who were given an overall higher." EX1002 at 182; EX1003 at ¶ 138. Indeed, far from being unexpected, these results are consistent with the results that Dr. Jaimes observed when treating patients with calcineurin inhibitors like voclosporin. *See* EX1003 at ¶¶ 131-132.

Thus, the "unexpected results" presented during prosecution lack credibility and do not support a finding of non-obviousness.

2. Other Objective Indicia

Petitioner is unaware of any other relevant objective indicia of nonobviousness that apply to the '036 patent. Should Patent Owner come forward with evidence of other objective indicia, Petitioner reserves the right to respond further and rebut any such evidence.

VI. 35 U.S.C. § 325 DOES NOT BAR INSTITUTION

Grounds 1 and 2 rely on three references, two of which were not before the Examiner. Under a proper application of the two-part analysis in *Advanced Bionics*, discretionary denial under Section 325 is not appropriate here. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential).

As an initial matter, Petitioner does not dispute that AURA-LV was before the Examiner and is therefore "substantially the same" under *Advanced Bionics*' first inquiry. *Advanced Bionics*, Paper 6 at 8. The Examiner erred, however, in

crediting the unexpected results presented by the applicant. These results are the only reason the Examiner found the applicant had overcome the *prima facie* case of obviousness based on AURA-LV. *See* EX1002 at 233 ("The declaration…is sufficient to overcome the rejection of claims based upon Applicants unexpected results."). As discussed in detail in Section V(D)(1) above, these allegedly unexpected results are not commensurate with the full scope of the claims, nor are they consistent with the disclosures in the patent itself. Once the weight of these unexpected results is dismissed, the original *prima facie* case of obviousness found repeatedly by the Examiner in AURA-LV stands. *See* EX1002 at 62-64, 107-115. Therefore, the Examiner erred in a manner that was material to the patentability of the claims of the '036 patent. *See Advanced Bionics*, Paper 6 at 8.

Notwithstanding this material error by the Examiner, Petitioner is not relying on "the same or substantially the same" art or arguments previously considered by the Examiner regarding AURA-LV. Both grounds in this Petition rely on additional prior art—Papp and Ha—which were never made of record during examination.

First, there was no rejection during the prosecution based on the limitations related to "reducing the daily dosage" or "stopping the administering of voclosporin" if a subject's eGFR "decreases by more than a target % in the range of 20-45%." Thus, there can be no overlap between arguments made during

examination and arguments raised in this Petition concerning reducing or stopping treatment. *Advanced Bionics*, Paper 6 at 9, n.10 & 10. This limitation is found in claim 1 and thus applies to every challenged claim in this Petition.

Second, Papp and Ha are materially different from the art of record, and not cumulative. *Id*. None of the prior art of record during examination included examples of subjects whose treatment was withdrawn based on a decrease in the subject's eGFR levels; Papp does. *See* EX1006 at 1339, 1341. None of the prior art of record specifically taught a predetermined baseline eGFR value of approximately 60 mL/min/1.73 m^2; Papp does. *Id*. at 1337. None of the prior art of record included determining the eGFR of a subject who stopped treatment at a third point in time and resuming administering an immunosuppressant like voclosporin if the eGFR value has recovered; Ha does. EX1007 at 2, 4.

Finally, even if any of the arguments Petitioner makes can be construed as "the same" as a previously presented argument, for the same reasons discussed above, the Examiner erred in a manner material to the patentability of the challenged claims.

For at least these reasons, discretionary denial under Section 325(d) is not warranted here.

VII. CONCLUSION

The cited prior art references identified in this Petition contain teachings that

were not previously considered during examination of the '036 patent. In sum, these references provide new, non-cumulative teachings which indicate a reasonable likelihood of success that claims 1-13 of the '036 patent are not patentable. Accordingly, Petitioner respectfully requests institution of an IPR for each claim of the '036 patent as presented herein.

VIII. MANDATORY NOTICES UNDER 37 C.F.R § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The following real parties in interest are identified: Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Industries, Inc.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any disclaimers, reexamination certificates or petitions for *inter partes* review for the '036 patent. Petitioner is not aware of any civil actions pending which involve the validity or infringement of the '036 patent.

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel.

Lead Counsel	Backup counsel
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D. Service Information

Please address all correspondence and service to the address listed above. Petitioner consents to electronic service by email at IPR46207-0029IP1@fr.com (referencing No. 46207-0029IP1 and cc'ing PTABInbound@fr.com, morrison@fr.com, renner@fr.com, and kraning@fr.com).

IX. PAYMENT OF FEES – 37 C.F.R. § 42.103

Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 06-1050 for the fee set in 37 C.F.R. § 42.15(a) for this Petition and further authorizes payment for any additional fees to be charged to this Deposit Account.

Respectfully submitted,

Dated: February 24, 2022

/Susan E. Morrison/

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for *inter partes* review totals 13,951 words, which is less than the 14,000 allowed under 37 CFR § 42.24.

Dated February 24, 2022

/Susan E. Morrison/

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on February 24, 2022, a complete and entire copy of this Petition for *Inter Partes* Review, Power of Attorney, and all supporting exhibits were provided via Federal Express, to the Patent Owner by serving the correspondence address of record as follows:

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