UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOCON BIOLOGICS INC.,
Petitioner

v.
JANSSEN BIOTECH, INC.,
Patent Owner

IPR No. IPR2023-01444

U.S. Patent No. 10,961,307

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,961,307

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1003	Janssen Research & Development, LLC published clinical overview summary for Phase 3 clinical trial for ustekinumab in UC (NCT02407236) on ClinicalTrials.gov ("NCT-236")
1004	Stelara® Prescribing Information (Sept. 2016) (the "Stelara-PI(2017)")
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1009	Danese & Fiocchi, *Ulcerative Colitis*, N Engl J Med., 365:1713-1725 (2011)
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1011	Ahern et al., *Interleukin-23 Drives Intestinal Inflammation through Direct Activity on T Cells*, Immunity, 33:279-288 (Aug. 2010)
1012	Uhlig et al., *Differential Activity of IL-12 and IL-23 in Mucosal and Systemic Innate Immune Pathology*, Immunity, 25:309-318 (Aug. 2006)
1013	Yen et al., *IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6*, J of Clinical Investigation, 116(6):1310-1316 (May 2006)
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1031	Sands et al., *Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis*, N Engl J Med 381(13):1201- 1214 (Sept. 26, 2019)
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1053	International Publication Number WO 2015/119841 A1 issued to Zuniga et al. ("WO 2015/119841")
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1055	Stelara, European Medicines Agency https://www.ema.europa.eu/en/medicines/human/EPAR/stelara
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1063	Sequence published with International Publication Number WO 2015/119841 A1 issued to Zuniga et al. (WO 2015/119841) available at patentscope.wipo.int
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1070	Ustekinumab (Stelara), *Ottawa (ON): Canadian Agency for Drugs and Technologies in Health*; 2017 Apr., available athttps://www.ncbi.nlm.nih.gov/books/NBK476200/?report=printable
1071	Declaration of Noah S. Frank
1072	Listing of Challenged Claims of the '307

Petitioner Biocon Biologics Inc. ("Petitioner") submits this Petition for *Inter Partes* Review of claims 1-34 (the "Challenged Claims") of U.S. Patent No. 10,961,307 ("the '307" (Ex.1001)), assigned to Patent Owner, Janssen Biotech, Inc. ("Janssen" or "PO").

I. INTRODUCTION

The Challenged Claims should never have issued. They are drawn to known methods of treating ulcerative colitis ("UC") with ustekinumab that Janssen publicly disclosed in a Phase 3 clinical trial summary published in 2015—well before the '307's alleged 2018 priority date. To avoid this invalidating public disclosure during prosecution, Janssen amended the Challenged Claims to include the clinical trial ***results***, arguing this was missing in the clinical trial summary. Case law, however, firmly establishes that incorporating inevitable results from known methods ***cannot save*** otherwise anticipated claims. Moreover, the Challenged Claims are obvious because, as of the alleged priority date, multiple sources had reported successful off-label use of ustekinumab to treat UC using the claimed method.

II. 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 real party-in-interest for Petitioner is Biocon Biologics Inc. In addition, in order to assist members of the Board in identifying potential conflicts, Trial Practice Guide, 77 Fed. Reg. 48,756, 48,759 (20212), Biocon also identifies the

following additional parties pursuant to § 42.8(b)(1): Biocon Limited, Biocon Biologics Limited, and Biocon Biologics UK Limited.

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

The '307 was previously asserted by PO in *Janssen Biotech, Inc. v. Amgen Inc.*, Case No. 1:22-cv-01549-MN (D. Del. Nov. 29, 2022), but the case is no longer pending.

C. Lead and Back-Up Counsel and Service Information Under 37 C.F.R. § 42.8(b)(3) & (4)

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Power of Attorney accompanies this Petition pursuant to 37 C.F.R. § 42.10(b). Petitioner consents to electronic service by email at BioconBiologics-UstekinumabSTELERAIPR@winston.com,

III. PAYMENT OF FEES (37 C.F.R. § 42.103)

Petitioner authorizes the Office to charge the filing fee and any other necessary fee to Deposit Account No. 501814.

IV. REQUIREMENTS UNDER 37 C.F.R. §§ 42.104 AND 42.108

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

Petitioner certifies the '307 is eligible for IPR and Petitioner is not barred or estopped from requesting IPR on the grounds identified herein.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b)

Petitioner requests IPR of claims 1-34 and requests the Board find the claims unpatentable under 35 U.S.C. §§ 102 and 103 (post-AIA):

Ground	Claims	Basis of Invalidity
1	1-4, 6-22, 24-34	Anticipated over NCT-236 (Ex.1003)
2	1-34	Obvious over NCT-236 (Ex.1003) in view of Ochsenkühn (Ex.1005) and Stelara-PI(2017) (Ex.1004)

This Petition is supported by the Declaration of Alan V. Safdi, M.D., Ex.1002.

V. STATEMENT OF MATERIAL FACTS

1. NCT-236 discloses the use of ustekinumab for treatment of ulcerative colitis. Ex.1003 at 1.

2. Amino acid sequences of ustekinumab, including amino acid sequences SEQ ID NOS:1-8, 10-11, were known prior to September 24, 2018. Ex.1002 at Appx.I.

3. The known amino acid sequences of ustekinumab correspond to SEQ ID NOS:1-8, 10-11 as claimed in the '307.

4. NCT-236 discloses that ustekinumab in the form of Stelara® was administered to patients. Ex.1003 at 1, Exs.1064-1071.

VI. FACTUAL BACKGROUND

A. IBD (Crohn's and UC) and its historical treatment

"Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which includes Crohn's disease (CD) and ulcerative colitis (UC)." Ex.1050 at 1; Ex.1002 ¶35. Both Crohn's disease ("Crohn's") and UC have overlapping epidemiological, clinical, and therapeutic characteristics. Ex.1002 ¶35; Ex.1050 at 1; Ex.1009 at 2 ("[M]ultiple genes in the interleukin-23 signaling pathway overlap in ulcerative colitis and Crohn's disease"); Ex.1011 at 1 ("The activity of IL-23 is more prominent in the mucosal tissues, such as the intestine, than in the systemic immune compartment enhancing its attractiveness as a therapeutic target in IBD."); Ex.1001 at 1:39-44. By September 24, 2018, a person of ordinary skill in the art (POSA) understood that cytokines, including interleukin IL-12 and IL-23, were involved in the pathogenesis of UC and Crohn's. Ex.1002 ¶¶36-37; Ex.1011 at 1-10; Ex.1012 at 10; Ex.1013 at 1-7; Ex.1014 at 1; Ex.1009 at 2; Ex.1001 at 1:62-2:61.

B. Biologics and IBD

There is no cure for either Crohn's or UC; the goal is to induce and maintain remission. Ex.1002 ¶42. Given their overlapping characteristics, Crohn's and UC have historically been treated with the same or similar therapies. *Id*. ¶¶38-42.

Several biologic therapies were available to treat IBD as of September 24, 2018. *See, e.g.,* Ex.1002 ¶¶38-41; Ex.1010; Ex.1017; Ex.1001 at 2:38-41. Among these were TNF-alpha blockers such as infliximab ("Remicade"), adalimumab ("Humira"), golimumab ("Simponi"), and certolizumab ("Cimzia"), which inhibit inflammation- causing proteins in the intestine. Ex.1002 ¶39; Ex.1010 at 1-2. Integrin blockers such as vedolizumab ("Entyvio") and natalizumab ("Tysabri"), which prevent inflammation- causing white blood cells from entering the GI tract, were also available. Ex.1002 ¶40; Ex.1010 at 1-2; *see also* Ex.1006. Of these six biologics approved for IBD, vedolizumab, adalimumab, and infliximab were successfully used to treat both Crohn's and UC. Ex.1002 ¶40; Ex.1010 at 2, 6; *see also* Ex.1006; Ex.1007; Ex.1008. Finally, interleukin blockers (such as ustekinumab) were developed to treat IBD by targeting the interleukin-12 and interleukin-23 (IL-12/23) proteins associated with inflammation in the GI tract. Ex.1002 ¶41; Ex.1010 at 8. At the time of the invention, many new IBD therapies were being tested for both UC and Crohn's. Ex.1002 ¶39 (citing Ex.1016 at 4 (Table 1)):

Table 1. Emerging Targeted Therapies for IBD and Their Current Status in Development[a]

Drug	Formulation	Target	Admin.	Clinical status[b]	
				CD	UC
PF-04236921	Fully human mAb	IL-6	s.c.	–	–
Ustekinumab	Fully human mAb	IL-12/IL-23 (p40)	i.v./s.c.	Approved[c]	Phase III
AMG-139	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II	–
BI-655066	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II	–
LY3074828	Humanized mAb	IL-23 (p19)	i.v./s.c.	Phase II	Phase II
Tofacitinib	Small molecule	JAK1/JAK3	Oral	–[d]	Phase III
Filgotinib	Small molecule	JAK1	Oral	Phase III	Phase III
Peficitinib	Small molecule	JAK1/JAK3	Oral	–	–
Mongersen	Antisense oligonucleotide	*SMAD7*	Oral	Phase III	Phase II
Laquinimod	Small molecule	?	Oral	–	–
Natalizumab	Humanized mAb	α_4-Integrin	i.v.	Approved[e]	–
AJM300	Small molecule	α_4-Integrin	Oral	–	–
Vedolizumab	Humanized mAb	$\alpha_4\beta_7$	i.v.	Approved[f]	Approved[f]
AMG 181	Fully human mAb	$\alpha_4\beta_7$	s.c.	Phase II	Phase II
Etrolizumab	Humanized mAb	β_7-Integrin	i.v./s.c.	Phase III	Phase III
PF-00547659	Fully human mAb	MAdCAM-1	i.v./s.c.	–	Phase II
Ozanimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II	Phase III
Etrasimod	Small molecule	$S1P_1$	Oral	–	Phase II
Amiselimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II	–

C. Ustekinumab structure

Ustekinumab is an IgG1 humanized monoclonal antibody that targets the common p40 subunit of IL-12 and IL-23. Ex.1002 ¶43; Ex.1014 at 3; Ex.1001 at 2:45-53. Upon binding to p40, ustekinumab prevents IL-12 and IL-23 from binding the cell surface IL-12Rβ1 receptor protein, and effectively neutralizes IL-12 and IL-23 mediated cellular responses. Ex.1002 ¶43; Ex.1015 at 5.

The complete sequence for ustekinumab, including the sequences claimed in the '307, SEQ ID NOS: 1-8 and 10-11, was published in several places before September 24, 2018. *See, e.g.,* Ex.1002 at ¶¶44-48, Appx.I; Ex.1053; Ex.1063; Ex.1052; Ex.1022 at 4; Ex.1023 at 11; Ex.1018; Ex.1019; Ex.1020; Ex.1021; Ex.1025.The PTE Applications and the PMDA explicitly label the CDR sequences for the heavy and light chain.

D. Ustekinumab was known as an effective treatment for diseases related to the IL-12/23 pathway, including Crohn's

Before September 2018, ustekinumab was proven safe and effective as a treatment for diseases related to the IL-12/23 pathway. Ex.1002 ¶49. Ustekinumab, under the brand name Stelara®, was first approved by the FDA in 2009 for treatment of adults with chronic moderate to severe plaque psoriasis. Ex.1002 ¶49; Ex.1024. It was approved in 2016 for the treatment of Crohn's. Ex.1002 ¶49; Ex.1004 ("Stelara-PI(2017)"). Stelara® was available for intravenous and subcutaneous administration, and the clinical studies demonstrated that it was well-tolerated intravenously and subcutaneously. Ex.1002 ¶49; Ex.1004 at 1; Ex.1026; Ex.1024.

E. The prior art taught that ustekinumab was effective in treating UC

By September 24, 2018, multiple sources had reported successful off-label use of ustekinumab to treat UC. Ex.1002 ¶50. Ochsenkühn, for example, describes seventeen UC patients treated with ustekinumab at 6mg/kg body weight as an infusion and 90mg as a subcutaneous injection every 8 weeks, where clinical

remission was achieved in 65% (11/17) patients at 1, 3, and 6 months as compared to 35% (6/17) in remission at the start of the study. *See, e.g.,* Ex.1002 ¶50; Ex.1005 ("Ochsenkühn") at 2. Kolios describes a patient treated with ustekinumab, resulting in cessation of the patient's UC for up to 2 years. *See, e.g.,* Ex.1002 ¶50; Ex.1034. Afonso reports a case study where two patients with UC received ustekinumab as 90mg weekly (4 doses) and 90mg every 2 or 8 weeks thereafter as maintenance doses, concluding, "[u]stekinumab is a therapeutic approach for IBD treatment in clinical practice…." Ex.1035; Ex.1002 ¶50. In 2017 the Canadian Agency for Drugs and Technologies in Health noted that "[t]here is potential for ustekinumab to be used off-label as a treatment option for ulcerative colitis." Ex.1070. And in 2014, Tarr ***explicitly*** noted that "UC" was an "Off-label indication[]" for "Ustekinumab (Stelara)." Ex.1033 at 2.

F. Public announcement of Janssen's Phase 3 clinical study for UC

Janssen publicized the design of its Phase 3 clinical trial for ustekinumab in UC treatment (NCT02407236) on ClinicalTrials.gov by April 2015. Ex.1002 ¶¶51-55; Ex.1054 at 1. This trial disclosed all aspects of the UC treatment regimen claimed in the '307. Ex.1002 ¶52. Janssen relied on the Phase 2 trial safety results from the Crohn's and psoriasis studies to justify its "direct-to-Phase-3" strategy for UC. Ex.1002 ¶51; Ex.1027 at 25 ("the shared biology and the similar response to current

treatments between Crohn's disease and UC, provide[d] a substantial scientific and clinical rationale to justify" Phase 3 study).

The summary describes two randomized, double-blind, placebo-controlled clinical studies with an estimated enrollment of 951 adult patients with moderately to severely active UC who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. Ex.1002 ¶53; Ex.1003 at 2-4. The study proposes an 8-week intravenous induction study followed by a 44-week subcutaneous randomized withdrawal maintenance study for a total of 52 weeks of therapy. *Id.* The study further proposes randomizing patients at Week 0 to receive a single intravenous administration of ustekinumab of approximately 6mg/kg, 130mg or placebo, and then randomizing patients to receive a subcutaneous maintenance regimen of either 90mg ustekinumab every 8 weeks, or every 12 weeks, or placebo for 44 weeks. *Id.*

The study also discloses a series of primary and secondary endpoints that reflected August 2016 FDA guidance for Phase 3 UC clinical trials. Ex.1002 ¶54; Ex.1029 at 11-12. Other Phase 3 clinical studies for drugs treating UC such as Remicade, Humira, Simponi, and Entyvio included identical or similarly defined outcomes. Ex.1002 ¶54; Ex.1060 (Remicade); Ex.1061 (Adalimumab); Ex.1062 (Vedolizumab).

G. Janssen's Phase 3 trial was well underway by September 24, 2018, and its results were published soon thereafter

The NCT-236 clinical trial began in August 2015 and concluded in August 2018. Ex.1002 ¶56; Ex.1003 at 2; Ex.1031 (Sands) at 2. The study results were published in The New England Journal of Medicine by Sands et al. on September 26, 2019. *Compare* Ex.1003 at 1 (describing "ClinicalTrials.gov Identifier: NCT02407236"), *with* Ex.1031 at 1 (same); *see also* Ex. 1031 at 2; Ex.1002 ¶56. Sands describes the exact treatment regimen of NCT-236. Ex.1002 ¶¶56-57; Ex.1031 at 1. Sands explains that 961 patients were randomly assigned to receive an intravenous induction dose of ustekinumab (either 130mg, a weight-range-based dose that approximated 6mg per kilogram of body weight) or placebo. *Id.* Patients who responded to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks, every 8 weeks) or placebo. *Id.*

Sands confirms that the steps taught in NCT-236 are effective for treating UC, reporting, the "percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab … was significantly higher than that among patients who received placebo," Ex.1031 at 1, and "the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks … or every 8 weeks

… than among those assigned to placebo." *Id*. Sands concludes that "[u]stekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis." *Id*; Ex.1002 ¶58.

Based on the results of this Phase 3 study, Janssen received FDA approval for UC in October 2019. Ex.1032; Ex.1055; Ex.1002 ¶59.

VII. SUMMARY OF THE '307

A. Brief Description of the '307 (Ex.1001)

The '307 claims methods of treating moderately to severely active UC using an anti-IL-12/IL-23p40 antibody. Ex.1002 ¶61. The claimed antibody comprises certain SEQ IDs representing particular regions of ustekinumab. Each of the independent claims also requires that the subject "is a responder to treatment" as evidenced by at least one measure chosen from an array of seven potential response indicators. Ex.1001 at claims 1, 19, 33, 34; Ex.1002 ¶62.

The '307 recognizes that at the time of invention, "[t]he involvement of the IL - 12/23 pathway in the pathogenesis of IBD is well established, and an important role for IL-12/IL-23 pathway in intestinal inflammation has been elucidated in colitis." Ex.1001 at 1:62-65; Ex.1002 ¶61. The patent describes that "Ustekinumab (STELARA®) is a fully human immunoglobulin G1 mAb to human IL-12/23p40 that prevents IL-12 and IL-23 bioactivity by inhibiting their interaction with their cell surface IL-12Rβ1 receptor protein… Through this mechanism of action,

ustekinumab effectively neutralizes IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses." Ex.1001 at 2:45-53; Ex.1002 ¶61. The '307 also describes how prior Phase 2 clinical studies demonstrated the efficacy and safety of ustekinumab in induction therapy in Crohn's. Ex.1001 at 2:53-3:19; Ex.1002 ¶61.

Some of the dependent claims limit the response criteria to a single measure of response and/or require particular timing for a response. *See, e.g.*, Ex.1001 at claims 10-18 ("44 weeks after week 0"), claims 24-32 ("by week 16"); Ex.1002 ¶63.

The independent claims of the '307 are almost identical with only minor differences. For example, claim 1 recites "administering to the subject a pharmaceutical composition comprising *a clinically proven safe and clinically proven effective amount* of an anti-IL-12/IL-23p40 antibody." Ex.1001 at claim 1[a]; Ex.1002 ¶64. Independent claims 19, 33, and 34 recite a more specific treatment: "intravenously administering to the subject an anti-IL-12/IL-23p40 antibody […] in a first pharmaceutical composition at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration at week 0 of the treatment" and "subcutaneously administering to the subject the anti- IL-12/IL-23p40 antibody in a second pharmaceutical composition at a dosage of 90 mg per administration at week 8 of the treatment." Ex.1001 at claims 19, 33, 34; Ex.1002 ¶64.

B. Relevant Prosecution History

During prosecution, the Examiner recognized that NCT-236 expressly disclosed using ustekinumab to treat UC, as well as various parameters and endpoints. Ex.1036 at 46-53; Ex.1002 ¶65.[1] The Examiner thus rejected ***all*** claims as obvious and anticipated under §§ 102 and 103. Ex.1036 at 46-53*;* Ex.1002 ¶65.

To overcome this rejection, PO amended the claims to recite that "the subject is a ***responder*** to treatment**"** as measured by the exact same response criteria that had been disclosed in NCT-236, arguing "the CT reference did not include any clinical trial results.… Due to the uncertainty of clinical outcomes and the failure of numerous medicines to satisfy designated clinical trial endpoints, the posting of elements of a clinical trial in advance of conduct of the trial do not anticipate or render obvious the subject matter of the claims." Ex.1036 at 32; Ex.1002 ¶66. As PO recognized in remarks accompanying the amended claims, the only material

[1] In the 7/16/2020 Notice of References Cited the Examiner refers to NCT02407236 webpage "[a]ccessed from the internet 7/13/20." Ex.1036 at 54. In response, PO refers to the "initial posting of the CT reference (April 2, 2015 according to the www.clinicaltrials.gov record)," but it is unclear whether the Examiner considered a prior art version of the webpage, such as the one Petitioner identifies. *Id*. at 32.

difference between the original and amended claims were *the results* of carrying out the NCT-236 Clinical Trial. Ex.1036 at 32; Ex.1002 ¶66.

Rather than address the propriety of claiming results that inevitably flow from performing prior-art steps, the Examiner withdrew the rejection without comment. Ex.1002 ¶67. The Examiner also failed to address any other prior art (such as Ochsenkühn) that demonstrated successful treatment of UC with ustekinumab. Indeed, the Examiner discussed only ***three*** references—NCT-236, the 2009 EMA approval of Stelara® for psoriasis, and US2020/0262908 (Ex.1049), and relied solely on NCT-236 for rejecting the claims. Ex.1036 at 4, 48-54. The Examiner declined to rely upon the 2009 EMA approval of Stelara® for Psoriasis because it "does not teach more than the CT reference." Ex.1036 at 52; Ex.1002 ¶67. The Examiner declined to reject the claims over Jones, which disclosed treating a UC patient with ustekinumab, because it did not disclose the "amount of ustekinumab [that] would have the inherent effects (i.e. meeting the 'endpoint' requirements of the instant claims')." Ex.1036 at 4.

C. '307 Priority Date

The '307 claims priority to Provisional Application Nos. 62/895,774, filed September 4, 2019, 62/769,818, filed November 20, 2018, and 62/735,501, filed September 24, 2018. Ex.1001 at cover; Ex.1002 ¶60. Petitioner's grounds are based on prior art that predates the 102(b)(1) date of September 24, 2019, and the 102(a)

provisional filing date of September 24, 2018, but reserves its right to challenge the priority date[s]. Ex.1002 ¶68.

VIII. LEVEL OF ORDINARY SKILL IN THE ART

A POSA in the field of the '307 as of September 2018 had knowledge regarding the mechanism of action, diagnosis, clinical trials, and treatment of IBDs, including at least UC and Crohn's disease, and had the ability to understand results and findings presented or published in the field. A POSA also had knowledge of the structure of antibodies used to treat IBD. A POSA may have worked as part of a multidisciplinary team including specialists, including, for example, a clinician, a biochemist knowledgeable about antibody sequences, and a formulation chemist. Typically, such a person would have an M.D. and residency training in gastroenterology and/or a Ph.D. in immunology, biochemistry, or a related field.

IX. PETITIONER'S PRIOR ART REFERENCES

A. NCT-236 (Ex.1003)

The clinical trial summary for Stelara® bearing NCT number NCT02407236 ("NCT-236") was published by April 2015. *See* Ex.1054 at 1; Ex.1002 ¶72. The accompanying Affidavit of Nathaniel Frank-White from the Internet Archive verifies that NCT-236 in Ex.1003 was accessible on the Internet no later than October 7, 2015. Ex.1028 at 16-20; Ex.1002 ¶72.NCT-236 qualifies as prior art under 35 U.S.C. § 102(a)(1) because it was publicly available prior to September 24, 2018, the filing

date of the provisional application to which the '307 claims priority. NCT-236 was considered and applied as a single reference during prosecution. Ex.1002 ¶72.

NCT-236 summarizes a Phase 3 clinical trial for Stelara® as indicated for UC. The trial evaluated "the efficacy and safety of ustekinumab as intravenous (IV: into the vein) infusion in induction study in participants with moderately to severely active Ulcerative Colitis (UC) and as subcutaneous (SC) administration in maintenance study in participants with moderately to severely active Ulcerative Colitis (UC) who have demonstrated a clinical response to Induction treatment with IV ustekinumab." Ex.1003 at 1; Ex.1002 ¶73. The treatment arm of NCT-236 discloses the same method of treatment of UC using an anti-IL-12/23 antibody (ustekinumab) with the same dosing regimen and response criteria (primary and secondary outcome measures) as recited in the '307 claims. Ex.1003 at 1-3; Ex.1002 ¶73.

B. Ochsenkühn (Ex.1005)

Ochsenkühn et al., "P759 Ustekinumab as rescue treatment in therapy-refractory or -intolerant ulcerative colitis," *Journal of Crohn's and Colitis*, 12(S1):S495 (February 2018) ("Ochsenkühn"), qualifies as prior art under 35 U.S.C. § 102(a)(1) because it was published prior to September 24, 2018. Ex.1002 ¶74. The Examiner did not consider Ochsenkühn during prosecution.

Ochsenkühn presents a retrospective data analysis of 17 UC patients who were given ustekinumab as a rescue therapy between 2016 and 2017. Ex.1005 at 2; Ex.1002 ¶75. The treatment involved administering ustekinumab at 6 mg per kg of body weight as an infusion and a 90 mg ustekinumab subcutaneous injection every 8 weeks. *Id.* Ochsenkühn reports that "clinical remission was achieved in 65% (11/17) at 1, 3, and 6 months, whereas only 35% (6/17) of patients were in remission at the start of the study." *Id*. Based on these results, the authors affirm "[u]stekinumab was effective as rescue medication in therapy-refractory or -intolerant UC" and proclaim "[i]t seems possible that large ongoing trials will confirm our findings …." *Id*.

C. Stelara® Prescribing Information (Ex.1004)

Stelara®'s prescribing information for use in Crohn's disease ("Stelara-PI(2017)") published on the Janssen website by at least February 25, 2017, and thus qualifies as prior art under 35 U.S.C. § 102(a)(1). Ex.1004; Ex.1028 at 369-370; Ex.1002 ¶76. The Examiner did not consider the Stelara® Prescribing Information during prosecution.

Stelara-PI(2017) describes the treatment of psoriasis, psoriatic arthritis, and Crohn's and that Stelara® was available as an intravenous infusion of 130 mg of ustekinumab in 26 mL and as a subcutaneous injection of 45 mg of ustekinumab in 0.5 mL or 90 mg of ustekinumab in 1 mL. *See* Ex.1004 at 3, 16; Ex.1002 ¶77.

X. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(B)(3)

Claims are construed under the claim-construction principles set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc); 37 C.F.R. § 42.100(b). Petitioner reserve the right to respond to any constructions PO submits.

A. "a clinically proven… amount of an anti-IL-12/IL-23p40 antibody" (claim 1)

Independent claim 1 of the patent recites "a clinically proven… amount" of antibody. *See* Ex.1001 at claim 1. As an initial matter, "a clinically proven… amount" should be construed as a non-limiting statement of intended effect and not given patentable weight. As the Federal Circuit described in *Bristol-Myers Squibb v. Ben Venue Laboratories*, claim language for "an [] effective amount" was non-limiting because an "expression of intended result essentially duplicates the dosage amounts recited in the claims that are also described in the specification" and "[t]he express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim." 246 F.3d 1368, 1375 (Fed. Cir. 2001). Since the language requiring that the amount be "clinically proven" safe and effective does not result in any "manipulative difference in the steps of the claims," it should not be limiting. *See In Re: Copaxone Consol. Cases,* 906 F.3d 1013, 1023 (Fed. Cir. 2018) (language that "does not change the express dosing amount or method already disclosed in the

claims, or otherwise result in a manipulative difference in the steps of the claims," should be construed as non- limiting).

The term "a clinically proven… amount" should also be construed as non-limiting as the term would otherwise be indefinite. *See Geneva Pharms. v. GlaxoSmithKline,* 349 F.3d 1373, 1384 (Fed. Cir. 2003) (rejecting indefinite proposed construction). The specification defines "clinically proven safe" and "clinically proven effective" as follows:

> ***The term "clinically proven safe,"*** as it relates to a dose, dosage regimen, treatment or method with anti-IL-12/IL-23p40 antibody of the present invention (e.g., ustekinumab), ***refers to a favorable risk:benefit ratio*** with an acceptable frequency and/or acceptable severity of treatment-emergent adverse events (referred to as AEs or TEAEs) compared to the standard of care or to another comparator.

Ex.1001 at 10:4-33; Ex.1002 ¶80.

> The terms ***"clinically proven efficacy" and "clinically proven effective"*** as used herein in the context of a dose, dosage regimen, treatment or method ***refer to the effectiveness of a particular dose, dosage or treatment regimen***. Efficacy can be measured based on change in the course of the disease in response to an agent of the present invention.… The degree of improvement generally is determined by a

> physician, who can make this determination based on signs, symptoms, biopsies, or other test results, and who can also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

Ex.1001 at 9:11-38; Ex.1002 ¶80. The specification provides a second definition of "clinically proven":

> As used herein, unless otherwise noted, the term "clinically proven" (used independently or to modify the terms "safe" and/or "effective") shall mean that it has been proven by a clinical trial wherein the clinical trial has met the approval standards of U.S. Food and Drug Administration, EMEA or a corresponding national regulatory agency.

Ex.1001 at 10:34-42; Ex.1002 ¶81.

Yet the patent does not provide any instruction on 1) how to determine a "favorable risk:benefit ratio," 2) a "degree of improvement" sufficient to render a dose "effective," or 3) whether a clinical trial will meet the approval standards of FDA, EMEA, or any other "corresponding national regulatory agency." Because "clinically proven" references undefined or changing standards, it is indefinite, and should be afforded no weight. Ex.1002 ¶82.

Lastly, the term "clinically proven" should be afforded no weight because "a construction that would require empirical testing is incorrect." *Homeland*

Housewares v. Whirlpool Corp., 865 F.3d 1372, 1375 (Fed. Cir. 2017). If "clinically proven" were given weight, it would require that a clinical trial be run to "prove" safety and efficacy, even if the claimed method steps had been known in the prior art for years.

Nevertheless, for the purposes of this Petition and without waiving its right to challenge the above definitions and definiteness of this term in district court, Petitioner applies the definitions excerpted above.

XI. GROUND 1: NCT-236 ANTICIPATES CLAIMS 1-4, 6-22, AND 24-34

NCT-236 anticipates the Challenged Claims. By publishing NCT-236 years before the earliest effective filing date of the '307, PO introduced the methods disclosed in NCT-236 into the public domain. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (single prior art reference that discloses each claim limitation, either explicitly or inherently, anticipates); *cf. Impax Lab'ys v. Aventis Pharms.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) ("[P]roof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation."). Sands later reported the clinical trial results obtained by carrying out the methods of NCT-236, which validated the efficacy inherent in treating UC with ustekinumab using this protocol. *See* Ex.1031 at 1 ("ClinicalTrials.gov number, NCT02407236"). This ultimately led to FDA approval for using Stelara® in treating UC. Ex.1032 at 1.

The Examiner correctly noted NCT-236 anticipates the claims but issued the '307 based on a misstatement of law by Applicant. Applicant claimed that NCT-236 did not anticipate because "the CT reference did not include any clinical trial results," and "[d]ue to the uncertainty of clinical outcomes and the failure of numerous medicines to satisfy designated clinical trial endpoints, the posting of elements of a clinical trial in advance of conduct of the trial do not anticipate or render obvious the subject matter of the claims." Ex.1036 at 32. This argument stands in direct contrast to Federal Circuit precedent. *See, e.g.*, *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012); *King Pharms. v. Eon Labs.*, 616 F.3d 1267 (Fed. Cir. 2010).

In re Montgomery addressed this exact issue, affirming the Board's determination that claims directed to a method of using ramipril to prevent strokes were inherently anticipated by a clinical trial summary (HOPE) that disclosed a protocol for administering ramipril to stroke-prone patients, because "administering ramipril to stroke-prone patients inevitably treats or prevents stroke." 677 F.3d at 1381. HOPE described "a large, simple randomized trial of ... ramipril ... and vitamin E ... in the prevention of myocardial infarction, stroke, or cardiovascular death," which recruited "[o]ver 9000 [patients] at high risk for cardiovascular events such as myocardial infarction and stroke." *Id.* at 1378. Just as in the present case, "[t]he HOPE study ultimately found that patients receiving ramipril had a statistically

significant reduction in the risk of stroke, but these results were not published until after Montgomery's priority date." *Id.* at 1378.

While the Federal Circuit acknowledged that the HOPE protocol "d[id] not disclose actual results," it highlighted the HOPE protocol's nature as "an advanced stage of testing designed to secure regulatory approval" and explained "[w]e have repeatedly held that '[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.'" *Id.* at 1381-83 (citation omitted).

The court explained that "[i]t is well established that a patent may be secured, and typically is secured, before the conclusion of clinical trials," and invoked the MPEP, which states, "[i]f an applicant has initiated human clinical trials for a therapeutic product or process, [Patent & Trademark] Office personnel should presume that [] the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." *Id.* at 1382-83 (quoting § 2107.03). NCT-236 is a fully enabled Phase 3 clinical trial summary that describes methods for administering ustekinumab to patients with moderately to severely active UC and monitoring their response, just as recited in the claims of the '307.

Similarly, *King Pharmaceuticals v. Eon Labs* held that claims directed to methods of "increasing the bioavailability of metaxalone by administration of an

oral dosage form with food" were anticipated because "the natural result of taking metaxalone with food is an increase in the bioavailability of the drug." 616 F.3d at 1270, 1275-1276 (Fed. Cir. 2010). While "prior art disclose[d] taking metaxalone with food, but not the natural result of this process," the claims were nevertheless anticipated as "[a]n increase in metaxalone's bioavailability is… an inherent aspect of the prior art." *Id.* at 1275-76.

Other courts have followed this precedent. For example, in *GlaxoSmithKline v. Glenmark Pharmaceuticals, USA*, the district court held that claims directed to a method of using carvedilol to decrease mortality risk in congestive heart failure patients were anticipated by prior art which "summarized a planned 'multicentre trial' … 'to evaluate [the drug's] efficacy and safety,'" even though the results of the trial were unavailable before the priority date. 2017 WL 8944995, at *2, *18 (D. Del. May 2, 2017). The court found "if there are no actual differences in the treatment protocol when one is treating the symptoms of CHF versus when one is attempting to decrease a CHF patient's risk of mortality, then practicing the treatment protocol described in [the prior art] … will *necessarily (or inherently)* result in 'decreas[ing] [ ] the risk of mortality' in CHF patients." *Id*. at *14 (emphasis in original).

In line with these decisions, the Federal Circuit in *Schering Corporation v. Geneva Pharmaceuticals* held that a patent covering DCL, an antihistamine compound, was inherently anticipated by a prior art compound, loratadine, because

loratadine results in the creation of DCL in a patient's body after ingestion. 339 F.3d 1373, 1380- 1381 (Fed. Cir. 2003). The Federal Circuit held that it was irrelevant that "secret tests of loratadine before the critical date" were not prior art, because the prior art "need only describe how to make DCL," and "disclose[d] administering loratadine to a patient." *Id*. The court explained "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Id.* at 1380.

Just as in the above cases, NCT-236 expressly discloses a method that inevitably and inherently produces the results claimed in the '307. The inherency of the claimed results is confirmed by Sands, which reported the results of NCT-236 and led to FDA approval for treating UC with Stelara® using the claimed methods of treatment. *See supra* Section VI.F; Ex.1002 ¶¶51-55. Sands is thus "[e]xtrinsic evidence," that "can be used to demonstrate what is 'necessarily present' in a prior art embodiment even if the extrinsic evidence is not itself prior art," because it "helps to elucidate what the prior art consisted of."[2] *Hospira v. Fresenius Kabi USA*, 946

[2] While *In re Montgomery* stated that the results of the HOPE study "were not published until after Montgomery's priority date and thus are irrelevant to an anticipation analysis," 677 F.3d at 1378, subsequent Federal Circuit precedent makes

F.3d 1322, 1329-30 (Fed. Cir. 2020). Likewise, in *Monsanto Technology v. E.I. DuPont de Nemours & Company*, the Federal Circuit held that declarations that were not published may nevertheless be used in an anticipation analysis "in support of the prior art already of record" because "[i]t is well established that such reliance on extrinsic evidence is proper in an inherency analysis." 878 F.3d 1336, 1345 (Fed. Cir. 2018).

Because all limitations of claims 1-4, 6-22, and 24-34 are expressly or inherently disclosed by NCT-236, these claims are invalid for anticipation. Ex.1002 ¶¶84-85.

A. Independent Claims 1, 19, 33, and 34 are Anticipated by NCT-236

Because NCT-236 discloses every aspect of the treatment regimen claimed in the independent claims, and the therapeutic effectiveness and responses cited in the claims naturally flowed from carrying out the NCT-236 protocol, these claims are invalid as anticipated. *Bristol–Myers Squibb*, 246 F.3d at 1376 ("Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent."); Ex.1002 ¶86.

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clear that while later evidence is not prior art, it may be used in an inherency analysis. *See Hospira*, 946 F.3d at 1329-30.

1. "A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising" (Preambles)[3]

To the extent the preambles are limiting, NCT-236 discloses the preambles. Ex.1002 ¶¶87-88. NCT-236 discloses the administration of "ustekinumab … in ***participants with moderately to severely active Ulcerative Colitis (UC)***." Ex.1003 at 1; Ex.1028 at 17.

2. administering a "pharmaceutical composition" comprising specific dosages (elements 1[a]/19[a]/33[a][c][d]/34[a][b])

The independent claims recite administering a "pharmaceutical composition" comprising "an anti-IL-12/IL-23p40 antibody" with minor differences in language. This element is expressly disclosed in NCT-236, which discloses the ***administration of "ustekinumab as intravenous (IV: into the vein) infusion in induction study***… and as ***subcutaneous (SC) administration in maintenance study*** in participants with moderately to severely active Ulcerative Colitis (UC)." Ex.1003 at 1; Ex.1002 ¶89. "Participant [sic] with clinical response in the Induction study will be eligible for the Maintenance study. The Maintenance study will be 44 weeks duration." Ex.1003 at 3. NCT-236 describes all of the dose amounts, delivery modes (intravenous or subcutaneous), Induction and Maintenance regimens, and dosing frequencies claimed in the independent claims. Ex.1003 at 2-3; Ex.1002 ¶¶89-92.

[3] Ex.1072 is a claim listing enumerating each claim element.

NCT-236 discloses administering to a subject "a pharmaceutical composition" by disclosing the administration of ustekinumab at each of the dosages recited in the claims. Ex.1002 ¶90. Three of the independent claims—claims 19, 33, and 34—recite "a. intravenously administering to the subject an anti-IL-12/IL-23p40 antibody [], in a first pharmaceutical composition at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration at week 0 of the treatment" and "b. subcutaneously administering to the subject the anti-IL-12/IL-23p40 antibody in a second pharmaceutical composition at a dosage of 90 mg per administration at week 8 of the treatment," Ex.1001 at claims 19[a]/33[a]/34[a], claims 33 and 34 further recite "followed by a maintenance therapy, wherein the maintenance therapy comprises subcutaneously administering to the subject the anti-IL-12/IL-23p40 antibody at a dosage of 90 mg per administration, once every 8 weeks or once every 12 weeks," Ex.1001 at claims 33[c]/34[b], and claim 33 further recites "wherein the maintenance therapy is provided for 44 weeks," Ex.1001 at claim 33[d]. All of these recited limitations are satisfied by the express disclosures of NCT-236.Ex.1003; Ex.1002 ¶¶90-92.

3. anti-IL-12/IL-23p40 antibody structural limitations (elements 1[b]/19[b]/33[b]/34[a])

The antibody structure requirements of the claims are inherently disclosed by NCT-236. Ex.1002 ¶93. Each independent claim recites administering to the subject an "anti-IL-12/IL-23p40 antibody" having certain SEQ IDs. *See* Ex.1001 at claims

1[b]/19[b]/33[b]/34[a]; Ex.1002 ¶93-97, Appx.I.NCT-236 expressly discloses the administration of ustekinumab, which is an anti-IL-12/IL-23p40 antibody. The amino acid sequence of ustekinumab, published in multiple places prior to September 24, 2018, contains all of the SEQ IDs recited within claim elements 1[b]/19[b]/33[b]/34[a]. *See supra* Sections V, VI.C; Ex.1002 ¶93-97, Appx.I; *see also Mylan Pharms. v. Regeneron Pharms.*, IPR2021-00881, Paper 94 at 28-29 (P.T.A.B. Nov. 9, 2022) (reference disclosing a VEGF Trap Eye protein inherently anticipated claimed VEGF antagonist sequences because "[t]he amino acid sequence and structural information for VEGF Trap-Eye ... was well-known and widely-published to skilled artisans.").

4. "clinically proven… amount" (element 1[a])

As discussed above, "a clinically proven... amount" should be construed as non- limiting. *See supra* Section X.A. Nevertheless, NCT-236 inherently discloses a "clinically proven safe and clinically proven effective amount of an anti-IL-12/IL-23p40 antibody" recited in claim 1. *See* Ex.1001 at claim 1[a]; Ex.1002 ¶98.

Janssen conceded that the claimed doses were inherently "clinically proven safe" when it relied on Phase 2/Phase 3 data from the Stelara® psoriasis and Crohn's studies to circumvent safety studies for the NCT-236 trial in its submission to the FDA. *See supra* Section VI.F; Ex.1027 at 25; Ex.1002 ¶99.

NCT-236 inherently discloses a "clinically proven effective amount" because performing the methods as described in NCT-236 necessarily demonstrates the effectiveness of the NCT-236 regimen. *See supra*, XI.A.1; Ex.1002 ¶¶100-101. NCT- 236 was "proven by a clinical trial wherein the clinical trial has met the approval standards of U.S. Food and Drug Administration." Ex.1001 at 10:34-39. These results naturally flowed from the NCT-236 disclosure, and NCT-236 inherently disclosed that the treatment is "clinically proven effective." *See King Pharms.,* 616 F.3d at 1275 (disclosure inherent where "the natural result flowing from the operation as taught would result in the performance of the questioned function.").

Additionally, even without construing "clinically proven effective amount," this limitation is satisfied as a matter of law. Claims 6 and 7 recite intravenous infusion of ustekinumab at 6 mg/kg or 130 mg at week 0 and subcutaneous injection of ustekinumab at 90 mg every 8 or 12 weeks after infusion. Ex.1001 at claims 6, 7. These same dosing regimens are in NCT-236. *See infra* Sections XI.D, XI.E; *see also* Ex.1002 ¶¶102-103. Because these claims depend from claim 1 (via claim 4), each of these doses is necessarily a "clinically proven effective amount." 35 U.S.C.A. § 112 ("A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). Thus these prior art administered "amounts" must necessarily satisfy "a clinically proven safe and

clinically proven effective amount of an anti-IL12/IL-23p40 antibody." Ex.1002 ¶¶98-104.[4]

5. "the subject is a responder to treatment by at least one measure of response to treatment selected from the group consisting of" (elements 1[c]/19[c]/33[e]/34[c])

NCT-236 inherently discloses the claimed measures of response. Ex.1002 ¶¶105-112. Each independent claim recites "after treating with the antibody, the subject is a responder to treatment by at least one measure of response to treatment selected from the group consisting of" one of the following measures:

(i) clinical remission based on at least one of the global definition of clinical remission with Mayo score ≤2 points with no individual subscore >1 and the US definition of clinical remission with absolute stool number ≤3, rectal bleeding subscore of 0 and Mayo endoscopy subscore of 0 or 1,

(ii) endoscopic healing with a Mayo endoscopy subscore of 0 or 1,

(iii) clinical response based on the Mayo endoscopy subscore,

(iv) improvements from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score,

(v) mucosal healing,

(vi) decrease from baseline in Mayo score, and

(vii) clinical response as determined by a decrease from baseline in the Mayo score by ≥30% and ≥3 points and a decrease from

[4] If the dosages in dependent claims 6 and 7 were not "a clinically proven safe and clinically proven effective amount," the '307 would fail to meet 35 U.S.C. § 112.

> baseline in the rectal bleeding subscore ≥1 points or a rectal bleeding subscore of 0 or 1. (1[d])

See Ex.1001 at claims 1[c], 19[c], 33[e], 34[c]; Ex.1002 ¶105.

Sands, reporting the results of NCT-236, confirms that subjects with moderately to severely active UC who received the treatments disclosed in NCT-236 responded according to the claimed measures of response. Ex.1002 ¶¶106-111; *see, e.g.*, *GlaxoSmithKline*, 2017 WL 8944995, at *2, *18 (patents anticipated by art which "summarized a planned 'multicentre trial' … to evaluate [the drug's] efficacy and safety," even though results of trial unavailable before priority date.); *Abbott Lab'ys v. Baxter Pharm. Prods.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) ("reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time").

Sands demonstrates therapeutic effectiveness of the induction and maintenance regimens disclosed in NCT-236, according to the response criteria identified therein. Ex.1031 at 2, 6, 8-9; Ex.1002 ¶107-112. Sands reports patient responses including clinical remission, endoscopic improvement, clinical response, and histo-endoscopic mucosal healing, as recited in the claims. Ex.1031 at 8; Ex.1002 ¶¶107-108. Sands reports that "Among patients who had a clinical response to induction treatment with ustekinumab, the percentages of patients who had clinical remission at week 44" were significantly higher in the groups receiving the Maintenance Therapy. Ex.1031 at 8-9, Fig. 3; Ex.1002 ¶¶110-111.

6. "the subject is a responder to treatment… and had previously failed or was intolerant of at least one therapy…" (element 19[d])

NCT-236 discloses the additional limitation of claim 19[d]. This limitation requires that the responder has previously failed or had been intolerant to other therapies, or had demonstrated corticosteroid dependence. NCT-236 expressly discloses these requirements in the Inclusion Criteria for the study. Ex.1003 at 4 ("Have failed biologic therapy, that is, have received treatment with 1 or more tumour necrosis factor (TNF) antagonists or vedolizumab"); Ex.1002 ¶¶113-114.

Sands confirms responses of patients meeting the eligibility criteria in 19[d]: "Eligible patients ***were required to have had an inadequate response to or unacceptable side effects from TNF antagonists, vedolizumab, or conventional (i.e., nonbiologic) therapy***." Ex.1031 at 2. The patient responses taught by NCT-236 and confirmed in Sands satisfy this limitation, and NCT-236 anticipates this claim. Ex.1002 ¶¶113-114.

B. Claims 2-3, 20-21

NCT-236 discloses the limitations of claims 2-3 and 20-21. Each of claims 2-3 and 20-21 recite SEQ IDs for the "anti-IL-12/IL-23p40 antibody" that are part of the publicly-known ustekinumab sequence. *See supra* Sections V, VI.C; Ex.1002 ¶¶115- 116.

C. Claims 4 and 22

Claims 4 and 22 recite a particular IV formulation, which is known to be the IV formulation of Stelara®. Ex.1002 ¶¶117-122. Stelara-PI(2017) discloses "STELARA® for Intravenous Infusion" available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL with the composition: EDTA disodium salt dihydrate (0.52 mg), L- histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg). Ex.1004 at 16. Simple math shows that this formulation is the composition recited in claims 4 and 22. Ex.1004 at 16; Ex.1002 ¶¶119-120. Stelara-PI(2017) also discloses that "STELARA® (ustekinumab) Injection" has a "pH of 5.7-6.3." Ex.1004 at 16; Ex.1002 ¶122.

NCT-236 expressly teaches the use of ustekinumab and teaches, via hyperlinks incorporated by reference, that the ustekinumab used is Stelara®. Ex.1071.[5] *Husky Injection Molding Sys. v. Athena Automation*, 838 F.3d 1236, 1248 (Fed. Cir. 2016) ("skilled artisan would understand the host document to describe

[5] The hyperlink from the 2015 version of NCT-236 to the Stelara labels is broken. Ex.1071 ¶3. However, a 2016 version of NCT-236 contains an active hyperlink. The 2015 and 2016 versions of NCT-236 are substantively identical, Ex.1071 ¶4, and the analysis in this Ground would not change depending on which version was used.

with sufficient particularity the material to be incorporated"). Because Stelara® was known to meet the limitations of claims 4 and 22, NCT-236 explicitly teaches them as well. Ex.1002 ¶118; *See Arbutus Biopharma Corp. v. ModernaTX*, 65 F.4th 656 (Fed. Cir. 2023) (affirming PTAB); *see also Adv. Display Sys. v. Kent State U.*, 212 F.3d 1272, 1282– 83 (Fed. Cir. 2000).

Alternatively, if NCT-236 is not found to teach the use of Stelara® by reference, NCT-236 nevertheless inherently discloses the limitation of claims 4 and 22 because a POSA would understand that "ustekinumab," as used in NCT-236, was Stelara®. Prior to the critical date, Stelara® was the only commercially available ustekinumab. Ex.1002 ¶¶118-120;*seealso*Ex.1041("Ustekinumab(Stelara) is a biologic medicine…"). Because NCT-236 was a Phase 3 trial, and there were no Phase 2 trials for the use of ustekinumab in UC, a POSA would have known that NCT-236 necessarily used Stelara®. Ex.1002 ¶118. Further, since NCT-236 discloses use of an IV infusion of ustekinumab, the Stelara® formation from Stelara-PI(2017) was necessarily used as it was the only Stelara® formulation for IV administration. Ex.1002 ¶119; Ex.1004. Moreover, NCT-236 was sponsored by Janssen, the manufacturer of Stelara, confirming Stelara® was used. Ex.1002 ¶118.

D. Claim 6

Claim 6 is dependent on claim 4 and recites intravenous administration at week 0 "at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per

administration." NCT-236 expressly discloses this intravenous dosage at week 0. Ex.1002 ¶123; Ex.1003 at 3.

E. Claim 7

Claim 7 is dependent on claim 6 and further recites subcutaneous administration at week 8 "at a dosage of about 90 mg per administration." Ex.1001. NCT-236 expressly discloses this subcutaneous dosage at week 8. Ex.1002 ¶124; Ex.1003 at 3.

F. Claim 8

Claim 8 recites the same limitation as 19[d]. NCT-236 expressly discloses this patient qualification criteria. *See supra* Section XI.A.6; Ex.1002 ¶125; Ex.1003 at 4.

G. Claim 9

Claim 9 recites: "The method of claim 7, wherein the antibody is administered in a maintenance dose every 8 weeks after the treatment at week 8 or every 12 weeks after the treatment at week 8." Ex.1001. NCT-236 expressly discloses Maintenance administration arms with administration every 12 or every 8 weeks "beginning Week 0 of Maintenance study through Week 44." Ex.1002 ¶126; Ex.1003 at 3.

H. Claims 10, 12-16, 18

These claims are dependent on claim 9 and each recites a different measure of patient response. NCT-236 inherently discloses each of the responses recited in these dependent claims upon completion of 44 weeks of Maintenance administration as shown by the week 44 results reported in Sands. Ex.1002 ¶127. Sands confirms that

each of these measures of response was observed in the NCT-236 trial results. Ex.1002 ¶127; *see also* Ex.1002 ¶106. Thus, NCT-236 inherently discloses these claims. Ex.1031 at 9; Fig. 3; Ex.1002 ¶127.

I. Claim 11

Claim 11 recites: "wherein the subject is in corticosteroid-free clinical remission at least 44 weeks after week 0." Ex.1001. NCT-236 expressly identifies this outcome. One of the Secondary Outcome Measures for the Maintenance Study of NCT-236 is the "[n]umber of [p]articipants with [c]linical [r]emission and not [r]eceiving [c]oncomitant [c]orticosteroids" measured at week 44. Ex.1003 at 2. Sands reports that this measure of response was observed in the NCT-236 trial results. Ex.1031 at 9, Fig. 3; Ex.1002 ¶128. Accordingly, NCT-236 inherently discloses claim 11. Ex.1002 ¶128.

J. Claims 17, 30

Claims 17 and 30 recite: "wherein the subject is identified as having a normalization of one or more biomarkers… [continuing at least 44 weeks after week 0]/[by week 16 of the treatment]." Ex.1001. Sands discloses that the claimed normalization of biomarkers is an inherent response to Induction of NCT-236: "Improvements ... in the partial Mayo scores and in concentrations of fecal calprotectin and lactoferrin and serum CRP support the clinical outcomes." Ex.1031

at 8; *see also id.* at 13. NCT-236 inherently discloses claims 17 and 30. Ex.1002 ¶129.

K. Claims 24-26, 28-29, and 31

These claims each recite a different measure of response "***by week 16 of the treatment***." Ex.1001 at cls. 24-26, 28-29, 31. A patient responding to treatment and satisfying these distinctly recited measures of claims 24-26, 28-29, and 31 was inherent to the disclosed Induction administration of ustekinumab in NCT-236, as described above in Section XI.A.5(3) and reflected in the results to Induction ***at week 8*** reported by Sands using the same measures of response. Ex.1031 at 8, Fig. 2. NCT-236 therefore inherently discloses claims 24-26, 28-29, and 31. Ex.1002 ¶130.

L. Claim 27

Claim 27 recites: "The method of any one of claims 19-21, wherein the subject is identified as having improvements from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score by week 16 of the treatment." Ex.1001. NCT-236 discloses the IBDQ outcome measure of claim 27 at week 8: "Induction Study – Mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score [Time Frame: Week 8]." Ex.1003 at 2. Sands shows that an improvement in IBDQ baseline was inherent to the Induction administration of ustekinumab at week 8: "Through week 8, the median changes from baseline in the IBDQ score were

significantly greater in both ustekinumab groups than in the placebo group." Ex.1031 at 8. NCT-236 inherently discloses claim 27. Ex.1002 ¶131.

M. Claim 32

Claim 32 recites: "The method of any one of claims 19-21, wherein the subject is not a responder to the treatment with the antibody by week 8 and is a responder to the treatment by week 16 of the treatment." Ex.1001 at claim 32. NCT-236 inherently discloses this claim. Ex.1002 ¶¶132-134.

Delayed-responders were inherent to the NCT-236 disclosure. NCT-236 discloses an arm of the Induction study for "Nonresponders at Week 8." Ex.1003 at 3. Sands confirms that: "***patients who did not have a clinical response to intravenous ustekinumab and who received 90 mg of subcutaneous ustekinumab at week 8***, a total of 59.7% (139 of 233) ***had a delayed clinical response at week 16***." Ex.1031 at 8; Ex.1002 ¶¶134.

XII. GROUND 2: THE COMBINATION OF NCT-236 IN VIEW OF OCHSENKÜHN AND STELARA-PI(2017) RENDERS THE CHALLENGED CLAIMS OBVIOUS

There are no differences between the subject matter claimed in the '307 and the prior art. As discussed in Ground 1, NCT-236 alone anticipates the '307 through express or inherent disclosure. However, should the Board find that NCT-236 does not anticipate, NCT-236 nevertheless renders the claimed methods obvious in view

of Ochsenkühn and Stelara-PI(2017).[6] NCT-236 and Ochsenkühn disclose the claimed method of treating UC with ustekinumab by administering a dosage that Stelara- PI(2017) teaches was safe, and Ochsenkühn reports patients that qualified as "responders" according to the criteria enumerated in the claims. Ex.1002 ¶¶135-136. As explained in Ground 1, the claimed results are inherent. *See supra* XI. To the extent they are not, a POSA would have reasonably expected that the claimed methods of treatment were clinically safe and effective and would achieve the claimed results. Accordingly, the claims of the '307 are obvious.

A. A POSA Had A Motivation to Combine the References

A POSA would have been motivated to combine NCT-236, Ochsenkühn, and Stelara-PI(2017) because of the express disclosures in these references and their overlapping and complementary subject matter. Ex.1002 ¶¶137-143.

A POSA reading NCT-236 on September 24, 2018 would have known that the FDA had previously approved Stelara® for Crohn's Disease. Ex.1038 at 1; Ex.1002 ¶139. Given that UC and Crohn's are the two most prevalent IBDs, and their known connection to the IL12/IL23 pathway, a POSA would have found Stelara®'s Prescribing Information for treatment of Crohn's highly relevant for application to

[6] Petitioner incorporates by reference evidence of anticipation by NCT-236 in its obviousness analysis.

UC. Ex.1002 ¶139. A POSA would also have been aware that numerous biologic therapies such as infliximab, adalimumab, and vedolizumab were already in use for both Crohn's and UC. *See supra* Section VI.B, Ex.1010 at 2; Ex.1002 ¶140. When NCT-236 published, a POSA would have known that Stelara® was the only ustekinumab available and would have recognized that the method of treatment described in NCT- 236 was identical to the method in Stelara-PI(2017) for treating Crohn's. *See* Ex.1002 ¶¶119, 141, 143; Ex.1041.

Ochsenkühn detailed that "ustekinumab was provided as a rescue treatment after colectomy had been offered to [the UC patients]." Ex.1005 at 2. This treatment regimen presented an attractive, safe, non-surgical option, particularly for patients who had not responded to available UC treatments. Ex.1002 ¶142. A POSA would have been motivated to combine Ochsenkühn, NCT-236, and Stelara-PI(2017) upon realizing that all three publications used the same method of treatment and dosing regimen. *Id.* ¶143. Ochsenkühn even noted that "[p]re-approval trials are on-going" for the use of ustekinumab to treat UC and that "it seems possible that large ongoing trials will confirm our findings and ustekinumab could become a new therapeutic option for refractory UC." Ex.1005 at 2; Ex.1002 ¶143. As NCT-236 was the only FDA trial evaluating the effectiveness of ustekinumab to treat UC, Ex.1002 ¶143, a POSA would have readily combined these references.

B. A POSA Had A Reasonable Expectation That the Claimed Treatment Methods Would Meet the Claimed Clinical Results

The claimed results are inherently disclosed by NCT-236. *See supra* Section XI.A.5; Ex.1002 ¶¶144-150. Petitioner's inherency analysis under Ground 1 also applies to obviousness, where, as here, a property is necessarily present in the prior art combination. *See Alcon Rsch. v. Apotex*, 687 F.3d 1362, 1369 (Fed. Cir. 2012); *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *see also In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

Even if not inherent, a POSA had a reasonable expectation from the teachings of NCT-236, Ochsenkühn, and Stelara-PI(2017) that the claimed treatment regimens would produce the results claimed in the '307. Ex.1002 ¶144-150. A POSA would have taken the detailed clinical trial protocol, NCT-236, which recites every aspect of the claimed method of treatment, including the drug administered, the treatment indication (UC), dosing regimen, and patient population, and combined it with Ochsenkühn and Stelara-PI(2017). From this combination, a POSA would have reasonably expected that the NCT-236 trial would result in the claimed responses, including demonstration of safety and effectiveness. Ex.1002 ¶144.

First, a POSA would examine NCT-236, a Phase 3 clinical study in its final stages, and understand that because it was fully enrolled and passed its estimated primary completion date (April 2018), but had not been cancelled due to futility, it was likely to be successful. Ex.1002 ¶145-146. A POSA would understand that the

study was designed to have the primary outcome reflect what clinical investigators expected to be achievable. Ex.1030 at 7-8; Ex.1002 ¶146. Based on that understanding, a POSA would have had a reasonable expectation of success. *See In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012). In fact, Sands confirms that ***every*** outcome measure tested in NCT-236 was met. *See* Ex.1002 ¶147.

Second, a POSA would have been aware of other clinical trials for UC and FDA guidance. A POSA would know that the endpoints disclosed in NCT-236 matched the endpoints set forth in an August 2016 FDA guidance for Phase 3 UC clinical trials. Ex.1029 at 11-12; Ex.1002 ¶147. A POSA would also recognize that other Phase 3 clinical studies for drugs treating UC such as infliximab, adalimumab, and vedolizumab included identical and similarly defined outcomes. Ex.1060; Ex.1061; Ex.1062; Ex.1002 ¶148. A POSA would recognize that these other biologics were approved for both Crohn's and UC, which would provide an expectation that Stelara®, which was already approved for Crohn's, would work for UC, particularly given their shared pathways. Ex.1002 ¶148.

Third, a POSA would have been aware of other publications detailing the off-label use of Stelara® for UC, such as Ochsenkühn. Ex.1002 ¶149. Ochsenkühn's successful treatment of UC patients and explicit reference to the Stelara® clinical trials, including the authors' conclusions that "[u]stekinumab was effective as rescue medication in therapy-refractory or -intolerant UC" and that "[i]t seems possible that

large ongoing trials will confirm our findings ...” would have provided a POSA further assurance that the NCT-236 trial was likely to be successful. Ex.1005 at 2; Ex.1002 ¶149. Indeed, the Federal Circuit has recently held that while an ongoing Phase 3 trial may not, “have given a POSA an expectation of success… in and of itself,” the ongoing trial may be used “as one piece of evidence, combined with other prior art references, to support an obviousness determination.” *Vanda Pharms. v. Teva Pharms. USA*, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023) (nonprecedential). Here, Ochsenkühn provides that additional evidence.

A POSA’s reasonable expectation of success is also confirmed by PO’s admissions. Ex.1002 ¶150. In its Clinical Protocol, submitted to the FDA on April 20, 2016, PO stated that “[d]ata from completed Phase 2 studies of ustekinumab in Crohn’s disease, ***along with the shared biology and the similar response to current treatments between Crohn’s disease and UC***, provide a substantial scientific and clinical rationale to justify a direct-to-Phase-3 approach to the study of ustekinumab in UC.” Ex.1027 at 25. PO further noted that “biologic therapies currently approved for the treatment of UC are either TNF-α or integrin inhibitors and, when tested, these therapies have also demonstrated efficacy in Crohn’s disease,” and cited studies demonstrating the efficacy of adalimumab, infliximab and vedolizumab in treating Crohn’s. *Id.* at 42, 134-35. Ultimately, PO stated that although “Ustekinumab has not been studied in UC[, h]owever, considering the similarities in

the genetics and biology of UC and Crohn's disease, ***it is reasonable to assume that ustekinumab will also be effective in UC***." *Id.* at 58.In addition, the patent itself recognizes that at the time of invention, "[t]he involvement of the IL - 12 / 23 pathway in the pathogenesis of IBD is well established, and an important role for IL-12/IL-23 pathway in intestinal inflammation has been elucidated in colitis," Ex.1001 at 1:62-65, "Ustekinumab (STELARA®) … prevents IL-12 and IL-23 bioactivity," *id.* at 2:45-47, and that Phase 2 clinical studies demonstrate the efficacy and safety of ustekinumab in induction therapy in Crohn's, *id.* at 2:53-3:19. *See also* Ex.1001 at 2:38-45.

C. The References in this Ground Disclose Independent Claims 1, 19, 33, and 34

1. "A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising" (Preambles)

To the extent the preamble is limiting, it is disclosed by NCT-236. *See supra* Section XI.A.1. Ochsenkühn also discloses this limitation. Ex.1002 ¶¶152-153. Ochsenkühn discloses in its title, "Ustekinumab as a rescue treatment in therapy-refractory or -intolerant ulcerative colitis." Ochsenkühn further reports treating "[a] total of 17 UC patients," and that "[a]t the start of the rescue therapy, 65% of patients (11/17) had moderately or severely active disease." Ex.1005 at 2.

2. administering a "pharmaceutical composition" comprising specific dosages (elements 1[a]/19[a]/33[a][c][d]/34[a][b])

NCT-236 discloses this limitation. *See supra* Section XI.A.2. Additionally, Ochsenkühn and Stelara-PI(2017) disclose this limitation because both references explicitly teach the use of a pharmaceutical composition of Stelara® in the claimed dosages. Ex.1002 ¶¶154-157.

For example, Ochsenkühn states: "All [UC] patients received ustekinumab as approved for Crohn's disease (6 mg/kg body weight as an infusion and 90 mg ustekinumab as s.c. injection every 8 weeks)." Ex.1005 at 2; Ex.1002 ¶156. Stelara-PI(2017) describes administering STELARA® for Crohn's in dosing ranges that include 6 mg/kg intravenous induction infusion at week 0 followed by 90 mg subcutaneous maintenance dose 8 weeks after the induction, then every 8 weeks thereafter. Ex.1004 at 4; Ex.1002 ¶156. A POSA would understand that a maintenance dose is to be continued indefinitely, provided there are no adverse events or other changes necessitating cessation of treatment. Ex. 1002 ¶157. Accordingly, these publications disclose claim elements 1[a]/19[a]/33[a][c][d]/34[a][b].

3. anti-IL-12/IL-23p40 antibody structural limitations (elements 1[b]/19[b]/33[b]/34[a])

NCT-236 discloses this limitation. *See supra* Section XI.A.3. Additionally, Ochsenkühn and Stelara-PI(2017) disclose this limitation because both references

explicitly teach the use of Stelara, an anti-IL-12/IL-23p40 antibody with an amino acid sequence that contains all of the SEQ IDs recited in claim elements 1[b]/19[b]/33[b]/34[a]. *See supra* Section XI.A.3; Ex.1002 ¶158.

4. "clinically proven safe… amount" (element 1[a])

NCT-236 alone renders this claim anticipated. *See supra* Section XI.A.4; Ex.1002 ¶159-160. Stelara-PI(2017) also teaches administration of ustekinumab according to the claimed dosing regimen to be "clinically proven safe," as administered to Crohn's and psoriasis patients.Ex.1002 ¶160.Janssen's reliance on the earlier approved indications for Stelara® to support its direct-to-phase 3 UC trial is further evidence that the claimed regimen was clinically proven safe. *See supra* Section I.F; Ex.1002 ¶160. Compared to a Phase 2 trial which ***evaluates*** the effectiveness and further evaluates a drug's safety over a Phase 1 trial, a Phase 3 trial ***confirms*** effectiveness and collects information to allow the treatment to be used safely.[7] The Phase 3 nature of the study implies a level of effectiveness and safety was already known. Ex.1002 ¶99, 136, 146, 164. Based on this information and the results of Ochsenkühn, a POSA would have recognized that the claimed Induction and Maintenance regimen was already clinically proven safe for Crohn's and would

[7] https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research

also be clinically proven safe for moderately to severely active UC patients. Ex.1002 ¶99, 136, 146, 164.

5. "clinically proven effective amount" (element 1[a])

NCT-236 alone renders this claim anticipated. *See supra* XI.A.4. This limitation is further obvious by three independent analyses: (1) the prior art satisfies the express definition provided for "clinically proven effective;" (2) a POSA would have a reasonable expectation that the Phase 3 clinical trial described in NCT-236 would successfully result in regulatory approval in view of Ochsenkühn; and (3) in view of dependent claims 6 and 7, this limitation is met as a matter of law. *See* Ex.1002 ¶¶161- 169.

a. The prior art discloses the patent's definition of "clinically proven effective"

NCT-236 alone renders this claim anticipated. *See supra* XI.A.4. Ochsenkühn additionally meets the patent's express definition of "clinically proven effective" for the recited treatment regimen. As described above, Ochsenkühn discloses the claimed treatment regimen and reports that "clinical remission was achieved in 65% (11/17) at 1, 3, and 6 months, whereas only 35% (6/17) of patients were in remission at the start of the study." Ex.1005 at 2; Ex.1002 ¶161. The authors of Ochsenkühn conclude based on these results that "[u]stekinumab was effective as rescue medication in therapy- refractory or -intolerant UC." *Id.* A POSA would have

understood that these publications disclose the patent's definition of "clinically proven effective." Ex.1002 ¶¶161-162.

b. The prior art provides a POSA a reasonable expectation of "clinically proven effective"

Even if "clinically proven effective" requires successful results from an approved trial, a POSA would have had a reasonable expectation of successful clinical trial results for the claimed dosing regimen in treating UC. Ex.1002 ¶¶163-165. A POSA would have understood Ochsenkühn's success in treating UC patients using the claimed treatment regimen. Ex.1002 ¶165. Indeed, Ochsenkühn specifically concludes, "[i]t seems possible that large ongoing trials will confirm our findings and ustekinumab could become a new therapeutic option for refractory UC." Ex.1005 at 2; Ex.1002 ¶165. A POSA would understand Ochsenkühn to be referring to the NCT-236 trial and suggesting that their own preliminary finding would be confirmed by the larger scale trial that was designed with sufficient patient enrollment to justify regulatory approval of ustekinumab for UC. Ex.1002 ¶165. Accordingly, claim element 1[a], is met by this Ground. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success."); *Hospira v. Genentech*, IPR2017- 00737, 2018 WL 5262656, at *21 (P.T.A.B. Oct. 3, 2018) ("Conclusive proof of efficacy is not necessary to show obviousness."); *Acorda Therapeutics v. Roxane Lab'ys*, 903 F.3d 1310, 1333-34 (Fed. Cir. 2018) (POSA "can draw reasonable inferences about the

likelihood of success even without a perfectly designed clinical trial showing a statistically significant" result).

c. The prior art satisfies this limitation as a matter of law

This limitation is also satisfied as a matter of law in view of dependent claims 6 & 7 for the same reasons described above. *See supra* Section XI.A.4. These same dosing regimens are taught in NCT-236, Ochsenkühn and Stelara-PI(2017). *See infra* Sections XII.G, XII.H; *see also* Ex.1002 ¶¶167-169.

6. "the subject is a responder to treatment by at least one measure of response to treatment…" (elements 1[c]/19[c]/33[e]/34[c])

These seven response criteria were expressly disclosed in NCT-236 as Primary Outcome Measures or Secondary Outcome Measures and the corresponding response was inherently disclosed by NCT-236. *See supra* Section XI.A.5; Ex.1002 ¶¶170-210. To the extent they are not inherent, a POSA would have reasonably expected that responders in the NCT-236 clinical trial would meet these Outcome Measures. Ex.1002 ¶¶172-210. This expectation would flow from a POSA's understanding of the NCT- 236 clinical trial as of September 24, 2018, combined with Ochsenkühn's disclosure of "clinical remission" following the claimed treatment. Ex.1002 ¶¶172-176. Indeed, Sands confirms that ***every*** outcome measure tested in NCT-236 was met, confirming a reasonable expectation of success. *See* Ex.1002 ¶147.

a. A POSA would have reasonably expected responders with response measure (i)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (i), since clinical remission is the most favorable clinical outcome measure and this measure was identified as a Primary Outcome Measure in NCT-236. Ex.1002 ¶177.

A POSA, understanding how clinical trials are designed, would have understood that the Primary Outcome Measures reflect a reasonable expectation of success of achieving those Measures. Ex.1002 ¶¶178-179. A POSA would have understood that NCT-236 would not have been proposed, pursued, and approved if there was not an expectation that patients would achieve the Primary Outcome Measures.Ex.1002 ¶¶179-180. Those Measures expressly call for the "number of patients with clinical remission," which corresponds to the first response criteria listed in the claims. Ex.1002 ¶180.

Ochsenkühn would have bolstered a POSA's expectation of success to achieve clinical remission according to the claimed criteria. Ex.1002 ¶181. Ochsenkühn reported that the primary outcome of treatment of UC patients with ustekinumab was "clinical remission at 3 and 6 months." Ex.1005 at 2 ("clinical remission was achieved in 65% (11/17) at 1, 3, and 6 months"); Ex.1002 ¶181-182. While Ochsenkühn refers to clinical remission according to the "modified Truelove and Witts colitis activity index (CAI)," Ex.1005 at 2, a POSA would have understood

from the strong initial response to IV Induction and the typical Induction-Maintenance response reported for these patients that at least some patients in Ochsenkühn's study would have achieved the Primary Outcome Measure of clinical remission set forth in NCT-236.Ex.1002 ¶¶183-186.[8]

A POSA's expectation of success would have been bolstered by the knowledge of the ongoing NCT-236 trial as of September 24, 2018. Ex.1002 ¶¶187-188. A POSA would have known that patient recruitment for the NCT-236 trial began in October of 2015 and was closed by September 8, 2017, culminating with a total enrollment of 966 patients. *See* Ex.1046; Ex.1047; Ex.1002 ¶188. Given that the Induction and Maintenance treatment arms of NCT-236 were 8 weeks and 44 weeks respectively (i.e., 52 weeks), a POSA would have recognized that the great majority of these 966 patients would have at least substantially completed both the Induction Study and Maintenance Study portion of the trial by September 24, 2018. Since the study was ongoing and had not been halted a full year after patient recruitment closed, a POSA would have reasonably expected that some number of patients in the NCT-236 trial had experienced clinical remission. Ex.1002 ¶188.

[8] Dr. Safdi confirms that the responses reported under the modified Truelove and Witt index would have provided a POSA ample reason to expect NCT-236 patients to satisfy the claimed clinical remission criteria. Ex.1002 ¶¶183-186.

b. A POSA would have reasonably expected responders with response measure (ii)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (ii). Ex.1002 ¶¶189-191. This response measure is one of the Secondary Outcome Measures identified in NCT-236. A POSA would have expected that a subset of the patients achieving clinical remission under the Primary Outcome Measure of NCT-236 would also satisfy this measure. Dr. Safdi opines that in his practice, he has observed that about 15-20% of patients who have clinical remissions characterized in part by absolute stools of ≤3 also demonstrate endoscopic healing. This is consistent with the endoscopic healing percentages that were ultimately observed for patients in the NCT-236 trial. Ex.1002 ¶¶189-191; Ex.1031 at 6-8.

c. A POSA would have reasonably expected responders with response measure (iii)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (iii). Ex.1002 ¶¶192-193. A POSA would have understood that a patient satisfying the response criteria (ii) would also satisfy this limitation, because the responder would have endoscopic healing with a Mayo endoscopy subscore of 0 or 1. Ex.1002 ¶192. Moreover, the NCT-236 trial was designed such that eligible patients for the study had an initial Mayo endoscopy subscore of ≥2 before treatment, hence the trial design selected for patients who

would show clinical response based on the Mayo subscore. Ex.1002 ¶192. In view of this trial design and the understanding that a subset of clinical responders to treatment is likely to have an improved endoscopy score, a POSA would reasonably expect to see responders according to this criterion. Ex.1002 ¶193.

d. A POSA would have reasonably expected responders with response measure (iv)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (iv). Ex.1002 ¶¶194-197. This response measure is one of the Secondary Outcome Measures identified in NCT-236. NCT-236 describes IBDQ as "used to evaluate the disease-specific health-related quality of life across 4 dimensional scores: bowel (loose stools, abdominal pain), systemic (fatigue, altered sleep pattern), social (work attendance, need to cancel social events), and emotional (anger, depression, irritability)." Ex.1002 ¶¶194-196. A POSA would understand that Ochsenkühn reported clinical remission according to a modified Truelove and Witts CAI score, which relies on factors that overlap with the IBDQ factors, such as diarrhea and abdominal pain and cramping, and general well-being. Ex.1002 ¶¶197.Based on Ochsenkühn as well as the NCT-236 trial design, which monitors change from baseline IBDQ, a POSA would have reasonably expected to observe responders with improvements in IBDQ. Ex.1002 ¶194-197.

e. A POSA would have reasonably expected responders with response measure (v)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (v). Ex.1002 ¶¶198-200. The '307 defines "mucosal healing" as "a Mayo endoscopic sub-score of 0 or 1." Ex.1001 at 72:17. Similarly, NCT-236 characterizes endoscopic healing as "improvement in the endoscopic appearance of ***the mucosa*** ... defined as Mayo endoscopic subscore = 0 or 1," and lists this measure as a Secondary Outcome Measure. Accordingly, this limitation is obvious for the same reasons as response measure (ii), discussed above. Ex.1002 ¶198-200.

f. A POSA would have reasonably expected responders with response measure (vi)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical remission as claimed in (vi). Ex.1002 ¶¶201-202. A POSA would have understood that Ochsenkühn's patients would have had a "decrease from baseline in Mayo score." *Id.* Although Ochsenkühn reports responses based on the modified Truelove and Witts CAI score, a POSA would have known that this score correlates with a reduction in the baseline Mayo score, because both share common input parameters of stool frequency and rectal bleeding/bloody stool. Moreover, the substantial decrease in the median scores of Ochsenkühn's patients in response to

treatment strongly suggest to a POSA that their baseline Mayo score would also have decreased. Ex.1002 ¶¶203-204.

g. A POSA would have reasonably expected responders with response measure (vii)

A POSA would have expected at least some patients in the NCT-236 trial to achieve clinical response as claimed in (vii). Ex.1002 ¶¶205-210. This response measure is one of the Secondary Outcome Measures after Induction or Maintenance identified in NCT-236. A POSA would have understood that this clinical response is less stringent than the "clinical remission" definition provided as a Primary Outcome Measure of NCT-236. Clinical remission requires a Mayo score ≤ 2 points (down from a baseline score of 6-12) and a rectal bleeding subscore of 0. Accordingly patients that satisfy response measure (i) also satisfy this measure (vii), and a POSA would reasonably have expected responders in NCT-236 to satisfy this measure.Ex.1002 ¶¶205-210.

7. "the subject is a responder to treatment… and had previously failed or was intolerant of at least one therapy…" (element 19[d])

NCT-236 discloses this limitation. *See supra* Section XI.A.6. Additionally, Ochsenkühn discloses this limitation because it teaches that the subject previously failed or was intolerant to other specified therapies. Ex.1002 ¶¶211-213. Ochsenkühn states: "[a]ll patients (17/17) previously had been steroid-refractory or -dependent and had recently failed all of the following drugs: purine analogues, anti-

TNF-antibodies and anti-integrin antibodies" and some patients "had intolerable side effects under TNF-or integrin blocking treatment, which had to be stopped." Ex.1005 at 2. Accordingly, these publications disclose claim element 19[d]. Ex.1002 ¶¶211-213.

D. Claims 2-3, 20-21

NCT-236 alone renders this claim anticipated. *See supra* XI.B. Nevertheless, even if not anticipated, these claims are obvious because a POSA would have understood that the amino acid sequences recited in claims 2-3 and 20-21 are sequences within ustekinumab, and those sequences were publicly known as of the priority date. *See supra* Section V; Ex.1002 ¶214.

E. Claims 4, 22

NCT-236 alone renders this claim anticipated. *See supra* XI.C. Nevertheless, even if not anticipated, they are obvious. Ex.1002 ¶215. A POSA viewing NCT-236, which discloses "ustekinumab," and was sponsored by Janssen, the manufacturer of Stelara®, would have found it obvious to use Stelara® when practicing the method of NCT-236. Moreover, Ochsenkühn specifically teaches the use of Stelara® for treatment of UC. Ex.1005 at 2. As the only available ustekinumab at the time, a POSA would naturally use Stelara®, as disclosed in Stelara-PI(2017). As described above, *see* XI.C, Stelara-PI(2017) discloses the limitations of claims 4 and 22. Ex.1002 ¶215.

F. Claims 5, 23

Claims 5 and 23 depend from claims 1-3 and 22, respectively, which are anticipated and/or rendered obvious by NCT-236. *See* Sections XI, XII. Claims 5 and 23 recite a particular subcutaneous formulation that is rendered obvious by Stelara-PI(2017). Ex.1002 ¶¶216-220.

Stelara-PI(2017) teaches a subcutaneous formulation of ustekinumab with the same ingredients as claims 5 and 23 and in the same amounts, except for L-histidine, which Stelara-PI(2017) teaches at a range of 4.8-6.4 mM, whereas the claims recite "6.7 mM L-histidine." Ex.1004 at 16; Ex.1002 ¶¶216-217. The '307 explains that "histidine and histidine monohydrochloride hydrate" are "buffering components," "preferably added to provide improved pH control," and "[v]ariations to this process would be recognized by one of ordinary skill in the art," including the "pH at which the formulation is prepared." Ex.1001 at 32:64-65, 30:40-42, 32:51-57; Ex.1002 ¶218. Stelara-PI(2017) also discloses a "pH of 5.7-6.3." Ex.1004 at 16; Ex.1002 ¶218. Since the '307 recognizes that pH is a known variable to be optimized, and the concentration of L-histidine affects pH, Stelara-PI(2017)'s 4.8-6.4 mM L-histidine makes obvious the claimed 6.7 mM L-histidine. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("it is not inventive to discover the optimum or workable ranges by routine experimentation."). Because Stelara-PI(2017) states concentrations that disclose or render obvious the claimed

formulations, Stelara-PI(2017) renders obvious claims 5 and 23. Ex.1002 ¶¶216-220.

G. Claim 6

NCT-236 discloses this limitation. *See supra* Section XI.D. Additionally, Ochsenkühn and Stelara-PI(2017) expressly disclose this limitation and a POSA would understand that UC patients would respond to this dosing regimen. Ex.1002 ¶221. For example, Ochsenkühn states: "All [UC] patients received ustekinumab as approved for Crohn's disease (***6 mg/kg body weight as an infusion*** and 90 mg ustekinumab as s.c. injection every 8 weeks)." Ex.1005 at 2 ; Ex.1002 ¶221. Intravenous administration of STELARA®(ustekinumab) as approved for Crohn's in dosing ranges that include 6 mg/kg at week 0 satisfies this limitation. Ex.1004 at 4; Ex.1002 ¶221.

H. Claim 7

NCT-236 discloses this limitation. *See supra* Section XI.E. Additionally, Ochsenkühn and Stelara-PI(2017) expressly disclose this limitation and a POSA would understand that UC patients would respond to this dosing regimen. Ex.1002 ¶222. For example, Ochsenkühn states: "All patients received ustekinumab as approved for Crohn's disease (6mg/kg body weight as an infusion and ***90 mg ustekinumab as s.c. injection every 8 weeks***)." Ex.1005 at 2. Subcutaneous

administration of STELARA®(ustekinumab) as approved for Crohn's at 90 mg at week 8 satisfies this limitation. Ex.1004 at 4.

I. Claim 8

Claim 8 recites the same limitation as 19[d] and is satisfied by Ochsenkühn and NCT-236 for the same reasons as described. *See supra* Section XII.C.7; Ex.1002 ¶223.

J. Claim 9

NCT-236 discloses this limitation. *See supra* Section XI.G. Additionally, Ochsenkühn and Stelara-PI(2017) expressly disclose this limitation and a POSA would understand that UC patients would respond to this dosing regimen. Ex.1002 ¶224. For example, Ochsenkühn states: "All patients received ustekinumab as approved for Crohn's disease (6mg/kg body weight as an infusion and 90 mg ustekinumab as s.c. injection ***every 8 weeks***)." Ex.1005 at 2. STELARA® (ustekinumab) as approved for Crohn's is administered as a subcutaneous maintenance dose of 90 mg at week 8, "then every 8 weeks thereafter" satisfies this limitation. Ex.1004 at 4.

K. Claims 10, 12-16, 18

Dependent claims 10, 12-16, 18 each require that the subject has achieved each of the individual seven claimed measures, "continues/continuing at least 44 weeks after week 0." Ex.1001. A POSA would have understood these claims to be obvious because they reflect what a POSA would have expected to see in patient

responses. *Ecolab v. FMC Corp.*, 569 F.3d 1335, 1349 n.2 (Fed. Cir. 2009) (affirming obviousness where only routine experimentation required to arrive at the claimed parameter.). As described above with respect to claim elements 1[c]/19[c]/33[e]/34[c] a POSA would have expected at least some patients to have a sustained clinical remission following the treatment disclosed in NCT-236, and thereby meeting all Primary and Secondary Outcome Measures. *See supra* Section XI.A.5; Ex.1002 ¶225. A POSA would have understood that Crohn's patients, for instance, had experienced remissions lasting at least through 44 weeks of treatment. Ex.1002 ¶225.

L. Claim 11

NCT-236 discloses this claim. *See supra* Section XI.I. Claim 11 is also obvious because a POSA would have known to identify these patients and would have reasonably expected that at least one patient in clinical remission would also be corticosteroid-free. *Id.* ¶¶226-227.

M. Claims 17, 30

NCT-236 discloses these claims. *See supra* Section XI.J. To the extent NCT-236 does not anticipate claims 17 and 30, it renders them obvious as a POSA would have understood that "[s]ponsors are encouraged to prospectively collect data for non- endoscopic markers of inflammation (such as C-reactive protein level, fecal

calprotectin and lactoferrin, or other putative biomarkers) throughout the trial" as described by FDA guidance for UC clinical trials. Ex.1002 ¶228; Ex.1029 at 14.

N. Claims 24-29, 31

Dependent claims 24-29, 31 each require that the subject has achieved each of the individual seven claimed measures "by week 16 of the treatment." Ex.1001. NCT- 236 discloses this limitation. *See supra* Sections XI.K(1), XI.L(2). These claims are also obvious because NCT-236 sets forth the criteria claimed in these limitations, and for the reasons stated above, a POSA would reasonably have expected to see responders that satisfy each of these limitations. Ex.1002 ¶¶229-230. As described above, a POSA would have reasonably expected that patients with moderately to severely active UC treated with the claimed dosing regimens would respond according to these known criteria. *See supra* Section XI.A.5; Ex.1002 ¶230.

O. Claim 32

NCT-236 discloses this limitation. *See supra* Section XI.M. NCT-236 further renders Claim 32 obvious because NCT-236 identifies this patient population. Ex.1002 ¶231. NCT-236 has a treatment arm for "[p]articipants without clinical response to induction treatment ustekinumab (130 mg or 6 mg/kg [IV]) at Week 8 but in clinical response at Week 16 after receiving Induction Ustekinumab at week 8 (delayed responders)." Ex.1003 at 3.

XIII. NO SECONDARY CONSIDERATIONS

Petitioner is not aware of any secondary considerations (or the requisite nexus) that would support a finding of non-obviousness. Ex.1002 ¶¶232-233. Even if there were, they cannot overcome the strong *prima facie* case of obviousness. *See Wyers v. Master Lock*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

If PO alleges that the method of treating UC with STELARA® (ustekinumab)— as taught by the combination of NCT-236, Ochsenkühn, and Stelara-PI(2017)—yielded unexpected results, that argument should be rejected. The fact of the Phase 3 clinical study, which NCT-236 describes and Ochsenkühn acknowledges, indicates that clinicians expected the claimed method of treatment to work. Ex.1002 ¶234; Ex.1005 at 2; Ex.1003. Indeed, Ochsenkühn expressly stated that treating patients with moderately to severely active UC with "ustekinumab as approved for Crohn's" was "effective ... in a large IBD referral center." Ex.1005 at 2. Ochsenkühn further noted that "[p]re-approval trials are on-going" for the use of ustekinumab to treat UC (i.e., NCT-236) and that "[i]t seems possible that large ongoing trials will confirm our findings and ustekinumab could become a new therapeutic option for refractory UC." Ex.1005 at 2. The mere clinical approval based on NCT-236 was therefore not, as of September 24, 2018, an unexpected result. Ex.1002 ¶234.

To the extent PO argues long-felt but unmet need, that argument fails. By 2018, the claimed method of treatment, including its specific dosing regimen and response criteria, was publicly disclosed by PO, and thus any "unmet" need had already been fulfilled. Ex.1002 ¶235; Ex.1003. Other gastroenterologists had also been implementing methods like that claimed since before 2018. Ex.1005 at 2.

Should PO allege commercial success, PO will be unable to establish that the success is attributable to the claimed method. "If commercial success is due to an element in the prior art, no nexus exists." *Tokai Corp. v. Easton Enters.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011). As explained throughout this Petition, there is nothing patentably distinguishable in the '307's claims over the prior art, and Ochsenkühn already put the method of effectively treating UC patients with ustekinumab (as approved for Crohn's) into the prior art. Ex.1002 ¶236.

Finally, PO will not be able to establish that any secondary considerations support the full scope of the claims. "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 v. Apotex*, 754 F.3d 952, 965 (Fed. Cir. 2014).

Petitioner reserves the right to respond to any assertions of secondary considerations that PO alleges during this proceeding.

XIV. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. 35 U.S.C. § 325(d)

The Board should not exercise discretionary denial under § 325(d), particularly in view of the new information presented and strong showing of invalidity in the foregoing Grounds. The exercise of the Board's discretion under § 325(d) involves a two-part framework that considers: (1) whether the same or substantially the same art or arguments were previously presented to the Office (*Becton Dickinson* Factors (a), (b) and (d)) and, if so, (2) whether Petitioner has demonstrated that the Examiner erred in a manner material to the patentability of the challenged claims (*Becton Dickinson* Factors (c), (e) and (f)). *See Advanced Bionic v. Med-EL Elektromedizinische Geräte*, IPR2019-01469, 2020 WL 740292, at *3-4 (P.T.A.B. Feb. 13, 2020) (precedential)). Both aspects of the two-part framework weigh against discretionary denial.

First, the Petition relies on non-cumulative material references, Ochsenkühn and Stelara-PI(2017), which were not presented or considered by the Examiner. Ochsenkühn discloses the effective "rescue treatment" of UC patients with ustekinumab for patients with moderately to severely active UC and that had failed other therapies. Ex.1005 at 2. Ochsenkühn specifically refutes and shows the error in the fundamental premise of the '307 that "[p]rior to the present invention, no studies had been conducted with ustekinumab for UC ... particularly moderately to

severely active UC, in subjects who had previously failed or were intolerant of a biologic therapy or other conventional therapy." Ex.1001 at 3:13-19. Ochsenkühn discloses the treatment of UC patients using "ustekinumab as approved for Crohn's disease," expressly teaching a POSA that the same Stelara® treatment regimen used for Crohn's could be used effectively for UC. Ex.1005 at 2. The teachings of Ochsenkühn (alone) and in combination with Stelara- PI(2017) and NCT-236 are new, non-cumulative information that was not before the Examiner. *See, e.g.*, *Ciena Corp. v. Capella Photonics*, IPR2021-00624, Paper 20 at 37 (P.T.A.B Nov. 16, 2021) (denying to exercise discretion where "obviousness combinations presented in this Petition ... present new evidence of unpatentability").

Second, the file history suggests that Examiner did not consider ***inherent*** anticipation of the issued claims by NCT-236 reference in view of the later-confirmed results from the corresponding clinical trial. *See* Ex.1036. A summary of an Examiner interview on October 5, 2020 discussed amendments to the then-pending claims and noted PO's argument that "it would not have been obvious that the endpoints would have been met by the claimed antibody, ***nor would a specific patient population defined by such endpoints be anticipated***." *See id* at 45. PO thereafter argued that "the CT reference did not include any clinical trial results" and "[t]he CT reference indicates that the results of the clinical trial were first posted December 23, 2019, after the filing date of the present application." Ex.1036 at 32.

There is nothing in the file history to indicate that the Examiner ever considered the inherent results of performing the NCT- 236 clinical trial, as reported in Sands. *See supra* Section VII.B. Finally, the Examiner did not have the benefit of the additional evidence and arguments Petitioner presents herein. *See, e.g.*, *Taro Pharms. U.S.A. v. Apotex Techs.*, IPR2017-01446, 2017 WL 6206129, at *8 (P.T.A.B. Nov. 28, 2017) (declining to deny institution under §325(d) where petitioner presented new declaration evidence).

B. 35 U.S.C. § 314(a)

The Board should not discretionarily deny institution under §314(a)—Petitioner has not previously filed a petition directed to any claims of the '307 Patent, so "this is not a case of follow-on petition or multiple petitions." *Halliburton Energy Services, Inc., v. U.S. Well Services, LLC,* IPR2022-00074, Paper No. 9 at 10-11 (May 12, 2022) (denying Patent Owner's arguments in favor of discretionary denial in view of *General Plastic Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017)). Only one petition against the '307 has been filed by another party, and that proceeding was terminated before Patent Owner filed its preliminary response.

XV. CONCLUSION

The Challenged Claims are unpatentable in view of the prior art as set forth in the Grounds asserted herein. Petitioner therefore requests that trial be instituted and the Challenged Claims cancelled.

Date: November 22, 2023

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R. § 42.24. According to the word processing system used to prepare this document, the brief contains 13,995 words.

/s/ *Scott Border*
Scott Border

CERTIFICATE OF SERVICE

In compliance with 37 C.F.R. §§ 42.105, 42.6(e), the undersigned hereby certifies that a copy of the foregoing Petition and supporting exhibits were served on the 22th day of November 2023, via Federal Express® overnight delivery directed to Patent Owner at the correspondence address of record:

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