

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD,
Petitioners,

v.

JANSSEN BIOTECH, INC.,
Patent Owner.

Case No. IPR2023-01103
U.S. Patent 10,961,307

**Declaration of Michael S. Epstein, M.D. in Support of Petition for *Inter Partes*
Review of U.S. Patent No. 10,961,307**

TABLE OF CONTENTS

I.	BACKGROUND AND QUALIFICATIONS	7
II.	MATERIALS AND OTHER INFORMATION CONSIDERED	10
III.	UNDERSTANDING OF THE LAW	10
	A. Level of Ordinary Skill in the Art	11
	B. Claim Construction	12
	C. Anticipation	12
	D. Obviousness.....	13
IV.	TECHNICAL BACKGROUND – STATE OF THE ART	18
	A. IBD (Crohn’s and Ulcerative Colitis) and its treatment historically	18
	B. Biologics and IBD	22
	C. Ustekinumab structure.....	25
	D. Ustekinumab was known as an effective treatment for diseases related to the IL-12/23 pathway, including Crohn’s	29
	E. The prior art taught that ustekinumab was effective in treating UC.....	30
	F. The complete study design for Janssen’s FDA phase 3 clinical study for UC was publicly known.....	32
	G. Janssen’s phase 3 trial was well underway by September 24, 2018, and its results were published soon thereafter	35
V.	THE ’307 PATENT	36
	A. Overview	36
	B. Relevant Prosecution History	40
	C. Priority Date	42

D.	Challenged Claims	42
VI.	SUMMARY OF THE ASSERTED PRIOR ART	43
A.	Invalidity Grounds.....	43
B.	NCT-236 (Ex. 1003)	43
C.	Ochsenkühn (Ex. 1005).....	44
D.	STELARA® Prescribing Information (Ex. 1004)	45
VII.	CLAIM CONSTRUCTION	47
A.	“a clinically proven . . . amount of an anti-IL-12/IL-23p40 antibody” (’307, claim 1)	47
VIII.	INVALIDITY	49
A.	Ground 1: NCT-236 Anticipates Claims 1-4, 6-22, 24-34	50
1.	Independent Claims 1, 19, 33, and 34 are Anticipated by NCT-236	50
2.	Dependent Claims 2-3 and 20-21	79
3.	Dependent Claims 4 and 22	80
4.	Dependent Claim 6	85
5.	Dependent Claim 7	85
6.	Dependent Claim 8	85
7.	Dependent Claim 9	86
8.	Dependent Claims 10, 12-16, 18 Reciting Maintenance Responses “continuing at least 44 weeks after week 0”.....	86
9.	Dependent Claim 11	87
10.	Dependent Claims 17, 30	88
11.	Dependent Claims 24-26, 28-29 and 31	88

B.	Ground 2: NCT-236 in view of Ochsenkühn and Stelara-PI(2017) Renders Obvious Claims 1-34	91
2.	A POSA had a Motivation to Combine the references in this Ground.....	92
3.	A POSA Had A Reasonable Expectation That the Treatment Regimens in the Independent Claims Would Meet Claim Limitations Requiring Certain Clinical Results	96
4.	The References in this Ground Disclose Independent Claims 1, 19, 33, and 34	106
5.	Dependent Claims 2-3, 20-21	149
6.	Dependent Claims 4 and 22	149
7.	Dependent Claims 5 and 23	150
8.	Dependent Claim 6	159
9.	Dependent Claim 7	160
10.	Dependent Claim 8	161
11.	Dependent Claim 9	161
12.	Dependent Claims 10, 12-16, 18	162
13.	Dependent Claim 11	163
14.	Claims 17, 30	165
15.	Dependent Claims 24-29, 31.....	166
16.	Dependent Claim 32	166
IX.	NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS	167
X.	CONCLUSION.....	169
XI.	APPENDIX I: SEQUENCE ANALYSIS	1
A.	Heavy Chain CDR Sequences (SEQ ID NOS:1-3).....	1

B.	Light Chain CDR Sequences (SEQ ID NOS:4-6)	4
C.	Heavy Chain Variable Region Sequence (SEQ ID NO:7).....	7
D.	Light Chain Variable Region Sequence (SEQ ID NO:8)	12
E.	Full Heavy Chain Sequence (SEQ ID NO:10).....	16
F.	Full Light Chain Sequence (SEQ ID NO:11)	20
XII.	APPENDIX II: CURRICULUM VITAE OF DR. MICHAEL EPSTEIN	1

I, Michael S. Epstein, declare as follows:

1. My name is Michael S. Epstein. I have been retained by Petitioner Samsung Bioepis Co., LTD (“Petitioner”) to submit this declaration in support of Petitioner’s Petition for *Inter Partes* Review (“IPR” or “Petition”). In this declaration I give my opinions as to whether claims 1-34 (“Challenged Claims”) of U.S. Patent No. 10,961,307 (“the ’307 Patent” (Ex. 1001)) assigned to Janssen Biotech, Inc. (“Janssen” or “Patent Owner”) are invalid. I provide scientific bases for these opinions as appropriate.

2. I have been asked to opine on whether the Challenged Claims are anticipated and/or rendered obvious by the prior art. My opinions are based on my years of education, research and experience, as well as my investigation and study of relevant materials. The materials that I studied for this Declaration include all exhibits cited in this Declaration and in the Petition. I may rely upon these materials and/or additional materials to rebut arguments raised by Patent Owner.

3. This declaration contains statements of my opinions formed to date and the bases and reasons for those opinions. I may offer additional opinions based on further review of materials in this case, including opinions and/or testimony of other expert witnesses. I make this declaration based upon my own personal knowledge and, if called upon to testify, would testify competently to the matters contained herein.

4. I am being compensated at my usual rate of \$1000 per hour for my time spent working on issues in this matter. I am also being reimbursed for any reasonable and customary expenses associated with my work and testimony. I have no financial interest in, or affiliation with, the Petitioner, real parties-in-interest, or the Patent Owner. My compensation is not dependent upon the outcome of, or my testimony in, the present IPR or any related litigation proceedings.

I. BACKGROUND AND QUALIFICATIONS

5. My current curriculum vitae, which includes additional detail about my education, experience and publications, is attached as Appendix II. Below I highlight some relevant aspects of my education and experience.

6. I am a gastroenterologist with over 30 years of experience and extensive medical training as a practicing clinician, including treating patients with a range of gastroenterological conditions, such as Inflammatory Bowel Disease (IBD) (including both Crohn's disease and Ulcerative Colitis ("UC")), Hepatology and Liver diseases.

7. I am the founder and principal physician at Digestive Disorders Associates, and am the president of the Maryland Diagnostic & Therapeutic Endo Center, both in Annapolis, Maryland. I am a staff gastroenterologist at the Anne Arundel Medical Center, Annapolis, and previously was a staff gastroenterologist at the Baltimore Washington Medical Center, Baltimore, Maryland. I am also

president of Investigative Clinical Research, where I lead clinical investigations for the treatment of IBD, IBS, Ulcerative Colitis, Crohn's disease and Hepatitis. I am board certified by the American Board of Internal Medicine with a sub-specialty in Gastroenterology.

8. I am a fellow of the American Gastroenterology Association and the American College of Gastroenterology, and a member of the Society of Gastrointestinal Surgeons.

9. Previously, I served as president of the medical staff of Anne Arundel Medical Center, and as chair of the Institutional Review Board. I am also the founder and former president of the Maryland Ambulatory Surgery Association.

10. I have been a principal and senior investigator in more than 200 clinical trials. Several clinical trials I participated in focused on UC. In 2001, I was a Principal Investigator in a study on the safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet) for the treatment of mildly to moderately active ulcerative colitis. In 2007, I was a Principal Investigator in a phase IV, multicenter, open-label study to assess the clinical recurrence related to compliance with treatment with MMX mesalamine 2.4 g/day given once daily for the maintenance of quiescent ulcerative colitis.

11. I have authored more than a dozen publications, abstracts, and poster sessions. I have published research articles and review articles in the *American*

Journal of Gastroenterology, Maryland Medical Journal, American Journal of Surgical Pathology, and Society of Air Force Journal and Gastroenterology, among others. In 2016, I published a paper on a novel delivery system that is an effective therapy for irritable bowel syndrome symptoms that was published in *Digestive Diseases and Sciences*.

12. I have consulted with many pharmaceutical and medical device companies primarily, but not exclusively, in the fields of Gastroenterology and Hepatology. I continue to perform my own research and have filed and received patents for medical devices. Additionally, I have served on advisory boards to the U.S. Food and Drug Administration (FDA).

13. I served in the U.S. Air Force at Andrews Air Base near Washington, D.C., and served extensively overseas in South America and Southeast Asia. I was awarded the Distinguished Service Medal for my service.

14. I received my B.A. with distinction in Molecular Biology and Cellular Development from the University of Colorado, Boulder, and my M.D. from the Robert Wood Johnson (UMDNJ) School of Medicine, Newark, New Jersey. Upon graduation, I completed an internship and residency in Internal Medicine at George Washington University Hospital and School of Medicine, Washington, D.C., and a fellowship in Gastroenterology and Hepatology from the Veterans Administration Medical Center and Georgetown University Hospital.

II. MATERIALS AND OTHER INFORMATION CONSIDERED

15. In addition to my general knowledge gained from my education and experience as a gastroenterologist, I have reviewed and considered, among other things, the '307 Patent, the prosecution history of the '307 Patent, and the prior art of record discussed herein.

16. I have also considered information from various sources in forming my opinions, including the Exhibits cited in this Declaration. I may rely upon these materials and/or additional materials to rebut arguments raised by Patent Owner. I may also consider additional documents and information, including documents that may not yet have been provided to me. My analysis of the materials relating to this matter is ongoing and I will continue to review any new material as it is provided. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information and on my continuing analysis of the materials.

17. Where my conclusions are based on certain assumptions that I have adopted, I have stated such assumptions in this Declaration.

III. UNDERSTANDING OF THE LAW

18. I am not an attorney. In forming my opinions in this Declaration, I applied the relevant legal principles provided to me by counsel, which are summarized below.

19. I understand that for a claim of a patent to be found patentable, it must be, among other things, new and not obvious in light of what came before it. Patents and publications which predate the invention are generally referred to as “prior art.”

A. Level of Ordinary Skill in the Art

20. I understand that an assessment of claims of the '307 Patent should be undertaken from the perspective of a person of ordinary skill in the art (“POSA”) as of the earliest claimed priority date, which I have assumed is September 24, 2018.

21. I have analyzed the '307 Patent and, in my opinion, a POSA in the field of the '307 Patent 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, to the extent described in the literature or publicly known, 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.

B. Claim Construction

22. I understand the first step in determining whether a patent claim is valid is to properly construe the claims. I further understand that claim terms are generally given their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, taking into account the claim language itself, specification, and prosecution history pertaining to the patent, as well as the relevant extrinsic evidence. I have applied this standard in formulating my opinions, and set forth my understanding of the scope of particular claim terms discussed below.

C. Anticipation

23. I understand that the law of anticipation is governed by the provisions of 35 U.S.C. § 102. I understand that the question of anticipation asks whether the claims cover something that is new, or novel. I am informed that the concept of anticipation requires that each and every element of a challenged claim is present in or otherwise taught by a single reference. In other words, I understand that one cannot combine two or more references to assert a finding of anticipation. However, I understand that if one reference incorporates by reference another, the second reference may be considered in the anticipation analysis. I understand that the content of a patent or other printed publication (i.e., a reference) should be interpreted the way a person of ordinary skill in the art would have interpreted the

reference as of the effective filing date. I further understand that the prior art reference must enable a POSA to make and use the claimed invention. A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter.

24. I also understand that an anticipatory reference does not need to explicitly describe each element because anticipation can occur when a claimed limitation is necessarily inherent or otherwise implicit in the relevant reference. I understand that an entire invention is inherent and in the public domain if it is the natural result flowing from the explicit disclosure of the prior art. Inherent anticipation does not require that a person of ordinary skill in the art would have recognized the inherent disclosure as of the critical date. I am also informed that, for inherent anticipation, information arising after the critical date may be used to show that the claimed subject matter, as disclosed in a prior art reference, was in fact inherent to the prior art.

D. Obviousness

25. I understand that a claim is unpatentable under 35 U.S.C. § 103 if the claimed subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of the invention. I understand that if the claimed invention is not anticipated by the prior art, the claim may still be invalid if the difference between the claimed subject matter and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a POSA. Thus, in considering the reason or motivation to combine references, it is essential to avoid using hindsight.

26. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations or objective indicia of obviousness or non-obviousness.

27. I understand that the content of a patent or other printed publication (i.e., a reference) should be interpreted the way a person of ordinary skill in the art would have interpreted the reference as of the effective filing date. I have assumed that the person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all of the relevant art at the time of the invention. The person of ordinary skill is not an automaton, and may be able to fit together the teachings of multiple patents employing ordinary creativity and the common sense that familiar items may have obvious uses in another context or beyond their primary purposes.

28. In determining the scope and content of the prior art, I understand that a reference is considered analogous art if it falls within the field of the inventor's endeavor or if it is reasonably pertinent to the particular problem with which the inventor was involved. A reference is reasonably pertinent if it logically would

have commended itself to an inventor's attention in considering their problem. If a reference relates to the same problem as the claimed invention, that supports use of the reference as prior art in an obviousness analysis.

29. I understand that an obviousness determination can be based on a single prior art reference or a combination of multiple prior art references or the knowledge of one of ordinary skill in the art. I have been informed by counsel that there are several recognized rationales for combining references or modifying a single reference to show obviousness. Some of these rationales include:

- combining prior art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;
- use of known technique to improve similar devices (methods, or products) in the same way;
- applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
- “obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design

incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

- some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

30. I also understand from counsel that an obviousness determination requires a reasonable expectation of success in achieving the claimed invention. I understand that a finding of a reasonable expectation of success does not require absolute predictability of success. I understand that evidence of a reasonable expectation of success, like evidence of a motivation to combine, may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. I understand that a range of concentrations may disclose a particular concentration when a POSA is able to determine optimum or workable ranges by routine experimentation.

31. I further understand that if an alleged invention is otherwise rendered obvious in view of the prior art, it is not patentable simply because the inventors discover an inherent property or a result that naturally flows from its application or use.

32. I understand that secondary considerations or objective indicia of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) the taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) teaching away; and (8) the simultaneous invention of the claimed subject matter. I also understand that there must be a relationship between any such secondary considerations and the invention. I further understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

33. I understand that any secondary considerations or objective indicia must bear a nexus to the claimed invention. Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention. I further understand that the patentee bears the burden of demonstrating that the relevant commercial success is attributable to the claimed invention, as opposed to other economic and commercial factors unrelated to the technical quality of the patented subject matter.

IV. TECHNICAL BACKGROUND – STATE OF THE ART

34. Here, I present the knowledge and terminology that would have been generally understood by a person of ordinary skill in the art in the relevant time period.

A. IBD (Crohn's and Ulcerative Colitis) and its treatment historically

35. “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, Pithadia & Jain, *Treatment of inflammatory bowel disease (IBD)*, Pharmacological Reports, 63:629-42 (2011) (“Pithadia”) at 1, Abstract. Crohn's disease (“Crohn's” or “CD”) and ulcerative colitis (“UC”) are related diseases with overlapping epidemiological, clinical, and therapeutic characteristics. *Id.*; Ex. 1009, Danese & Fiocchi, *Ulcerative Colitis*, N Engl J Med., 365:1713-25 (2011) (“Danese”) at 2 (“In addition, multiple genes in the interleukin-23 signaling pathway overlap in ulcerative colitis and Crohn's disease (e.g., *IL23R*, *JAK2*, *STAT3*, *IL12B*, and *PTPN2*).”); Ex. 1001 at 1:39-44 (“Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC), are chronic relapsing disorders characterized by destructive inflammation and epithelial injury in the gastrointestinal (GI) tract (Baumgart and Sandborn, J Clin Invest. 98:1010-1020 (1996); Danese and Fiocchi, N Engl J Med. 365:1715-1725 (2011)).”). Both are chronic conditions, with a relapsing-remitting course and are generally

characterized by inflammation of some portion(s) of the gastrointestinal (“GI”) tract. Ex. 1050 (Pithadia) at 1. While the conditions feature slight clinical and anatomical differences, given their similarities, they can be impossible to distinguish in patients, and confusion on which condition a patient has occurs in about 30% of patients.

36. By September 24, 2018, a POSA understood that cytokines, including interleukin (IL)-12 and IL-23, were involved in the pathogenesis of IBD, and that the IL-12/23 pathway specifically was involved in the pathogenesis of UC and Crohn’s. *See, e.g.,* Ex. 1011, Ahern et al., *Interleukin-23 Drives Intestinal Inflammation through Direct Activity on T Cells*, *Immunity*, 33:279-88 (Aug. 27, 2010) (“Ahern”) at 1-12; *see also* Ex. 1012, Uhlig et al., *Differential Activity of IL-12 and IL-23 in Mucosal and Systemic Innate Immune Pathology*, *Immunity*, 25:309-18 (Aug. 2006); Ex. 1013, Yen et al., *IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6*, *J. Clin. Invest.*, 116(5):1310-16 (May 2006); Ex. 1014, Aggeletopoulou et al., *Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn’s disease*, *World J Gastroenterol*, 24(36):4093-103 (Sept. 2018) (“Aggeletopoulou”) at 1; Ex. 1009 (Danese) at 2; Ex. 1010, Côté-Daigneault et al., *Biologics in inflammatory bowel disease: what are the data?*, *United European Gastroenterology Journal*, 3(5):419-28 (2015) (“Côté-Daigneault”) at 5; Ex. 1001

(’307 Patent) at 1:62-2:61. Specifically, a POSA understood that in inflamed tissues, bacterial stimulation was known to activate dendritic cells and macrophages, resulting in the activation of T-cells and the secretion of IL-12 and IL-23. Ex. 1014 (Aggeletopoulou) at 4. IL-12 is a heterodimeric cytokine comprised of two covalently linked subunits (p40 and p35). *Id.* at 3. IL-23 is another cytokine that bears structural similarity to IL-12 and contains the same p40 subunit. *Id.* IL-12 signals through the IL-12 receptor while IL-23 signals through the IL-23 complex (IL-23R). Ex. 1015, Pedersen et al., *Inflammatory pathways of importance for management of inflammatory bowel disease*, World J Gastroenterol, 20(1):64-77 (Jan. 2014) (“Pedersen”) at 5. As shown in the figure below, both molecules signal through the JAK/STAT pathway to further induce gene expression of pro-inflammatory genes:

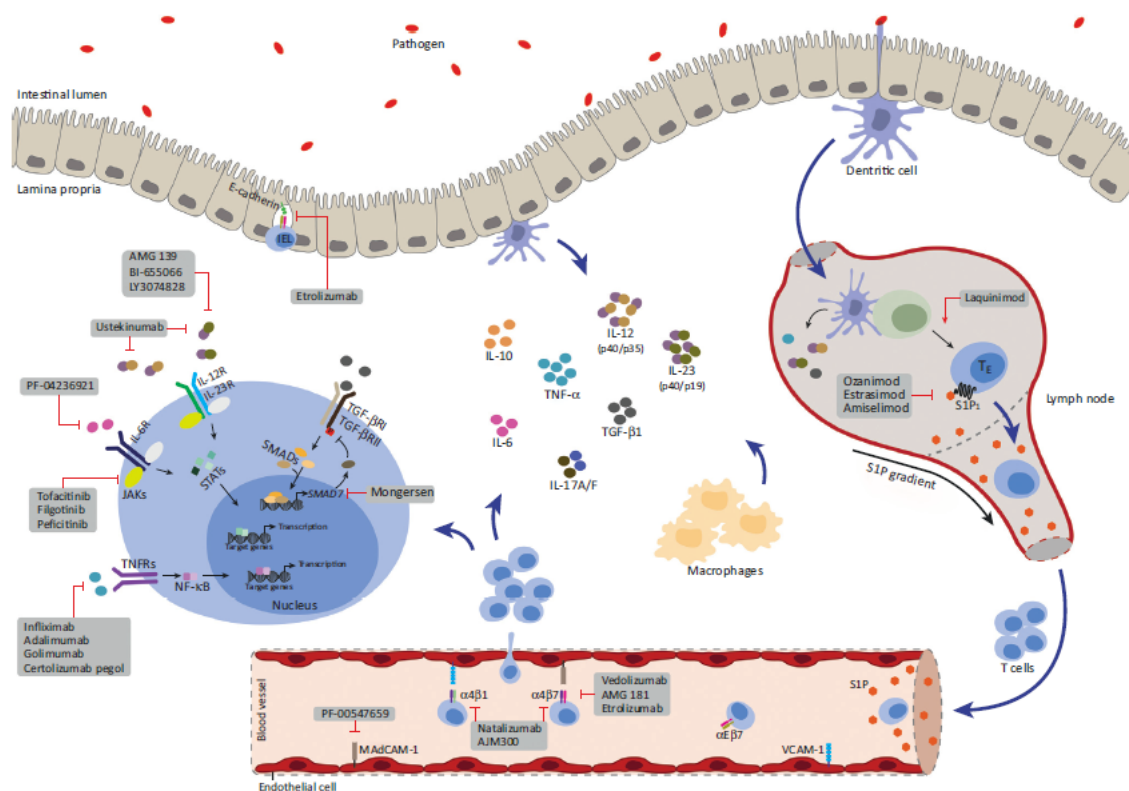


Figure 1. Current and Emerging Targeted Therapies for Inflammatory Bowel Disease and their Mechanisms of Action Which Include Blocking Extracellular Signal Molecules and their Underlying Pathways, Interference with Intracellular Signaling Pathways, and Perturbation of Leukocyte Trafficking into the Inflamed Intestinal Mucosa. Abbreviations: IEL, intraepithelial lymphocyte; IL, interleukin; JAK, Janus kinase; MadCAM, mucosal addressin cell adhesion molecule; NF-κB, nuclear factor-κB; P, phosphorylation; S1P, sphingosine-1-phosphate; S1P₁, S1P receptor 1; STAT, signal transducer and activator of transcription; T_E, effector T cell; TGF-β, transforming growth factor-β; TGF-βR, TGF-β receptor; T_H, naïve T cell; TNF-α, tumor necrosis factor-α; TNFR, TNF receptor; VCAM, vascular cell adhesion molecule.

Ex. 1016, Coskun et al., *Novel Targeted Therapies for Inflammatory Bowel Disease*, Trends in Pharmacological Sciences, 38(2):127-42 (Feb. 2017) (“Coskun”) at 3.

37. Patients with IBD show upregulated IL-12 and IL-23, and genetic variants of both IL-23R and the p40 subunit are associated with susceptibility to IBD. *Id.* at 5.

B. Biologics and IBD

38. Crohn's and UC have historically been treated with the same or similar therapies. Ex. 1010 (Côté-Daigneault); Ex. 1050 (Pithadia) at 1, Abstract; Ex. 1001 ('307 Patent) at 2:38-41. This was the case as of September 24, 2018, the asserted priority date of the '307 Patent. Ex. 1001 ('307 Patent). For patients with mild to moderately aggressive forms of IBD, therapy consisted of oral or topical anti-inflammatory drugs such as aminosalicylate-containing agents (5-ASAs). Ex. 1050 (Pithadia) at 1, 2. Treatments for more severe cases included use of antibiotics, corticosteroids, and immunomodulator therapies. *Id.* at 3-8. In some circumstances, surgical procedures were also used. *Id.* at 6.

39. Over time, various biologic therapies have been developed to help treat IBD, both for UC and CD. *See, e.g.*, Ex. 1010 (Côté-Daigneault), at 1-2; Ex. 1006 at 1 (ENTYVIO treating both UC and CD); Ex. 1007 at 1 (Humira treating both UC and CD); Ex. 1008 at 1 (Remicade treating both UC and CD); Ex. 1001 ('307 Patent) at 2:38-41. For example, as of September 24, 2018, TNF-alpha blockers such as infliximab ("Remicade"), adalimumab ("Humira"), golimumab ("Simponi"), and certolizumab ("Cimzia") were commonly used to treat IBD by blocking a small protein that causes inflammation in the intestine. Ex. 1010 (Côté-Daigneault); Ex. 1015 (Pedersen) at 3. POSA would have recognized that

emerging targeted therapies for IBD would be tested on both CD and UC populations. Ex. 1016 (Coskun) 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	–

40. Integrin blockers such as vedolizumab (“Entyvio”) and natalizumab (“Tysabri”), which prevent inflammation-causing white blood cells from entering the GI tract, were also used to treat IBD. *Id.*; *see also* Ex. 1006 (Vedolizumab Label). Of these six biologics approved for IBD, vedolizumab, adalimumab, and infliximab were successfully used to treat both Crohn’s and UC. Ex. 1010 (Côté-Daigneault) at 2, 6; *see also* Ex. 1006 (vedolizumab label revised 05/2014), Ex. 1007 (adalimumab label revised 7/2016); Ex. 1008 (infliximab label revised 01/2015).

41. Interleukin blockers (such as ustekinumab) treat IBD by targeting the interleukin-12 and interleukin-23 (IL-12/23) proteins associated with inflammation in the GI tract. Ex. 1010 at 5, 8. A POSA would have understood that “the inflammatory role of IL-12 and IL-23 provides a rationale for the development of blocking agents for IBD that are currently under clinical evaluation in Phase II or III trials, including ustekinumab, AMG-139/MEDI2070, BI-655066, and LY3074828 (Table 1).” Ex. 1016 (Coskun) at 5. Prior to September 24, 2018, IL-23-specific monoclonal antibodies, LY3074828, had entered Phase II for both UC (NCT02589665) and CD (NCT02891226). *Id.* at 5-6.

42. Regardless of the elected therapy, the aim of treatment for Crohn’s and UC has been the same: treatment of active disease followed by maintenance of remission. In clinical practice, diagnosis and treatment is generally focused on ensuring symptom-based outcomes as opposed to endoscopy-based improvement. Ex. 1051, Higgins et al., *Is Endoscopy Necessary for the Measurement of Disease Activity in Ulcerative Colitis?*, Am J Gastroenterol, 100:355-61 (2005) (“Higgins”) at 1 (“In clinical practice, many patients are treated based on their symptoms without endoscopic evaluation. However, invasive indices are commonly used in clinical research.”). POSAs often classify patients as having achieved clinical remission when they are having no more than two semi-formed, non-bloody stools per day. I note, however, based on my prior clinical experience, both treating

patients and in clinical trials, that among the patients who experience symptomatic improvement, such as those reported in Ex. 1005, Ochsenkühn et al., *P759 Ustekinumab as rescue treatment in therapy-refractory or -intolerant ulcerative colitis*, Journal of Crohn's and Colitis, 12:S495 (Feb. 2018) ("Ochsenkühn"), a POSA would expect that at least 15-20% also eventually experience endoscopic and mucosal improvement. This percentage of patients is also consistent with the percentage reported as experiencing endoscopic healing following induction administration in the NCT-236 clinical trial. See Ex. 1031, Sands et al., *Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis*, N Engl J Med, 381(13):1201-14 (Sept. 26, 2019) ("Sands") at 8, Fig. 2. To date, there is no medical cure for either disease, thus the goal of treatment has generally been to suppress active inflammatory disease medically in an attempt to conserve the small bowel.

C. Ustekinumab structure

43. Ustekinumab is an IgG1 humanized monoclonal antibody that was known by the priority date of the '307 Patent to target the common p40 subunit of the IL-12 and IL-23. Ex. 1014 (Aggeletopoulou) at 3; Ex. 1001 ('307 Patent) at 2:45-53. Ustekinumab binds to p40 to prevent IL-12 and IL-23 from binding the cell surface IL-12R β 1 receptor protein, thereby effectively neutralizing IL-12 and

IL-23 mediated cellular responses and suppressing inflammation in the GI tract.
Ex. 1015 (Pedersen) at 5.

44. The complete sequence for ustekinumab, including the sequences claimed in the '307 Patent, was published and well-known before September 24, 2018. While I present a subset of my analysis below, my complete findings are in Appendix I.

45. On March 23, 2017 the entire sequence for ustekinumab was published in WO2017/049035, an application by Amgen Inc.:

SEQ ID NO	Description	Sequence
17	Ustekinumab HC	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRY SPSFQGGVTMSVDKSITTAYLQWNSLKASDTAMYYCARRRPGQGYDFWGGQTLVTVSSS STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSQSVMEALHNHYTQKSLSLSPGK
18	Ustekinumab LC	DIQMTQSPSSLSASVGDRVTITCRASQGISWLAWYQQKPEKAPKSLIYAASSLQSGVPS RFGSGSGTDFTLTISSLQPEDFATYYCQQYNIYPYTFGGGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

See Ex. 1052 (WO2017/049035) (“’035 Application”) at 96 (describing SEQ ID NOS: 17-18 as the ustekinumab HC and LC, respectively).

46. The heavy and light chain sequences were also published by the Japanese Pharmaceuticals and Medical Devices Agency (“PMDA”) on July 12, 2017. The JP PMDA published a report titled “Report on the Deliberation Results” for STELARA®, dated December 6, 2010, which was at least available on July 12, 2017. Ex. 1022 (PMDA Report). The report describes ustekinumab as

“a recombinant human IgG1 monoclonal antibody against the p40 subunit of human interleukin-12 and interleukin-23” that is composed of “2 H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 214 amino acid residues each.” *Id.* at 3. The report provided the following sequence for ustekinumab:

Heavy Chain

```

EVQLVQSGAE VKKPGESLKI SCKGSGYSPT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY 60
                        22-96
SPSFQGGVMT SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS 120
                        146-202
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTWSW NSGALTSGVH TFPAVLQSSG 180
                        222 228 231
LYSLSSVTV PSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP 240
                        LC HC HC N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
                        263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 360
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL DSDGSFFLYS KLTVDKSRWQ 420
369-427
QGNVFCFSVM HEALHNHYTQ KSLSLSPGK 449

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Light Chain

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DIQMTQSPSS LSASVGDRVT ITCPASOGIS SWLAWYQQKP EKAPKSLIYA ASSLQGVPS 60
                        23-68
RFGSGSGGTD PTLTISSLQP EDFATYYCQO YNIYPTPGQ GTKLEIKRTV AAPSVFIFPP 120
                        134-194
SDEQLKSGTA SVVCLLNIFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSSTLT 180
LSKADYEKHK VYACEVTHQG LSPVTKSPN RGECC 214
                        HC

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Figure 1. Heavy and light chains of ustekinumab

Amino acid sequences of the heavy and light chains of ustekinumab are indicated in the single-letter code. Complementarity-determining regions are underlined.
H-chain K449: partial processing

Id. at 4; *see also* Ex. 1023 (PMDA Screenshot) at 11.

47. The claimed sequences were also published in U.S. Patent No. 7,166,285 (“the ’285 patent”) published September 29, 2005, as well as in Patent Term Extension (PTE) Applications that were filed in November 2009 for the ’285 patent and a related patent, U.S. Patent No. 6,902,734. Ex. 1020 (’734 PTE Application); Ex. 1021 (’285 PTE Application); Ex. 1019 (’285 Patent), certificate of correction, SEQ ID NOS:1-6.¹ The PTE Applications and the PMDA explicitly label the CDR sequences for the heavy and light chain. The sequence published in the ’734 PTE Application and the ’285 PTE Application is below:

¹ The ’285 patent has a certificate of correction correcting a mistake in the sequence of CDR 3 (corresponding to SEQ ID NO:3). Ex. 1019 (’285 Patent), certificate of correction. The PTE Applications were stamped as received by the Patent Office on November 20, 2009, and I understand they would have become part of the publicly available patent file histories for each of the patents at that time.

(A)	
FW1	EVQLVQSGAEVKKPGESLKISCKGSGYSFT
CDR1	TYWLG
FW2	WVRQMPGKGLDWIG
CDR2	IMSPVDSDIRYSPSFQG
FW3	QVTMSVDKSITTAYLQWNSLKASDTAMYICAR
CDR3	RRPGQGYFDF
FW4	WGQGTLLVTVSS
CH1	SSTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
HINGE	EPKSCDKTHTCPPCPAPELLG
CH2	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAK
CH3	GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFPSCSVMHREALHNHYTQKS LSLSPGK
 (B)	
FW1	DIQMTQSPSSLSASVGDRVTITC
CDR1	RASQGISSWLA
FW2	WYQQKPEKAPKSLIY
CDR2	AASSLQS
FW3	GVPSRFGSGSGTDFTLTISSLQPEDFATYYC
CDR3	QQYNIYPYT
FW4	FGQGTKLEIK
CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTK SFNRGEC

Ex. 1020 ('734 PTE Application) at 2; Ex. 1021 ('285 PTE Application) at 2. A summary of the above publications and other example publications of the ustekinumab sequence are in Appendix I.

48. Accordingly, all of the claimed SEQ ID numbers in the '307 Patent were in the prior art before September 24, 2018.

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

49. Ustekinumab has been known to POSAs as a safe and effective treatment for diseases related to the IL-12/23 pathway since at least 2009. Under the brand name STELARA®, ustekinumab was first approved in September 2009

for the treatment of adult patients with chronic moderate to severe plaque psoriasis. Ex. 1024, STELARA® Prescribing Information (Sept. 2009) (“First Approved Label”). It was also approved by the FDA in September 2016 for the treatment of Crohn’s. Ex. 1004, STELARA® Prescribing Information (Sept. 2016) (“Stelara-PI(2017)”). The clinical studies supporting these approvals demonstrated that ustekinumab was generally well tolerated by patients intravenously and subcutaneously. Ex. 1026, Feagan et al., *Ustekinumab as Induction and Maintenance Therapy for Crohn’s Disease*, N Engl J Med, 375(20):1946-60 (Nov. 17, 2016) (“Feagan”); Ex. 1024 (First Approved Label).

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

50. By September 24, 2018, several prior art publications also described the successful off-label use of ustekinumab to treat UC. Ochsenkühn describes seventeen UC patients treated with ustekinumab at 6mg/kg body weight as an infusion and 90 mg as s.c. injection every 8 weeks, and 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. 1005 (Ochsenkühn) at 2. Another publication, Kolios et al., describes a single patient treated with ustekinumab which resulted in cessation of the patient’s UC for up to 2 years. *See, e.g.*, Ex. 1034, Kolios et al., *Paradoxical ulcerative colitis during adalimumab treatment of psoriasis resolved by switch to ustekinumab*, British Journal of

Dermatology, 178:551-55 (2018). A third publication, Afonso *et al.*, reports a study involving two patients with ulcerative colitis administered ustekinumab as 90 mg weekly (4 doses) and 90 mg every 2 or 8 weeks thereafter as maintenance doses and concluded that “[u]stekinumab is a therapeutic approach for IBD treatment in clinical practice” Ex. 1035, Afonso et al., *CP-202 Ustekinumab treatment in refractory inflammatory bowel disease*, European Journal of Hospital Pharmacy, 24(Suppl. 1):A90 (2017). In addition, the Canadian Agency for Drugs and Technologies in Health noted in 2017 that “[t]here is potential for ustekinumab to be used off-label as a treatment option for ulcerative colitis,” and warned of potential effects such a treatment would have on treatment costs in its “Issues for Consideration.” Ex. 1070, Ustekinumab (Stelara), Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Apr. In fact, Tarr et al. explicitly noted that “UC” was an “Off-label indication[]” for “Ustekinumab (Stelara)” in South Africa:

Table 1. Biologic drugs in South Africa

Biologic drug	Mechanism of action	Route of administration	Registered indications	Off-label indications	Major adverse effects
Ustekinumab (Stelara)	IL-12/23 monoclonal antibody		PS, PSA,* CD*	UC	Serious infections

Ex. 1033, Tarr et al., *Superheroes in autoimmune warfare: Biologic therapies in current South African practice*, S Afr Med J, 104(11):787-791 (Nov. 2014) at 2.

F. The complete study design for Janssen’s FDA phase 3 clinical study for UC was publicly known

51. Janssen relied on phase 2 trial safety results from the Crohn’s and psoriasis studies to support its “direct-to-Phase-3” (the UNIFI trial) strategy for use of ustekinumab for the treatment of UC. Ex. 1027, Janssen Research & Development, NCT02407236 Clinical Protocol (Amendment 2) (Apr. 20, 2016)² (“Phase 3 Clinical Protocol”) at 25. Janssen explained to the FDA that “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 a direct-to-Phase-3 approach.” *Id.* at 7, 25.

52. By April 2015, Janssen published the clinical overview summary for its Phase 3 clinical trial for ustekinumab in UC (NCT02407236) on ClinicalTrials.gov, Ex. 1003 (“NCT-236”); Ex. 1054 (History of Changes for Study NCT02407236), which included detailed parameters of the study. *See* Ex. 1003 (NCT-236) at 1-3. As I discuss in greater detail below, the methods of treatment in NCT-236 describe every aspect of the method of treating UC that is claimed in the independent claims of the ’307 Patent and most of its dependent claims. *See id.* at 1-3.

² I note that while Ex. 1027 was submitted to FDA prior to the alleged priority date, it does not appear to have been public at that time.

53. Specifically, NCT-236 describes a “Phase 3, randomized (assignment of study drug by chance), double-blind (neither the participant or study staff will know the identity of study drugs), placebo-controlled (placebo is an inactive substance that is compared with a drug to test whether the drug has a real effect in a clinical trial), parallel-group (a medical research study comparing the response in 2 or more groups of participants receiving different interventions)” in 951 adult patients with moderately to severely active ulcerative colitis 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. 1003 (NCT-236) 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.* at 1-2. The study proposes randomizing patients at Week 0 to receive a single intravenous administration of ustekinumab of approximately 6 mg/kg, 130 mg or placebo, and then randomizing patients to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks. *Id.* at 2-3.

54. The study also discloses a series of primary and secondary endpoints for each study. I note that these reflect endpoints that the FDA set out in an August 2016 industry guidance document for phase 3 UC clinical trials. Ex. 1029,

FDA, Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry (Aug. 2016) (“Clinical Trial Endpoints”) at 11-12. In particular, consistent with the FDA’s guidance that “*Clinical remission . . . and clinical response . . . have been accepted as primary endpoints in clinical trials that have supported prior approvals of treatments of UC,*” *id.* at 12, the primary outcome recited in NCT-236 was listed as the number of participants with clinical remission as defined by the global definition of Clinical remission (i.e., using the Mayo score). *See* Ex. 1003 (NCT-236) at 1-2. This is significant, in part, because in my opinion a POSA would recognize that primary outcomes are the most important outcomes of a study and represent the main reason the trial is being conducted, such that investigators typically select primary outcomes that they anticipate being able to achieve. *See* Ex. 1030, Smith et al., eds., *Field Trials of Health Interventions: A Toolbox*, 3rd ed. (Oxford: Oxford University Press, 2015) (“Smith”) at 7-8. Other phase three clinical studies for drugs treating UC such as Remicade (infliximab), Humira (adalimumab), and Entyvio (vedolizumab) included identical or similarly defined outcomes. Ex. 1060 (Remicade Study); Ex. 1061 (Humira Study); Ex. 1062 (Entyvio Study).

55. Indeed, in my experience working on clinical trials (including as a clinical research physician for a clinical trial involving a new molecular entity developed by Eli Lilly), phase 3 trials are designed to ensure consistent and

repeatable results. In addition to selecting achievable primary outcomes, investigators carefully select various parameters to ensure that the study's outcomes and conclusions related to efficacy are reliable. Such parameters include (1) the study's hypothesis, (2) the size of enrollment (for statistical power calculation), and (3) the patient population demographics.

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

56. The clinical trial corresponding to NCT-236 began in August 2015. Ex. 1003 (NCT-236) at 2; Ex. 1031 (Sands) at 2. The study ran for three years until August 2018, and its results were published in The New England Journal of Medicine on September 26, 2019. Cf. Ex. 1003 (NCT-236) at 1 (describing "ClinicalTrials.gov Identifier: NCT02407236"), with Ex. 1031 (Sands) at 1 (describing "ClinicalTrials.gov number, NCT02407236"). The study results describe the exact treatment regimen set forth in NCT-236. Ex. 1031 (Sands) at 1. Specifically, the results explain that 961 patients were randomly assigned to receive an intravenous induction dose of ustekinumab (either 130 mg, a weight-range-based dose that approximated 6 mg per kilogram of body weight, or placebo), after which patients who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned again to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks, every 8 weeks, or placebo). *Id.*

57. Sands confirms that by following the steps taught in NCT-236, the “percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg . . . or 6 mg per kilogram . . . was significantly higher than that among patients who received placebo,” 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.*

58. In view of these findings, the results conclude that “[u]stekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis.” *Id.* In fact, Sands demonstrated that every outcome measure described in NCT-236 was met. *See infra* ¶147.

59. I note that upon submitting the results of its phase 3 study to the FDA, Janssen received FDA approval for the use of ustekinumab in UC in October 2019. Ex. 1032, Janssen Press Release: *Janssen Announces U.S. FDA Approval of STELARA® (ustekinumab) for the Treatment of Adults with Moderately to Severely Active Ulcerative* (Oct. 21, 2019); Ex. 1055, Stelara, European Medicines Agency.

V. THE '307 PATENT

A. Overview

60. The '307 Patent is entitled “Methods of Treating Moderately to Severely Active Ulcerative Colitis by Administering an Anti-IL12/IL23

Antibody.” Ex. 1001 (’307 Patent). The ’307 Patent was filed on September 24, 2019 and claims priority to a provisional application No. 62/769,818 filed November 20, 2018 and an earlier provisional application No. 62/735,501 filed September 24, 2018. It issued on March 30, 2021. Representative claim 1 is provided below:

1. A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising
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, wherein
the antibody comprises a heavy chain variable region and a light chain variable region,
the heavy chain variable region comprising: a complementarity determining region heavy chain 1 (CDRH1) amino acid sequence of SEQ ID NO:1; a CDRH2 amino acid sequence of SEQ ID NO:2; and a CDRH3 amino acid sequence of SEQ ID NO:3; and
the light chain variable region comprising: a complementarity determining region light chain 1 (CDRL1) amino acid sequence of SEQ ID NO:4; a CDRL2 amino acid sequence of SEQ ID NO:5; and a CDRL3 amino acid sequence of SEQ ID NO:6,
wherein 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:
 - (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 $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.

61. The '307 Patent relates to a method of treating moderately to severely active ulcerative colitis using an anti-IL-12/IL-23p40 antibody. The patent acknowledges that, by the time of the 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 ('307 Patent) at 1:62-65. The patent further acknowledges that ustekinumab's mechanism of action in preventing IL-12 and IL-23 bioactivity was known in the prior art, describing 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-12R[β]1 receptor protein (Investigator's Brochure: STELARA® (ustekinumab), edition 18. Janssen Research & Development, LLC (2017)). Through this mechanism of action, ustekinumab effectively neutralizes IL-12 (Th1)- and IL-23 (Th17)-

mediated cellular responses.” *Id.* at 2:45-53. The ’307 Patent also highlights the Phase 2 clinical studies demonstrating the efficacy and safety of ustekinumab in induction therapy in Crohn’s, and explicitly notes the overlap in effective biologic therapies for Crohn’s and UC. *Id.* at 2:38-3:19.

62. All claims of the ’307 Patent limit the anti-IL-12/IL-23p40 antibody used during treatment to certain SEQ IDs that reflect the complementarity determining regions (CDRs) of ustekinumab. Each of the independent claims also requires that a subject administered the antibody “is a responder to treatment” by at least one measure selected from a group of “Seven Claimed Responses.” *Id.* at claims 1, 19, 33, 34.

63. Some of the dependent claims limit the type of response to a specific one of these “Seven Claimed Responses (or another response) and/or refer to different time periods of a treatment for the identified claimed response. *See, e.g., id.* at claims 10-18 (“at least 44 weeks after week 0”), claims 24-32 (“by week 16 of the treatment”).

64. Although largely similar, the independent claims of the ’307 Patent feature some differences. The independent claims differ, for example, in their recitation of the dosages administered to a subject. Hence, independent 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.” *Id.* at claim 1[a] (emphasis added). In contrast, independent claims 19, 33, and 34 recite “*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.” *Id.* at claims 19[a], 33[a], 34[a] (emphasis added); Ex. 1072.

B. Relevant Prosecution History

65. During prosecution, the Examiner reviewed NCT-236 and noted that NCT-236 expressly disclosed the use of ustekinumab for the treatment of UC, including noting that the “routes of administration and endpoints” were taught by NCT-236. Ex. 1036 (’307 Patent File History) at 52.³ The Examiner also noted

³ With the Office Action Summary dated July 16, 2020, the Examiner included a Notice of References Cited which refers to the NCT02407236 webpage “[a]ccessed from the internet 7/13/20.” Ex. 1036 (’307 Patent File History) at 54. In Patent Owner’s response to this rejection, Patent Owner cites the “initial posting of the CT reference (April 2, 2015 according to the www.clinicaltrials.gov record.”

that although the “[f]ormulation[] . . . do[es] not appear to be taught by” NCT-236, nevertheless, “it would be expected that the [NCT-236] formulation, which was being used in Phase 3 human trials, would be identical to that claimed.” *Id.* at 52. As a result, the Examiner rejected all of the claims as obvious and anticipated under §§ 102 and 103. *Id.* at 46-53. The entirety of the Examiner’s non-final rejection spans half of a page and is excerpted below.

Claims 1-33 are rejected under 35 U.S.C. 102(a)(1) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over as being unpatentable over ClinicalTrials.gov (“CT”). The claims are drawn to the use of ustekinumab (STELARA®) for the treatment of UC.

CT teaches the use of this drug for the instantly claimed purpose. The claims also recite IV and SC administration, as well as various parameters/endpoints. These routes of administration and endpoints are taught by CT (see “Arms and Interventions” and “Outcome Measures”). Formulations such as those recited in claims 4 and 5 do not appear to be taught by CT. However, it would be expected that the CT formulation, which was being used in Phase 3 human trials, would be identical to that claimed. Regardless, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955). Regarding claims such as 8, CT is silent regarding the use of the antibody in patients not responsive to other treatments. However, it would have been expected, or it would have been obvious to have used such a novel treatment in those not responding to current (at the time) treatments.

Id. at 52

Id. at 32. It is not clear whether the Examiner or Patent Owner considered a prior art version of the webpage such as Ex.1003.

66. In response to the Examiner's rejection, Patent Owner amended the claims to require a *responder* according to response criteria that had been disclosed in NCT-236 and stated "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." *Id.* at 32. Patent Owner recognized that the only material difference between the original and amended claims was *the result* obtained from the NCT-236 human trials. *Id.*

67. Following Patent Owner's amendment, the Examiner withdrew his rejection without further comment.

C. Priority Date

68. I have been asked to assume for the purposes of the present declaration that the priority date of the '307 Patent is September 24, 2018.

D. Challenged Claims

69. I understand that Petitioner is challenging the validity of claims 1-34 of the '307 Patent in the Petition for *Inter Partes* Review to which this declaration will be attached. Those claims are reproduced in Ex. 1072.

VI. SUMMARY OF THE ASSERTED PRIOR ART

70. There are a number of patents and publications that constitute prior art to the '307 Patent. I have reviewed and considered the prior art discussed in this section, as well as the other Exhibits cited in this Declaration.

A. Invalidity Grounds

71. Based on my review and analysis of the materials cited herein, my opinions regarding the understanding of a POSA in the 2018 timeframe, and my training and experience, it is my opinion that the Challenged Claims of the '307 Patent are invalid based on the following grounds:

Grounds	Claims	Statutory Basis	Prior Art
1	1-3, 6-22, 24-34	§ 102	Anticipated by NCT-236
2	1-34	§ 103	Obvious over NCT-236 in view of Ochsenkühn and Stelara-PI(2017)

B. NCT-236 (Ex. 1003)

72. NCT number NCT02407236 ("NCT-236") was published on ClinicalTrials.gov by April 2015. *See* Ex. 1003; Ex. 1054. As shown by the accompanying Affidavit of Nathaniel Frank-White from the Internet Archive, NCT-236 was available for download from the Internet no later than October 7, 2015. Ex. 1028, Frank-White Aff. at 16-20. I understand that 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 Patent claims priority. I further understand that NCT-236 was considered and applied as a single reference, not in combination with other references, during prosecution of the '307 Patent.

73. NCT-236 summarizes a Phase 3 clinical trial for STELARA® where “the efficacy and safety of ustekinumab as intravenous (IV: into the vein) infusion [was evaluated] 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 (NCT-236) at 1. NCT-236 discloses in the treatment section 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 Patent claims. *Id.* at 1-2.

C. Ochsenkühn (Ex. 1005)

74. I understand that Ochsenkühn qualifies as prior art under 35 U.S.C. § 102(a)(1) because it was published in the Journal of Crohn's and Colitis prior to

September 24, 2018.⁴ *See* Ex. 1005. I also understand that the Examiner did not consider Ochsenkühn during prosecution of the '307 Patent.

75. Ochsenkühn describes a retrospective data analysis involving 17 UC patients who received ustekinumab (6 mg/kg body weight as an infusion and 90 mg as s.c. injection every 8 weeks), between 2016 and 2017 as rescue therapy. Ex. 1005 (Ochsenkühn) at 2. Ochsenkühn describes 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.* The authors of Ochsenkühn concluded that “[u]stekinumab was effective as rescue medication in therapy-refractory or -intolerant UC” and proclaimed “[i]t seems possible that large ongoing trials will confirm our findings” *Id.*

D. STELARA® Prescribing Information (Ex. 1004)

76. I understand that the prescribing information for STELARA® for use in treating Crohn’s disease (“Stelara-PI(2017)”) was 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) because it was published prior to September 24, 2018. Ex. 1004

⁴ The Journal of Crohn’s and Colitis is a monthly peer-reviewed medical journal covering inflammatory bowel diseases that I regularly review as part of my practice.

(Stelara-PI(2017)); Ex. 1028, Frank-White Aff. at 147-160. I further understand that the Examiner did not consider the STELARA® Prescribing Information during prosecution.

77. Stelara-PI(2017) describes treating psoriasis, psoriatic arthritis, and Crohn's using an intravenous infusion dose of 130 mg of ustekinumab in 26 mL and subcutaneous doses of 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to slightly yellow solution that may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, 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 (Stelara-PI(2017)) at 16.

VII. CLAIM CONSTRUCTION

78. For purposes of this *inter partes* review, I have considered the claim language, specification, and portions of the prosecution history, to determine the meaning of the claim language as it would have been understood by a person of ordinary skill in the art at the time of the invention. I have been advised by counsel that the “plain and ordinary meaning” or *Phillips* standard applies, where a claim term is given its plain and ordinary meaning in view of the specification from the view point of a person of ordinary skill in the art.

79. I have applied the *Phillips* standard in my analysis. Therefore, unless otherwise stated, I have applied the plain and ordinary meaning to claim terms.

A. “a clinically proven . . . amount of an anti-IL-12/IL-23p40 antibody” (’307, claim 1)

80. Independent claim 1 of the patent recites “a clinically proven . . . amount” of antibody. *See*, Ex. 1001 (’307 Patent) at claim 1. I have been instructed to apply the express definitions provided in the specification:

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. . . . In particular, “safe” as it relates to a dose, dosage regimen or treatment with an anti-IL12/23p40 or anti-IL23 antibody of the

present invention refers to with an acceptable frequency and/or acceptable severity of adverse events associated with administration of the antibody if attribution is considered to be possible, probable, or very likely due to the use of the anti-IL12/23p40 or anti-IL23 antibody.

Id. at 10:4-33.⁵

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.

Id. at 9:11-35.

81. The specification alternatively provides another definition of “clinically proven” that states that “clinically proven” means “that it has been proven by a clinical trial” that “has met the approval standards” of a “national regulatory agency”:

⁵ All emphasis has been added unless otherwise noted.

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. For example, the clinical study may be an adequately sized, randomized, double-blinded study used to clinically prove the effects of the drug.

Id. at 10:34-42.

82. I understand that these definitions may receive no patentable weight in order to avoid rendering the claims as invalid as indefinite. However, for purposes of this Declaration, I have been asked to apply each of the definitions excerpted above, as appropriate. Regardless of the definition applied, my overall analysis does not change.

VIII. INVALIDITY

83. Based on my review and analysis of the materials cited herein, my opinions regarding the understanding of a POSA in the 2018 timeframe, and my training and experience, it is my opinion that the Challenged Claims are invalid in view of the invalidity grounds. *See* Section VI.A. The reasons for my conclusions are explained more fully below.

A. Ground 1: NCT-236 Anticipates Claims 1-4, 6-22, 24-34

84. NCT-236 (Ex. 1003) is a Phase 3 clinical trial summary that describes methods for administering ustekinumab to patients with moderately to severely active ulcerative colitis (UC) and monitoring their response, just as recited in the claims of the '307 Patent.

85. In my opinion, NCT-236 anticipates claims 1-4, 6-22, 24-34 of the '307 Patent because NCT-236 expressly discloses the administration of ustekinumab to patients with moderately to severely active UC and a patient's response is an inherent result of the administration of ustekinumab, as confirmed by Sands (Ex. 1031).

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

86. The '307 Patent has four independent claims—claims 1, 19, 33, and 34. Although there are distinctions between the claims, they have many of the same limitations. I therefore address the anticipation of their shared limitations together and their distinct limitations separately below.

- a. **“A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising” (Preambles) ⁶**

87. Each independent claim of the '307 Patent is a method claim that recites the same preamble: “A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising.” NCT-236 discloses the administration of “ustekinumab as intravenous (IV: into the vein) infusion in induction study in *participants with moderately to severely active Ulcerative Colitis (UC)*.” Ex. 1003 (NCT-236) at 1; Ex. 1028 at 17. NCT-236 also discloses administration of ustekinumab to “participants with moderately to severely active Ulcerative Colitis (UC)” and refers to the administration as “treatment”: “Official Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of *Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis*.” Ex. 1003 (NCT-236) at 1, 2 (“Maintenance Study - Number of Participants with Clinical Remission Among Participants in Clinical Response to IV Ustekinumab Induction *Treatment*”).

⁶ Ex. 1072 is a claim listing that enumerates each claim element.

88. Thus, in my opinion, NCT-236 discloses “[a] method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof,” as stated in claims 1, 19, 33, and 34.

b. administering a “pharmaceutical composition” (claim elements 1[a], 19[a], 33[a][c][d], 34[a][b])

89. The independent claims recite administering to the subject an anti-IL-12/IL-23p40 antibody in varying but substantially overlapping ways: claim 1 recites “administering to the subject a pharmaceutical composition comprising . . . [an] amount of an anti-IL-12/IL-23p40 antibody,” claims 19 and 33 recite “intravenously administering to the subject an anti-IL-12/IL-23p40 antibody in a first pharmaceutical composition,” and claim 34 recites “intravenously administering to the subject an anti-IL-12/IL-23p40 antibody.” Ex. 1001 (’307 Patent) at claims 1, 19, 33, and 34. NCT-236 discloses the *administration 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)” and therefore discloses administration to the subject as required by claim 1. Ex. 1003 (NCT-236) at 1.

90. In addition, three of the independent claims—claims 19, 33, and 34—recite specific dosages: “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,” *see* Ex. 1001 (’307 Patent) 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,” *see id.* at claims 33[c], 34[b], and claim 33 further recites “wherein the maintenance therapy is provided for 44 weeks,” claim 33[d], as shown in the following:⁷

⁷ I note that the structural limitations of the SEQ IDs in the claims for the antibody have been removed and are present in the ellipses (...), which are all satisfied by ustekinumab, as set forth above in Section IV.C and Section VIII.A.1.c.

19[a]	33[a]	34[a]
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	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	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 ...	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 ...	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,
	33[c]	34[b]
	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,	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, and
	33[d]	

	and wherein the maintenance therapy is provided for 44 weeks and	
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91. NCT-236 discloses each of the “administering” limitations, including the specific dosages recited in these claims. NCT-236 discloses that the trial “protocol will consist of 2 studies: an Induction study and a Maintenance study with unique endpoints.” Ex. 1003 (NCT-236) at 3. “Participant with clinical response in the Induction study will be eligible for the Maintenance study. The Maintenance study will be for 44 weeks duration.” *Id.* NCT-236 describes dosages of ustekinumab (which, as discussed above, is an anti-IL-12/IL-23p40 antibody) for treatment arms of the Induction study as an intravenous infusion and the Maintenance study subcutaneously as follows:

Experimental: Induction Study - Ustekinumab 130 milligram (mg) IV Participants will be randomized to receive <i>single dose of ustekinumab 130 mg as IV infusion at Week 0</i>. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.
Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive <i>ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0</i>. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.

Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive <i>ustekinumab 90 mg subcutaneously every 12 weeks, beginning Week 0 of Maintenance study through Week 44.</i>
Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.</i>

Id. at 3.

92. As shown in the following chart, each of the limitations recited in 19[a], 33[a][c][d], and 34[a][b] are disclosed by NCT-236. For example, NCT-236 discloses claim elements 19[a], 33[a], and 34[a] as follows:

Claim Limitation (19[a], 33[a], 34[a])	NCT-236 (Ex. 1003) at 3
a. intravenously administering to the subject an anti-IL-12/IL-23p40 antibody . . . in a first pharmaceutical composition at <i>a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration at week 0</i> of the treatment	Experimental: Induction Study - Ustekinumab 130 milligram (mg) IV Participants will be randomized to receive <i>single dose of ustekinumab 130 mg as IV infusion at Week 0.</i> Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.
	Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive <i>ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0.</i> Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.

Claim Limitation (19[a], 33[a], 34[a])	NCT-236 (Ex. 1003) at 3
b. subcutaneously administering to the subject the anti-IL-12/IL-23p40 antibody in a second pharmaceutical composition at <i>a dosage of 90 mg per administration at week 8</i> of the treatment	Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive <i>ustekinumab 90 mg subcutaneously</i> every 12 weeks, beginning Week 0 of Maintenance study through Week 44.
	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously</i> every 8 weeks, beginning Week 0 of Maintenance study through Week 44.

NCT-236 discloses claim elements 33[c] and 34[b] as follows:

Claim Limitation (33[c], 34[b])	NCT-236 (Ex. 1003) at 3
followed by a maintenance therapy, wherein the maintenance therapy comprises subcutaneously administering to the subject the anti-IL-	Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive <i>ustekinumab 90 mg subcutaneously every 12 weeks, beginning Week 0</i> of Maintenance study through Week 44.

Claim Limitation (33[c], 34[b])	NCT-236 (Ex. 1003) at 3
12/IL-23p40 antibody at <i>a dosage of 90 mg per administration, once every 8 weeks or once every 12 weeks</i>	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0</i> of Maintenance study through Week 44.

NCT-236 discloses claim element 33[d] as follows:

Claim Limitation (33[d])	NCT-236 (Ex. 1003) at 3
<i>wherein the maintenance therapy is provided for 44 weeks</i>	Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 12 weeks, beginning Week 0 of Maintenance study <i>through Week 44</i> .
	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study <i>through Week 44</i> .

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

93. In my opinion, a POSA would understand that the antibody structure requirements of the claims are inherently disclosed by NCT-236. Each

independent claim recites administering to the subject an “anti-IL-12/IL-23p40 antibody” having certain SEQ IDs, as follows:

Claims 1[b], 19[b], 33[b]	Claim 34[a]
wherein the antibody comprises a heavy chain variable region and a light chain variable region, the heavy chain variable region comprising: a complementarity determining region heavy chain 1 (CDRH1) amino acid sequence of SEQ ID NO:1; a CDRH2 amino acid sequence of SEQ ID NO:2; and a CDRH3 amino acid sequence of SEQ ID NO:3; and the light chain variable region comprising: a complementarity determining region light chain 1 (CDRL1) amino acid sequence of SEQ ID NO:4; a CDRL2 amino acid sequence of SEQ ID NO:5; and a CDRL3 amino acid sequence of SEQ ID NO:6,	an anti-IL-12/IL-23p40 antibody comprising a heavy chain variable region of the amino acid sequence of SEQ ID NO:7 and a light chain variable region of the amino acid sequence of SEQ ID NO:8,

94. NCT-236 expressly discloses the administration of ustekinumab, which is an anti-IL-12/IL-23p40 antibody. At the time of the invention, the amino acid sequence of ustekinumab was known, which contains all of the SEQ IDs recited within claim elements 1[b], 19[b], 33[b], and 34[a]. *See supra* IV.C.

95. SEQ ID NOS:1-6 are the CDR sequences of ustekinumab, which were known in the prior art by September 24, 2018, as can readily be observed in the charts included in Appendix I, Sections A-B

96. Similarly, SEQ ID NOS: 7 and 8 are the variable domains for the LC and HC of ustekinumab, which were known in the prior art by September 24, 2018, as can readily be observed in the charts included in Appendix I, Sections C-D.

97. Accordingly, a POSA would understand that NCT-236’s disclosure of ustekinumab inherently satisfies the antibody structural limitations of claim elements 1[b], 19[b], 33[b], 34[a].

d. “clinically proven safe and clinically proven effective amount” (claim element 1[a])

98. In my opinion, a POSA would understand that the dosage in NCT-236 is “a clinically proven safe and clinically proven effective amount of an anti-IL-12/IL-23p40 antibody” as recited in claim 1: “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” *See* Ex. 1001 (’307 Patent) at claim 1[a].

99. First, a POSA would consider the dosages disclosed in NCT-236 to be “clinically proven safe” because the same treatment regimen was shown to be safe during the phase 2/phase 3 trials from the STELARA® psoriasis and Crohn’s studies. *See supra*, Ex. 1027 (Phase 3 Clinical Protocol) at 25; Section IV.D; Ex. 1026 (Feagan); and Ex. 1024 (First Approved Label). In its submission to the FDA in March 2015 Patent Owner admitted as much—relying on phase 2 and phase 3 data from the STELARA® psoriasis and Crohn’s studies to circumvent safety studies for the NCT-236 trial. *See* Section IV.E; Ex. 1027 (Phase 3 Clinical Protocol) at 40. Janssen specifically stated that “the efficacy and safety of ustekinumab in Crohn’s disease has been evaluated in 2 completed Phase 2 clinical

studies (C0379T07 and C0743T26) and 2 completed Phase 3 induction studies (CNT01275CRD3001 and CNT01275CRD3002).” Ex. 1027 (Phase 3 Clinical Protocol) at 40. A POSA would consider the treatment regimen disclosed in NCT-236 to be “clinically proven safe” under both definitions of “clinically proven” discussed in Section VII.A, above. This is because (i) the phase 2 trials demonstrated safety, and (ii) the treatment regimen disclosed in NCT-236 were approved by a regulatory agency as safe for the original indications. Ex. 1027 (Phase 3 Clinical Protocol) at 25; Ex. 1024 (First Approved Label).

100. Second, it is my opinion that NCT-236 inherently discloses a “clinically proven effective amount,” because performing the methods as described in NCT-236 necessarily demonstrates the effectiveness of the regimen disclosed therein. Indeed, given that NCT-236 expressly discloses the same method as what is recited in the ’307 Patent, a POSA would understand that NCT-236 inevitably and inherently must produce the results claimed in the ’307 Patent. Moreover, as I discuss below, Sands reported the results from the clinical trial for NCT-236 (NCT02407236) and verified the inherent efficacy of treating UC patients with ustekinumab according to the NCT-236 protocol. I understand that these results served as the basis for FDA approval for treating UC with STELARA® using the claimed methods of treatment. *See* Section IV.G.

101. My opinion that the treatment regimen from NCT-236 inherently discloses a “clinically proven effective amount” is not impacted by the claim construction of “clinically proven.” As demonstrated at least by Sands, the dosage regimen in NCT-236 induced improvement in at least one indicator related to UC for some of the patients. Ex. 1031 (Sands). In addition, the administration of ustekinumab to moderately to severely active UC patients as set forth in 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. 1004 (UC Label). It is thus my opinion that a POSA would understand NCT-236 to inherently disclose that the treatment is “clinically proven effective.”

102. Third, a POSA would understand that NCT-236 discloses the administration of ustekinumab in a manner identical to the administration method as recited in dependent claims 6 and 7. Because claims 6 and 7 depend on claim 1, those doses must necessarily be “a clinically proven safe and clinically proven effective amount of an anti-IL-12/IL-23p40 antibody.” I compared the dosages in NCT-236 with the dosages recited in claims 6 and 7. As shown below, claim 7 is dependent on claim 6 and (through claim 4) dependent on independent claim 1:

4. The method of any one of claims 1-3

6. The method of claim 4, wherein the antibody is administered intravenously to the subject at week 0 of the treatment, at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.

7. The method of claim 6, wherein the antibody is further administered subcutaneously to the subject at week 8 of the treatment, at a dosage of about 90 mg per administration.

Ex. 1001 ('307 Patent) at claims 4, 6 and 7.

103. The administration method of claims 6 and 7 is identical to that of NCT-236 for ustekinumab:

Claims 6, 7	NCT-236 (Ex. 1003) at 3
6. The method of claim 4, wherein the antibody is administered intravenously to the subject at week 0 of the treatment, at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.	Experimental: Induction Study - Ustekinumab 130 milligram (mg) IV Participants will be randomized to receive <i>single dose of ustekinumab 130 mg as IV infusion at Week 0.</i> Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.
	Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive <i>ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0.</i> Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.
7. The method of claim 6, wherein the antibody is further administered subcutaneously to the subject at week 8 of the treatment, at a dosage of about 90 mg	Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously</i> every 12 weeks, beginning Week 0 of Maintenance study through Week 44.

Claims 6, 7	NCT-236 (Ex. 1003) at 3
per administration.	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously</i> every 8 weeks, beginning Week 0 of Maintenance study through Week 44.

104. Therefore, the administration in NCT-236 (which uses the same doses) must also be considered “a clinically proven safe and clinically proven effective amount of an anti-IL-12/IL-23p40 antibody” as recited in claim element 1[a]. Ex. 1001 ('307 Patent) at claim 1[a].

- e. **“the subject is a responder to treatment by at least one measure of response to treatment selected from the group consisting of” (claim elements 1[c], 19[c], 33[e], 34[c])**

105. In my opinion, a POSA would understand that administering ustekinumab to patients with moderately to severely active UC according to the methods of NCT-236 inherently results in a patient that is a responder to treatment as recited in claim elements 1[c], 19[c], 33[e], 34[c]. Each independent claim recites that “[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” the following “Seven Claimed Measures of Response”:

- (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 $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.

See Ex. 1001 ('307 Patent) at claims 1[c], 19[c], 33[e], 34[c]).⁸

106. I understand that the claim language reciting “the subject is a responder to treatment by at least one measure of response to treatment selected from the group consisting of [the Seven Claimed Measures of Response]” means that the independent claims can be met by satisfaction of any single measure of the Seven Claimed Measures of Response. Nevertheless, in my opinion, NCT-236 inherently discloses a subject that is a responder according to *each* of the Seven Claimed Measures of Response. Ex. 1003 (NCT-236) at 1-2. Sands reports the results of the NCT-236 study and confirms that subjects with moderately to

⁸ Minor differences in claim language have been omitted.

severely active UC who received the treatments disclosed in NCT-236 responded according to the Seven Claimed Measures of Response, as I describe in detail below. Ex. 1031 (Sands). As I explained above in Section IV.G, based on the design of NCT-236 as a phase 3 study, in my opinion Sands confirms the inevitably achieved results obtained by following the methods disclosed in NCT-236, and NCT-236 inherently discloses this claim. Some claim elements, such as 1[c], claim responses from the administration of “an anti-IL-12/IL-23p40 antibody” without reference to a particular administration, and are disclosed by NCT-236’s Induction and Maintenance studies. Other claim elements, such as 33[e] and 34[c], require responses from the administration of “an anti-IL-12/IL-23p40 antibody” during a maintenance administration, which is disclosed by NCT-236’s Maintenance studies. I demonstrate how the claimed responses are met by both the Induction and Maintenance studies below.

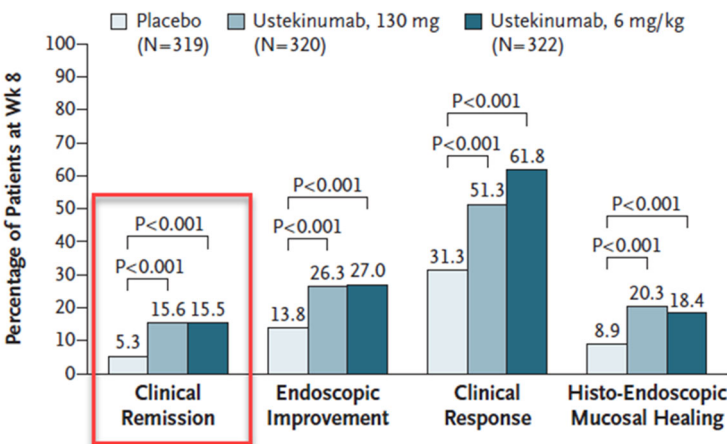
**(1) Inherent responses to the method of Induction
IV infusion of ustekinumab at 130 mg or 6
mg/kg expressly disclosed in NCT-236**

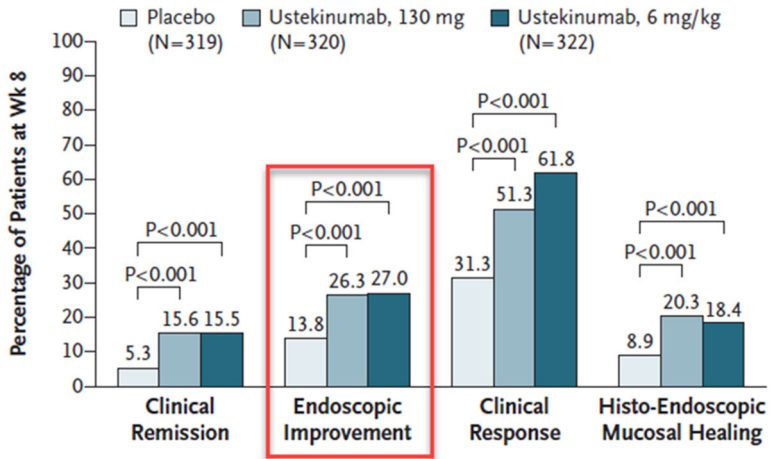
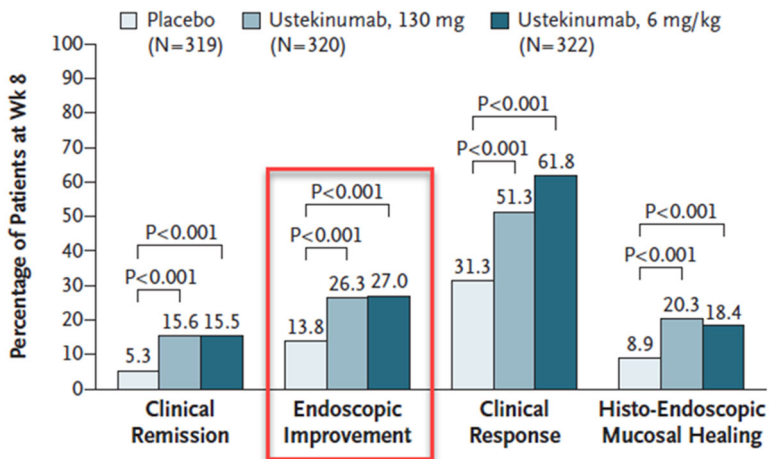
107. As I noted above, Sands confirms that patients responded to the IV Induction infusion set forth in NCT-236 according to the response criteria identified therein. Specifically, Sands reports: “At week 0 in the induction trial, patients were randomly assigned, in a 1:1:1 ratio, to receive a single intravenous infusion of 130 mg of ustekinumab, a weight-range-based dose that approximated

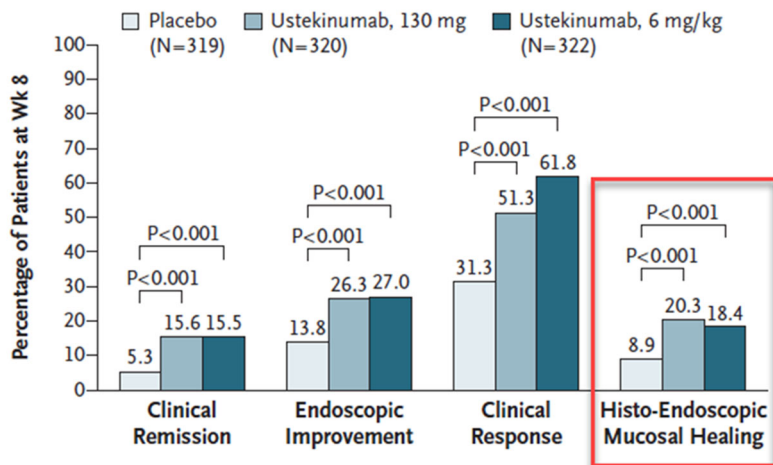
6 mg of ustekinumab per kilogram of body weight, or placebo.” Ex. 1031 (Sands) at 2, 6 (“At baseline in the induction trial, patients were randomly assigned to receive a single intravenous infusion of placebo (319 patients), ustekinumab at a dose of 130 mg (320), or ustekinumab at a dose approximating 6 mg per kilogram (322).”).

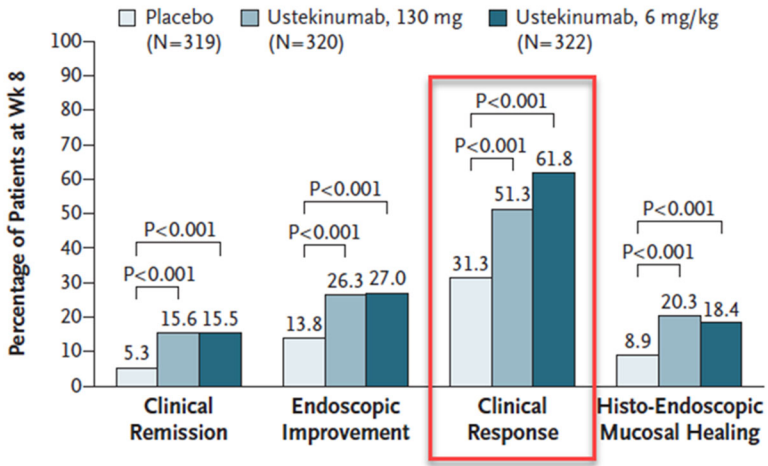
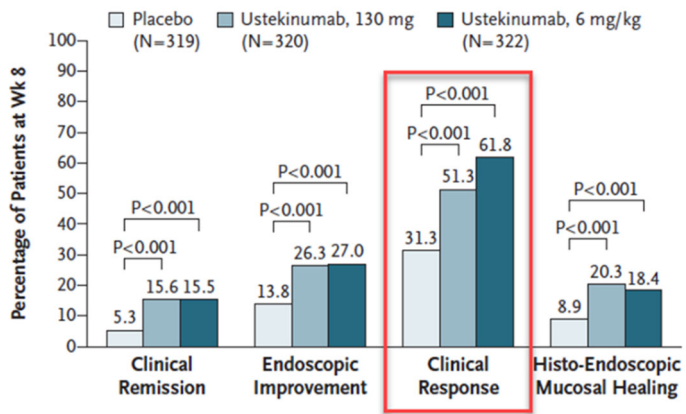
108. Sands reports patient responses with respect to “clinical remission” and other secondary measures, including each of the Seven Claimed Measures of Response:

Measure of Response	Sands (Ex. 1031)
(i) clinical remission based on at least one of the global definition of clinical remission with <i>Mayo score ≤ 2 points</i> with <i>no individual subscore > 1</i> and the US definition of clinical remission with <i>absolute stool number ≤ 3, rectal bleeding subscore of 0 and Mayo endoscopy subscore of 0 or 1,</i>	<i>“The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission (defined as a total score of ≤ 2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore > 1 [range, 0 to 3] on any of the four Mayo scale components).”</i> Ex. 1031 at 1. “An alternative primary end point of clinical remission that excluded the subscore on the physician’s global assessment component of the Mayo scale was also prespecified to support the FDA submission. <i>This definition required an absolute stool number of 3 or fewer (average daily stool number during 3 days before a visit), a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1.</i>” Ex. 1031 at 3.

Measure of Response	Sands (Ex. 1031)																				
	<table><thead><tr><th>Measure of Response</th><th>Placebo (N=319)</th><th>Ustekinumab, 130 mg (N=320)</th><th>Ustekinumab, 6 mg/kg (N=322)</th></tr></thead><tbody><tr><td>Clinical Remission</td><td>5.3</td><td>15.6</td><td>15.5</td></tr><tr><td>Endoscopic Improvement</td><td>13.8</td><td>26.3</td><td>27.0</td></tr><tr><td>Clinical Response</td><td>31.3</td><td>51.3</td><td>61.8</td></tr><tr><td>Histo-Endoscopic Mucosal Healing</td><td>8.9</td><td>20.3</td><td>18.4</td></tr></tbody></table> Ex. 1031 at 8 (annotated). “At week 8, the percentages of patients in clinical remission were higher in the groups that received ustekinumab at a dose of either 130 mg (15.6% [50 of 320 patients]) or 6 mg per kilogram (15.5% [50 of 322]) than in the placebo group (5.3% [17 of 319]) (P<0.001 for both comparisons with placebo) (Fig. 2). The results were similar for the alternative primary end point of clinical remission that excluded the subscore on the physician’s global assessment component of the Mayo scale: 16.6% (53 of 320 patients) and 18.9% (61 of 322) in the respective ustekinumab groups and 6.3% (20 of 319) in the placebo group (P<0.001 for both comparisons with placebo) (Fig. S2 in the Supplementary Appendix).” Ex. 1031 at 6-8.	Measure of Response	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)	Clinical Remission	5.3	15.6	15.5	Endoscopic Improvement	13.8	26.3	27.0	Clinical Response	31.3	51.3	61.8	Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4
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Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4																		
(ii) endoscopic healing with a Mayo endoscopy subscore of 0 or 1,	“Major secondary end points at week 8 were endoscopic improvement (defined as a Mayo endoscopic subscore of 0 or 1) <i>Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1.</i>” Ex. 1031 at 3, 8.																				

Measure of Response	Sands (Ex. 1031)
	 Ex. 1031 at 8 (annotated).
(iii) clinical response based on the Mayo endoscopy subscore,	“Major secondary end points at week 8 were endoscopic improvement (<i>defined as a Mayo endoscopic subscore of 0 or 1</i>)” and “Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1.” Ex. 1031 at 3, 8.  Ex. 1031 at 8 (annotated).
(iv) improvements from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score,	Major secondary end points at week 8 were . . . <i>change from baseline in the IBDQ score.</i>” Ex. 1031 at 3. “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.

Measure of Response	Sands (Ex. 1031)																				
	1031 at 6-8.																				
(v) mucosal healing,	“The percentages of patients who met major secondary end points or had histo-endoscopic <i>mucosal healing were significantly higher in both ustekinumab groups than in the placebo group</i> (Fig. 2).” Ex. 1031 at 8. <table><caption>Data from Figure 2: Percentage of Patients at Wk 8</caption><thead><tr><th>Endpoint</th><th>Placebo (N=319)</th><th>Ustekinumab, 130 mg (N=320)</th><th>Ustekinumab, 6 mg/kg (N=322)</th></tr></thead><tbody><tr><td>Clinical Remission</td><td>5.3</td><td>15.6</td><td>15.5</td></tr><tr><td>Endoscopic Improvement</td><td>13.8</td><td>26.3</td><td>27.0</td></tr><tr><td>Clinical Response</td><td>31.3</td><td>51.3</td><td>61.8</td></tr><tr><td>Histo-Endoscopic Mucosal Healing</td><td>8.9</td><td>20.3</td><td>18.4</td></tr></tbody></table> Ex. 1031 at 8 (annotated). “The percentage of patients who had histologic improvement was higher in both ustekinumab groups than in the placebo group, as was the percentage of patients who had histo-endoscopic mucosal healing.” Ex. 1031 at 9.	Endpoint	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)	Clinical Remission	5.3	15.6	15.5	Endoscopic Improvement	13.8	26.3	27.0	Clinical Response	31.3	51.3	61.8	Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4
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Clinical Response	31.3	51.3	61.8																		
Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4																		
(vi) decrease from baseline in Mayo score,	“Patients who had a clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of $\geq 30\%$ and of ≥ 3 points from baseline, with an accompanying decrease of ≥ 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1) entered the maintenance trial . . .” Ex. 1031 at 2. “Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8.																				

Measure of Response	Sands (Ex. 1031)
	 Ex. 1031 at 8 (annotated).
and (vii) clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.	<i>“Patients who had a clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of $\geq 30\%$ and of ≥ 3 points from baseline, with an accompanying decrease of ≥ 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1) entered the maintenance trial . . .”</i> Ex. 1031 at 2. “Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8.  Ex. 1031 at 8 (annotated).

109. Thus, Sands confirms that the IV Induction infusion of ustekinumab to treat moderately to severely active UC according to the methods of NCT-236 inherently results in responders that have clinical remission, endoscopic improvement, change in baseline IBDQ score, mucosal healing, and clinical response—i.e., each of the Seven Claimed Measures of Response. Accordingly, the Seven Claimed Measures of Response in elements 1[c], 19[c], 33[e], 34[c] are inherently disclosed by IV Induction infusion of ustekinumab in NCT-236.

(2) Inherent responses to subcutaneous Maintenance administration of 90 mg ustekinumab every 12 weeks or every 8 weeks as expressly disclosed in NCT-236

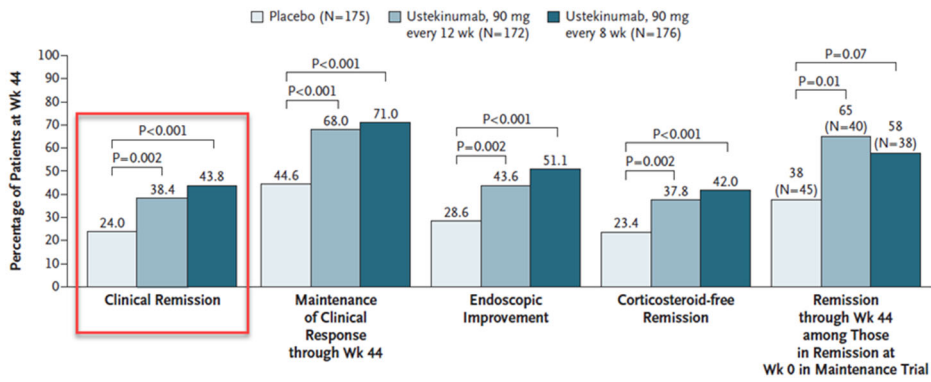
110. I understand that some claims further include limitations related to subcutaneous maintenance therapy at a dosage of 90 mg per administration, once every 8 weeks or once every 12 weeks. As discussed above, NCT-236 expressly disclosed and tested this maintenance administration. *See* Section VIII.A.1.c. Once again, a POSA would understand that Sands confirms that the response criteria recited in the claims were an inherent part of the NCT-236 maintenance administration. For example, Sands reports responders to the subcutaneous Maintenance injection of ustekinumab 90 mg every 12 or 8 weeks in patients that responded to the IV Induction dose of ustekinumab:

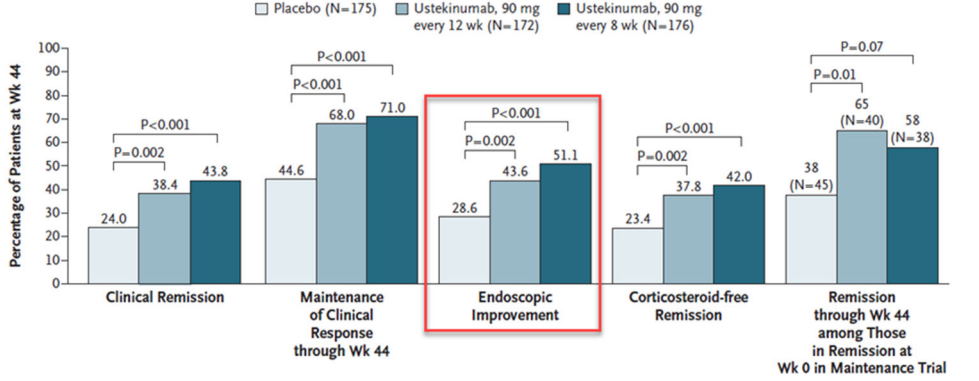
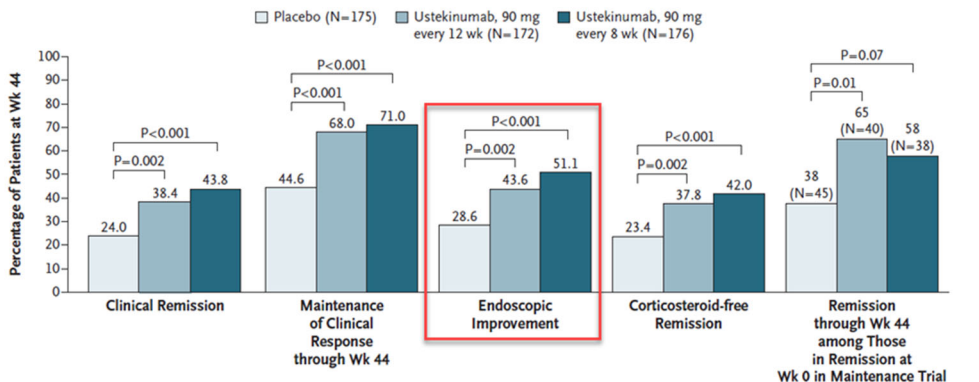
Patients who had a clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of $\geq 30\%$ and of ≥ 3 points from baseline, with an accompanying decrease of ≥ 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1) entered the maintenance trial At week 0 in the maintenance trial, patients were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous injections of 90 mg of ustekinumab every 12 weeks, 90 mg of ustekinumab every 8 weeks, or placebo through week 40 (Fig. 1).

Ex. 1031 (Sands) at 2-3.

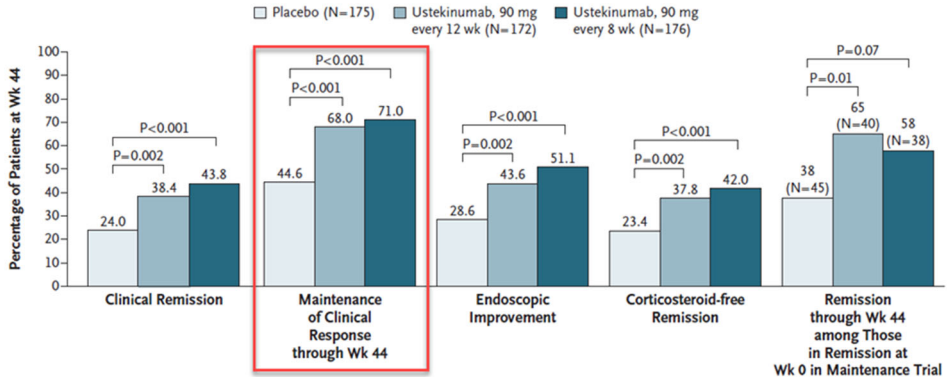
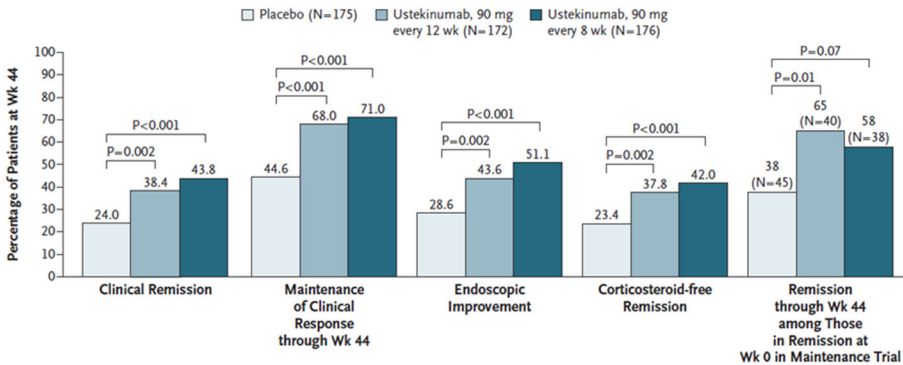
111. Sands confirms responders to the NCT-236 subcutaneous Maintenance injection of ustekinumab at 90 mg every 12 or 8 weeks with respect to each of the Seven Claimed Measures of Response:

Measure of Response	Sands (Ex. 1031)
(i) clinical remission based on at least one of the global definition of clinical remission with <i>Mayo score ≤ 2 points with no individual subscore > 1</i> and the US definition of	<i>“The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission (defined as a total score of ≤ 2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore > 1 [range, 0 to 3] on any of the four Mayo scale components).”</i> Ex. 1031 at 1. “An alternative primary end point of clinical remission that excluded the subscore on the physician’s global assessment component of the Mayo scale was also prespecified to support the FDA submission. <i>This definition required an absolute stool number of 3 or fewer (average daily stool number during 3 days before a visit), a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1.</i>” Ex. 1031 at 3.

Measure of Response	Sands (Ex. 1031)																								
clinical remission with <i>absolute stool number</i> ≤ 3 , <i>rectal bleeding subscore of 0</i> and <i>Mayo endoscopy subscore of 0 or 1</i> ,	“Among patients who had a clinical response to induction treatment with ustekinumab, the percentages of patients who had <i>clinical remission at week 44</i> (52 weeks after intravenous induction) were significantly higher in the groups that received 90 mg of ustekinumab every 12 weeks (38.4% [66 of 172 patients]) or every 8 weeks (43.8% [77 of 176]) than in the placebo group (24.0% [42 of 175]) (P = 0.002 and P<0.001, respectively, for the comparison with placebo) (Fig. 3). The results were similar for the alternative definition of clinical remission: 39.5% (68 of 172 patients) and 42.6% (75 of 176) in the respective ustekinumab groups and 24.6% (43 of 175) in the placebo group (P = 0.002 and P<0.001, respectively, for the comparison with placebo). Efficacy among prespecified subgroups was consistent with that in the overall randomized population. For both definitions of clinical remission, the results of sensitivity analyses were consistent. (See Figs. S4 and S5A through S5L and Table S5 in the Supplementary Appendix.)” Ex. 1031 at 8-9. <table><caption>Data from Figure 3: Percentage of Patients at Week 44</caption><thead><tr><th>Outcome</th><th>Placebo (N=175)</th><th>Ustekinumab 90 mg every 12 wk (N=172)</th><th>Ustekinumab 90 mg every 8 wk (N=176)</th></tr></thead><tbody><tr><td>Clinical Remission</td><td>24.0</td><td>38.4</td><td>43.8</td></tr><tr><td>Maintenance of Clinical Response through Wk 44</td><td>44.6</td><td>68.0</td><td>71.0</td></tr><tr><td>Endoscopic Improvement</td><td>28.6</td><td>43.6</td><td>51.1</td></tr><tr><td>Corticosteroid-free Remission</td><td>23.4</td><td>37.8</td><td>42.0</td></tr><tr><td>Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial</td><td>38 (N=45)</td><td>65 (N=40)</td><td>58 (N=38)</td></tr></tbody></table> Ex. 1031 at 9 (annotated).	Outcome	Placebo (N=175)	Ustekinumab 90 mg every 12 wk (N=172)	Ustekinumab 90 mg every 8 wk (N=176)	Clinical Remission	24.0	38.4	43.8	Maintenance of Clinical Response through Wk 44	44.6	68.0	71.0	Endoscopic Improvement	28.6	43.6	51.1	Corticosteroid-free Remission	23.4	37.8	42.0	Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial	38 (N=45)	65 (N=40)	58 (N=38)
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(ii) endoscopic healing with a Mayo endoscopy subscore of 0 or 1,	“Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1.” Ex. 1031 at 8.																								

Measure of Response	Sands (Ex. 1031)
	 Ex. 1031 at 8-9 (annotated).
(iii) clinical response based on the Mayo endoscopy subscore,	“Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1.” Ex. 1031 at 8.  Ex. 1031 at 8-9 (annotated).
(iv) improvements from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score,	“The percentage of patients who had histologic improvement was higher in both ustekinumab groups than in the placebo group, as was the percentage of patients who had histo-endoscopic mucosal healing. <i>Through week 44, median IBDQ scores were maintained or improved with ustekinumab every 12 weeks and every 8 weeks but worsened with placebo.</i> Improvements in partial Mayo scores and concentrations of CRP, lactoferrin, and calprotectin that were observed at baseline in the maintenance trial were maintained in both ustekinumab groups, whereas results for these measures worsened in the placebo group. (See Tables S13 through S19 in the Supplementary Appendix.)” Ex. 1031 at 9-11.

Measure of Response	Sands (Ex. 1031)
(v) mucosal healing,	“Histoendoscopic mucosal healing required both histologic improvement (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) and endoscopic improvement.” Ex. 1031 at 8. “The percentage of patients who had histologic improvement was higher in both ustekinumab groups than in the placebo group, as was the percentage of patients who had histo-endoscopic mucosal healing. Through week 44, median IBDQ scores were maintained or improved with ustekinumab every 12 weeks and every 8 weeks but worsened with placebo. Improvements in partial Mayo scores and concentrations of CRP, lactoferrin, and calprotectin that were observed at baseline in the maintenance trial were maintained in both ustekinumab groups, whereas results for these measures worsened in the placebo group. (See Tables S13 through S19 in the Supplementary Appendix.)” Ex. 1031 at 9-11.
(vi) decrease from baseline in Mayo score,	“Patients who had a clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of $\geq 30\%$ and of ≥ 3 points from baseline, with an accompanying decrease of ≥ 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1) entered the maintenance trial” Ex. 1031 at 2. “Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8.

Measure of Response	Sands (Ex. 1031)
	 Ex. 1031 at 9 (annotated).
and (vii) clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.	“Patients who had a <i>clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of $\geq 30\%$ and of ≥ 3 points from baseline, with an accompanying decrease of ≥ 1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1)</i> entered the maintenance trial” Ex. 1031 at 2. “Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8  Ex. 1031 at 9.

112. Thus, Sands demonstrates responders after both the IV Induction infusion at week 8 (*see* above Section VIII.A.1.e(1)) and subcutaneous

Maintenance injections at week 44 disclosed in NCT-236 that satisfy each of the Seven Claimed Measures of Response. The Seven Claimed Measures of Response in elements 1[c], 19[c], 33[e], 34[c] are also inherently disclosed by subcutaneous Maintenance injections of ustekinumab in NCT-236. NCT-236 thus inherently discloses claims elements 1[c], 19[c], 33[e], 34[c]].

- f. **“the subject is a responder to treatment . . . and had previously failed or was intolerant of at least one therapy selected from the group consisting of: an anti-TNF, vedolizumab, corticosteroids, azathioprine (AZA), and 6 mercaptopurine (6 MP), or the subject had demonstrated corticosteroid dependence” (claim element 19[d])**

113. Claim 19[d] includes an additional limitation that the responder has previously failed or has been intolerant to other therapies, or has demonstrated steroid dependence. Ex. 1001 ('307 Patent) at claim 19[d]. A POSA would understand that NCT-236 teaches this additional limitation. For example, as quoted below, NCT-236 expressly discloses this patient inclusion criterion:

Inclusion Criteria:

Has a clinical diagnosis of Ulcerative Colitis (UC) at least 3 months before Screening

Has moderately to severely active UC, defined as a Baseline (Week 0) Mayo score of 6 to 12, including a Screening endoscopy subscore of the Mayo score greater than or equal to ($\geq$) 2 as determined by a central reading of the video endoscopy

Have failed biologic therapy, that is, have received treatment with 1 or more tumour necrosis factor (TNF) antagonists or

vedolizumab at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment; **OR** Be naïve to biologic therapy (TNF antagonists or vedolizumab) or have received biologic therapy but have not demonstrated a history of failure to respond to, or tolerate, a biologic therapy and ***have a prior or current UC medication history that includes at least 1 of the following: a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]) OR b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) OR c. History of corticosteroid dependence*** (that is, an inability to successfully taper corticosteroids without a return of the symptoms of UC)

Ex. 1003 (NCT-236) at 4.

114. Sands reports responses of patients meeting the eligibility criteria in 19[c]: “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 (Sands) at 2. Thus, the patient responses reported in Sands and inherent to NCT-236 satisfy this limitation. It is therefore my opinion that NCT-236 anticipates Claim 19.

2. Dependent Claims 2-3 and 20-21

115. In my opinion, NCT-236 inherently anticipates claims 2, 3, 20, and 21. Claims 2-3 depend from claim 1, and claims 20-21 depend from claim 19:

2. The method of claim 1, wherein the antibody comprises the heavy chain variable region of the amino acid sequence of SEQ ID NO:7 and the light chain variable region of the amino acid sequence of SEQ ID NO:8.

3. The method of claim 1, wherein the antibody comprises a heavy chain of the amino acid sequence of SEQ ID NO:10 and a light chain of the amino acid sequence of SEQ ID NO:11.

20. The method of claim 19, wherein the antibody comprises the heavy chain variable region of the amino acid sequence of SEQ ID NO:7 and the light chain variable region of the amino acid sequence of SEQ ID NO:8.

21. The method of claim 19, wherein the antibody comprises a heavy chain of the amino acid sequence of SEQ ID NO:10 and a light chain of the amino acid sequence of SEQ ID NO:11.

Ex. 1001 ('307 Patent) at claims 2-3, 20-21.

116. As quoted above, each of claims 2, 3, 20, and 21 recite SEQ IDs for the “anti-IL-12/IL-23p40 antibody.” As discussed above, SEQ ID NOS:7-8 are the heavy and light chain variable regions for ustekinumab and were known in the prior art. Appendix I at Sections C-D. Similarly, SEQ ID NOS:10-11 are the complete heavy and light chains for ustekinumab and were also known in the prior art. Appendix I at Sections E-F. Accordingly, a POSA would understand the limitations in claims 2, 3, 20, and 21 to be inherently disclosed by the use of ustekinumab in NCT-236.

3. Dependent Claims 4 and 22

117. In my opinion, NCT-236 inherently anticipates claims 4 and 22. Claim 4 depends on the method of any one of claims 1-3, and claim 22 depends on any one of claims 19-21, and both recite, “wherein the [antibody is in a] pharmaceutical composition for intravenous administration compris[ing] a solution

comprising 10 mM L-histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL EDTA disodium salt, dehydrate, at pH 6.0,” respectively. Ex. 1001 (’307 Patent) at claims 4, 22.

118. I understand that NCT-236, through hyperlinks, discloses that the ustekinumab used was STELARA®.⁹ Exs. 1064-1069, 1071. As I explain below, the formulation of STELARA®, as disclosed in Stelara-PI(2017) teaches the limitations of claims 4 and 22. Therefore, NCT-236 expressly discloses these claim limitations. Nevertheless, if the Board finds that NCT-236 does not teach the use of STELARA® by incorporation by reference, it is my opinion that a POSA would nevertheless understand that “ustekinumab,” as used in NCT-236 was STELARA® because prior to the critical date, STELARA® was the only commercially available ustekinumab. *See* Ex. 1041 (“Ustekinumab (Stelara) is a biologic medication”). In addition, NCT-236 was sponsored by Janssen, the manufacturer of STELARA®, confirming a POSA’s understanding that

⁹ I understand from the accompanying declaration that a hyperlink in the 2015 version of NCT-236 is broken. Ex. 1071 ¶3. However, I understand that a 2016 version of NCT-236 contains an active hyperlink. Because the 2015 and 2016 versions of NCT-236 are substantively identical, Ex. 1071 ¶4, my analysis in this Ground would not change depending on which version was used.

STELARA® was used during the clinical trial. A POSA would have also been aware that only an approved ustekinumab could be used for the Phase 3 trial, and since STELARA® was the only FDA approved formulation of ustekinumab for IV administration, NCT-236 necessarily used that formulation of STELARA®. The formulation of STELARA®, as disclosed in Stelara-PI(2017) teaches the limitations of claims 4 and 22.

119. Stelara-PI(2017) discloses “STELARA® for Intravenous Infusion” is 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 (Stelara-PI(2017) at 16. Simple mathematical calculations show that this published formulation is the composition as recited in the claims. *Id.* at 16.

120. I have prepared the below molarity calculations for the above formulation recited in Stelara-PI(2017) to demonstrate that STELARA® comprises 10 mM L-histidine:

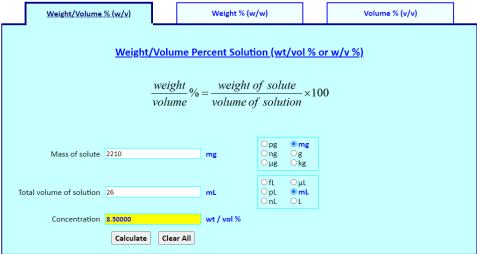
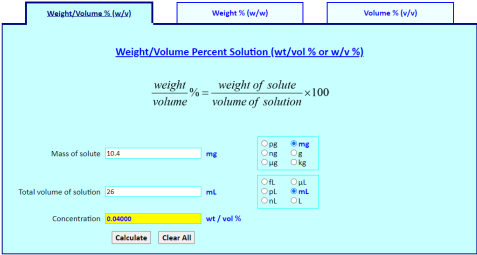
STELARA® IV Infusion – Histidine: mg/ml to mM					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ¹⁰
L-histidine	20	26	0.769	155.15	mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 0.76923 mg/ml Molecular Weight 155.15 mg/mmol Calculate Reset Molarity 0.005 mmole/ml 0.005 M
L-histidine hydrochloride monohydrate	27	26	1.038	209.63	mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 1.0384 mg/ml Molecular Weight 209.63 mg/mmol Calculate Reset Molarity 0.005 mmole/ml 0.005 M
L-histidine (total)					0.005 M + 0.005 M = 0.010 M = 10 mM

121. I have further analyzed the above formulations recited in Stelara-PI(2017) to demonstrate that STELARA® comprises 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL EDTA disodium salt, dehydrate:¹¹

¹⁰See <https://www.easycalculation.com/chemistry/mg-per-ml-to-molarity.php>

(mg/mL to M).

¹¹ The '307 patent refers to EDTA disodium salt, “dehydrate,” which appears to be a typo. The proper name is EDTA disodium salt “dihydrate.”

STELARA® Label (mg)	Concentration – Calculated (26 ml)	Claims 4 and 22
sucrose (2210 mg) ¹²		8.5% (w/v) sucrose
Polysorbate 80 (10.4 mg) ¹³		0.04% (w/v) polysorbate 80
L-methionine (10.4 mg)	10.4 mg/26 mL = 0.4 mg/mL	0.4 mg/mL L-methionine
EDTA disodium salt dihydrate (0.52 mg)	0.52 mg/26 mL = 0.02 mg/mL = 20 µg/mL	20 µg/mL EDTA disodium salt, dehydrate

122. Stelara-PI(2017) also discloses that STELARA® (ustekinumab) Injection has a “pH of 5.7-6.3.” Ex. 1004 at 16. A POSA administering

¹² https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v).

¹³ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v)

STELARA® to UC patients according to the treatment regimen disclosed in Stelara-PI(2017) for Crohn's patients would naturally have used the readily available composition disclosed in that label and already clinically proven to be safe.

4. Dependent Claim 6

123. Claim 6 is dependent on claim 4 and recites the intravenous administration of the antibody at week 0 “at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.” Ex. 1001 ('307 Patent), 120:49-52. NCT-236 expressly discloses intravenous administration at 6 mg/kg or 130 mg at week 0. *See* Section VIII.A.1.b above; Ex. 1003 at 3. Claim 6 is disclosed by NCT-236.

5. Dependent Claim 7

124. Claim 7 is dependent on claim 6 and further recites the subcutaneous administration of the antibody at week 8 “at a dosage of about 90 mg per administration.” Ex. 1001 ('307 Patent) at 120:53-55. NCT-236 expressly discloses subcutaneous administration at 90 mg at week 8. *See* Section VIII.A.1.b above; Ex. 1003 at 3. Claims 7 is disclosed by NCT-236.

6. Dependent Claim 8

125. Claim 8 recites: “The method of claim 7, wherein the subject had previously failed or was intolerant of at least one therapy selected from the group consisting of an anti-TNF, vedolizumab, corticosteroids, azathioprine (AZA), and

6 mercaptopurine (6 MP), or the subject had demonstrated corticosteroid dependence.” Ex. 1001 (’307 Patent) at 120:56-61. NCT-236 expressly discloses this patient population. *See supra* Section VIII.A.1.f; Ex. 1003 (NCT-236). It is thus my opinion that claim 8 is disclosed by NCT-236.

7. Dependent Claim 9

126. 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 (’307 Patent) at 120:63-65. 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. 1003 (NCT-236). It is thus my opinion that claim 9 is expressly disclosed by NCT-236.

8. Dependent Claims 10, 12-16, 18 Reciting Maintenance Responses “continuing at least 44 weeks after week 0”

127. In my opinion, NCT-236 inherently discloses each of the specific responses recited in these dependent claims upon completion of 44 weeks of Maintenance administration as confirmed by the week 44 results reported in Sands. These claims are dependent on claim 9 and each individually recites the following (continuing) patient responses to Maintenance administration at week 44: “clinical remission” (claim 10); “endoscopic healing” (claim 12); “clinical response based on the Mayo endoscopy subscore” (claim 13); “improvements from baseline in

Inflammatory Bowel Disease Questionnaire (IBDQ) score” (claim 14); “mucosal healing” (claim 15); “decrease from baseline in Mayo score” (claim 16); and “clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1 continuing at least 44 weeks after week 0” (claim 18). Each of the responses recited in these dependent claims are inherently satisfied by the subcutaneous Maintenance administration of 90 mg ustekinumab every 8 or 12 weeks disclosed in NCT-236, as reported by Sands. *See supra* Section VIII.A.1.e(2). It is thus my opinion that claims 10, 12-16, 18 are disclosed by NCT-236.

9. Dependent Claim 11

128. Claim 11 recites: “The method of claim 9, wherein the subject is in corticosteroid-free clinical remission at least 44 weeks after week 0.” NCT-236 expressly identifies this response. One of the Secondary Outcome Measures for the Maintenance Study of NCT-236 is the “number of participants with clinical remission and not receiving concomitant corticosteroids” measured at week 44. Ex. 1003 (NCT-236) at 2. Sands reports that this measure of response was observed in the NCT-236 trial results. Ex. 1031 at 9, Fig. 3. It is thus my opinion that claim 11 is disclosed by NCT-236.

10. Dependent Claims 17, 30

129. Claims 17 and 30 recite: “wherein the subject is identified as having a normalization of one or more biomarkers selected from the group consisting of C-reactive protein, fecal lactoferrin and fecal calprotectin [continuing at least]/[by] [44 weeks after week 0]/[week 16 of the treatment],” respectively. 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. It is thus my opinion that claims 17 and 30 are disclosed by NCT-236.

11. Dependent Claims 24-26, 28-29 and 31

130. Claims 24-26, 28-29, and 31 each recite one of the following: “The method of any one of claims 19-21, wherein the subject is [identified as having /identified as achieving (claim 26)/in (claim 31)] [a clinical remission based on at least one of the global definition and the US definition (claim 24)/an endoscopic healing (claim 25)/a clinical response based on the Mayo endoscopy subscore (claim 26)/a mucosal healing (claim 28)/a decrease from baseline in Mayo score (claim 29)/clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1 (claim 31)] *by week 16 of*

the treatment.” Each of the responses recited in these dependent claims are inherently satisfied by week 8 after the IV Induction infusion administration disclosed in NCT-236, as reported by Sands. *See supra*, Section VIII.A.1.e(1). It is thus my opinion that claims 24-26, 28-29 and 31 are disclosed by NCT-236.

a. Dependent Claim 27

131. Dependent 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 (’307 Patent) at 122:47-50. Improvement in baseline IBDQ 8 weeks after the IV infusion Induction administration of ustekinumab was inherently disclosed in NCT-236. *See* Ex. 1031 (Sands) at 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.”). NCT-236 expressly 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 (NCT-236) 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. It is thus my opinion that claim 27 is disclosed by NCT-236.

b. Dependent Claim 32

132. Dependent 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 (’307 Patent) at 123:1-4.

133. NCT-236 expressly discloses an arm of the Induction study for delayed-responders, as follows:

Induction study-Ustekinumab *Nonresponders at Week 8*

Participants *without clinical response to ustekinumab (130 mg or 6 mg/kg [IV]) at Week 8* will receive a single dose of ustekinumab 90 mg subcutaneously along with matching placebo intravenously (to maintain the blind). *Participants in clinical response at Week 16 (that is, delayed responders)* will be eligible to enter Maintenance study, but will not be randomized.

Ex. 1003 (NCT-236) at 3.

134. Delayed-responders were inherent to this express arm of NCT-236. The results of Sands confirm 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 (Sands) at 8. It is thus my opinion that claim 32 is disclosed by NCT-236.

B. Ground 2: NCT-236 in view of Ochsenkühn and Stelara-PI(2017) Renders Obvious Claims 1-34

135. In my opinion as discussed in Ground 1, NCT-236 alone renders claims 1-4, 6-22, and 24-34 of the '307 invalid as anticipated through express or inherent disclosure. NCT-236 nevertheless also renders the claimed methods obvious in view of Ochsenkühn and Stelara-PI(2017).¹⁴

136. As set forth in more detail in the following paragraphs, a POSA would have been motivated by the teachings of NCT-236, Ochsenkühn, and Stelara-PI(2017) to treat patients with moderately to severely active UC by administering Stelara-PI(2017) with an IV Induction dose of 6 mg/kg body weight (or 130 mg) at week 0 followed by subcutaneous maintenance doses of 90 mg every 8 weeks thereafter. In view of the knowledge of a POSA, the advanced status of the NCT-236 phase 3 clinical trial as of September 24, 2018, and the known successful treatment of UC patients refractory to other methods of treatment reported in Ochsenkühn, a POSA would have reasonably expected UC patients would respond to the treatment according to each of the outcome measures set forth in NCT-236. Accordingly, it is my opinion that the claims of the '307 Patent are obvious.

¹⁴ I incorporate by reference evidence of anticipation by NCT-236 in my obviousness analysis.

2. A POSA had a Motivation to Combine the references in this Ground

137. A POSA would have been motivated to combine NCT-236, Ochsenkühn, and Stelara-PI(2017) because of their express disclosures and teachings of overlapping and complementary subject matter with respect to the treatment of UC patients with ustekinumab.

138. A POSA would have known that NCT-236 was a phase 3 clinical trial studying the safety and efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active UC. Ex. 1003 (NCT-236) at 1. The NCT-236 clinical trial discloses the administration of ustekinumab as an IV Induction infusion at 6 mg/kg body weight at week 0 and subcutaneous Maintenance injection at 90 mg every 8 weeks of the treatment (for patients that responded to Induction):

Experimental: Induction Study - Ustekinumab 6 mg/kg IV

Participants will be randomized to receive ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.

Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w)

Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.

Ex. 1003 (NCT-236) at 3.

139. A POSA reading NCT-236 as of September 24, 2018 would have known that Janssen had received FDA approval for STELARA® (ustekinumab) for treating Crohn's Disease on September 26, 2016. *See* Ex. 1005 (Ochsenkühn) at 2 ("Ustekinumab is a monoclonal antibody targeting interleukins-12 and -23, commonly and successfully used in Crohn's disease."); Ex. 1038 at 1. A POSA knew that UC and Crohn's are the two most prevalent IBDs, both diseases were known to be related to the IL12/IL23 cytokine pathway, and many treatments effective in treating Crohn's are also effective in treating UC, and vice versa. *See* Ex. 1050 (Pithadia) at 1, Abstract; Ex. 1017, Sandborn et al., *A Randomized Trial of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients with Moderate-to-Severe Crohn's Disease*, *Gastroenterology*, 135:1130-141 (2008); Ex. 1001 ('307 Patent) at 2:38-41. A POSA would also have known that STELARA® (ustekinumab) for Crohn's patients was approved for administration as an IV Induction infusion at 6 mg/kg body weight at week 0 and a subcutaneous Maintenance injection of 90 mg 8 weeks after Induction, then every 8 weeks thereafter (precisely the same as the proposed Induction and Maintenance treatment arms of NCT-236):

2.3 Crohn's Disease		
<u>Intravenous Induction Adult Dosage Regimen</u>		
A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 [see <i>Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)</i>].		
Table 1: Initial Intravenous Dosage of STELARA®		
Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4
<u>Subcutaneous Maintenance Adult Dosage Regimen</u>		
The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.		

Ex. 1004 (Stelara-PI(2017)) at 4.

140. POSA would also have been aware that numerous biologic therapies such as infliximab, adalimumab, and vedolizumab were already in use to treat both Crohn's and UC. *See supra* Section IV.B, Ex. 1010 at 2.

141. A POSA would have understood (or at least found it obvious and would have fully expected) that STELARA® (ustekinumab) was being utilized within the NCT-236 clinical trial since it was the only ustekinumab drug formulation available, was manufactured by the sponsor, and was already approved for use in precisely the same Induction-Maintenance administration to treat Crohn's patients. A POSA reviewing the method of treatment proposed in NCT-236 would also have recognized that it was identical to the method in Stelara-PI(2017) for treatment of Crohn's. A POSA would therefore have been motivated

to combine the prescribing information for STELARA® (ustekinumab) as set forth in Stelara-PI(2017) with respect to the administration of ustekinumab set forth in NCT-236.

142. A POSA's motivation to combine NCT-236 with Stelara-PI(2017) is further demonstrated by Ochsenkühn. Ochsenkühn is entitled "Ustekinumab as Rescue Treatment in Therapy-Refractory or -Intolerant Ulcerative Colitis." Ex. 1005 (Ochsenkühn) at 2. It explains the aim of the study was "[t]o assess the clinical outcomes achieved with ustekinumab as rescue treatment in therapy-refractory or -intolerant UC" and reports the results from "[a] retrospective data analysis [that] was performed in 17 UC patients of [their] tertiary referral center who received ustekinumab between 2016 and 2017 as rescue therapy." *Id.* Ochsenkühn explained that "ustekinumab was provided as a rescue treatment after colectomy had been offered to [the UC patients] as only other option." *Id.* This treatment regimen was an attractive, safe, non-surgical option, particularly for patients who had not responded to available UC treatments. Ochsenkühn explained that "[p]re-approval trials are on-going" but noted that "so far no clinical observation data on the use of ustekinumab in ulcerative colitis (UC) is available." *Id.*

143. 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. Ochsenkühn even noted that “[p]re-approval trials are on-going” for the use of ustekinumab to treat UC 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 (Ochsenkühn) at 2. A POSA would have understood that the ongoing trials mentioned in Ochsenkühn referred to NCT-236 since that study was evaluating the use of ustekinumab to treat UC. As NCT-236 was a large-scale ongoing trial evaluating the effectiveness of ustekinumab to treat UC, it is my opinion a POSA would have readily combined these references.

3. A POSA Had A Reasonable Expectation That the Treatment Regimens in the Independent Claims Would Meet Claim Limitations Requiring Certain Clinical Results

144. In my opinion, a POSA would have had a reasonable expectation of success combining the teachings of NCT-236, Ochsenkühn, and Stelara-PI(2017) and, in doing so, arriving at the treatment responses claimed in the ’307 Patent. A POSA would have recognized that the treatment regimen in NCT-236 and Ochsenkühn is the same as for administration of STELARA® (ustekinumab) to Crohn’s patients pursuant to the teachings of Stelara-PI(2017) such that a POSA would have no trouble administering that same treatment to UC patients as expressly disclosed in NCT-236 and Ochsenkühn. By September 24, 2018, a POSA would have been familiar with treating CD patients with STELARA®

(ustekinumab) and there would be no difference in administering the same drug in the same way to patients diagnosed with the closely related moderately to severely active UC per NCT-236 and Ochsenkühn. From this combination, A POSA would have reasonably expected that the NCT-236 trial would result in the claimed responses, including sufficient demonstration of safety and effectiveness to warrant regulatory approval.

145. First, a POSA would have had a reasonable expectation that at least some UC patients receiving STELARA® (ustekinumab) according to the Induction-Maintenance administration taught in all three of these references would have been responders to treatment according to the measures of response in the claims. That is, a POSA would have reasonably expected, based on the treatments and “clinical remission” at 1 and 6 months disclosed in Ochsenkühn and the ongoing NCT-236 trial, that the administration of STELARA® (ustekinumab) as a 6 mg/kg IV Induction infusion and 90 mg subcutaneous Maintenance injection would have been a clinically safe and effective dosage regimen for treating moderately and severely active UC.

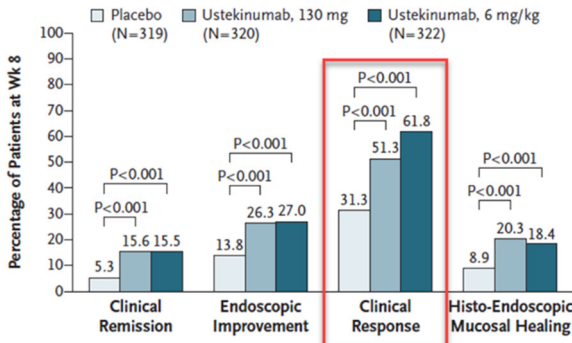
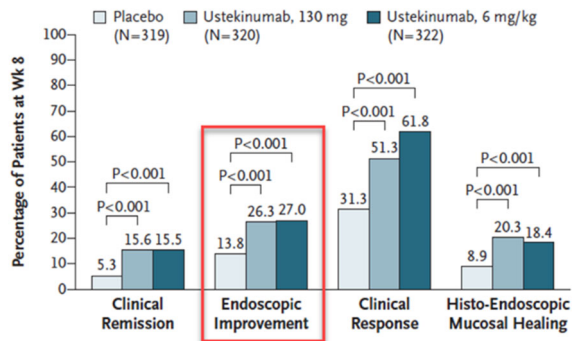
146. As a POSA would have understood, prior to engaging in any human clinical trial, the researchers would have to have sufficient data and analysis to support a belief that the trial will be successful. In that regard, the existence of the NCT-236 trial in and of itself is supportive of a belief that the treatment regimen

could be successful. A POSA would look at NCT-236, a phase 3 clinical study in its final stages, and understand that because it had been fully enrolled and passed its estimated primary completion date (April 2018), but had not been called off due to futility, that it was likely to be successful. In my experience, clinicians who are aware of clinical trials for an off-label use of a drug that is already known to be safe and effective (as is the situation for ustekinumab in NCT-236) rely on the existence of the clinical trial itself in order to recommend the treatment option to their own patients. The fact that NCT-236 was a direct-to-Phase 3 clinical trial, in an advanced stage without having been stopped for futility or safety by September 24, 2018, and that the exact same Induction-Maintenance dosing regimen was already approved for treating Crohn's (which shares the same underlying IL-12/IL-23p40 mechanism treated by ustekinumab), all support the reasonable expectation a POSA would have had that NCT-236 would meet its defined endpoints.

147. In fact, *every* primary and secondary outcome measure in NCT-236 was met, as reported in Sands, confirming that a POSA would have had a reasonable expectation of success that the chosen outcome measures in NCT-236 would meet the defined outcome measures. *Compare* Ex. 1003 at 1-2 *with* Ex. 1031:

NCT-236 (Ex. 1003) Outcome Measures	Sands (Ex. 1301) Results																				
Induction Study - Number of Participants With Clinical Remission [Time Frame: Week 8]	<table><thead><tr><th>Outcome</th><th>Placebo (N=319)</th><th>Ustekinumab, 130 mg (N=320)</th><th>Ustekinumab, 6 mg/kg (N=322)</th></tr></thead><tbody><tr><td>Clinical Remission</td><td>5.3</td><td>15.6</td><td>15.5</td></tr><tr><td>Endoscopic Improvement</td><td>13.8</td><td>26.3</td><td>27.0</td></tr><tr><td>Clinical Response</td><td>31.3</td><td>51.3</td><td>61.8</td></tr><tr><td>Histo-Endoscopic Mucosal Healing</td><td>8.9</td><td>20.3</td><td>18.4</td></tr></tbody></table> Ex. 1031 at 8 (annotated). “At week 8, the percentages of patients in clinical remission were higher in the groups that received ustekinumab at a dose of either 130 mg (15.6% [50 of 320 patients]) or 6 mg per kilogram (15.5% [50 of 322]) than in the placebo group (5.3% [17 of 319]) ($P<0.001$ for both comparisons with placebo) (Fig. 2). The results were similar for the alternative primary end point of clinical remission that excluded the subscore on the physician’s global assessment component of the Mayo scale: 16.6% (53 of 320 patients) and 18.9% (61 of 322) in the respective ustekinumab groups and 6.3% (20 of 319) in the placebo group ($P<0.001$ for both comparisons with placebo) (Fig. S2 in the Supplementary Appendix).” <i>Id.</i> at 6-8.	Outcome	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)	Clinical Remission	5.3	15.6	15.5	Endoscopic Improvement	13.8	26.3	27.0	Clinical Response	31.3	51.3	61.8	Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4
Outcome	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)																		
Clinical Remission	5.3	15.6	15.5																		
Endoscopic Improvement	13.8	26.3	27.0																		
Clinical Response	31.3	51.3	61.8																		
Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4																		

NCT-236 (Ex. 1003) Outcome Measures	Sands (Ex. 1301) Results																								
Maintenance Study - Number of Participants with Clinical Remission Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44]	<table><tr><th>Outcome</th><th>Placebo (N=175)</th><th>Ustekinumab, 90 mg every 12 wk (N=172)</th><th>Ustekinumab, 90 mg every 8 wk (N=176)</th></tr><tr><td>Clinical Remission</td><td>24.0</td><td>38.4</td><td>43.8</td></tr><tr><td>Maintenance of Clinical Response through Wk 44</td><td>44.6</td><td>68.0</td><td>71.0</td></tr><tr><td>Endoscopic Improvement</td><td>28.6</td><td>43.6</td><td>51.1</td></tr><tr><td>Corticosteroid-free Remission</td><td>23.4</td><td>37.8</td><td>42.0</td></tr><tr><td>Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial</td><td>38 (N=45)</td><td>65 (N=40)</td><td>58 (N=38)</td></tr></table>	Outcome	Placebo (N=175)	Ustekinumab, 90 mg every 12 wk (N=172)	Ustekinumab, 90 mg every 8 wk (N=176)	Clinical Remission	24.0	38.4	43.8	Maintenance of Clinical Response through Wk 44	44.6	68.0	71.0	Endoscopic Improvement	28.6	43.6	51.1	Corticosteroid-free Remission	23.4	37.8	42.0	Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial	38 (N=45)	65 (N=40)	58 (N=38)
Outcome	Placebo (N=175)	Ustekinumab, 90 mg every 12 wk (N=172)	Ustekinumab, 90 mg every 8 wk (N=176)																						
Clinical Remission	24.0	38.4	43.8																						
Maintenance of Clinical Response through Wk 44	44.6	68.0	71.0																						
Endoscopic Improvement	28.6	43.6	51.1																						
Corticosteroid-free Remission	23.4	37.8	42.0																						
Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial	38 (N=45)	65 (N=40)	58 (N=38)																						
	Ex. 1031 at 9 (annotated). “Among patients who had a clinical response to induction treatment with ustekinumab, the percentages of patients who had <i>clinical remission at week 44</i> (52 weeks after intravenous induction) were significantly higher in the groups that received 90 mg of ustekinumab every 12 weeks (38.4% [66 of 172 patients]) or every 8 weeks (43.8% [77 of 176]) than in the placebo group (24.0% [42 of 175]) (P = 0.002 and P<0.001, respectively, for the comparison with placebo) (Fig. 3). The results were similar for the alternative definition of clinical remission: 39.5% (68 of 172 patients) and 42.6% (75 of 176) in the respective ustekinumab groups and 24.6% (43 of 175) in the placebo group (P = 0.002 and P<0.001, respectively, for the comparison with placebo). Efficacy among prespecified subgroups was consistent with that in the overall randomized population. For both definitions of clinical remission, the results of sensitivity analyses were consistent. (See Figs. S4 and S5A through S5L and Table S5 in the Supplementary Appendix.)” <i>Id.</i> at 8-9.																								

NCT-236 (Ex. 1003) Outcome Measures	Sands (Ex. 1301) Results																				
Induction Study - Number of Participants with Clinical Response [Time Frame: Week 8] Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to ($\geq$) 30 percent (%) and ≥ 3 points, with either a decrease from induction baseline in the rectal bleeding subscore ≥ 1 or rectal bleeding subscore = 0 or 1.	“Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8.  <table><tr><th>Outcome Measure</th><th>Placebo (N=319)</th><th>Ustekinumab, 130 mg (N=320)</th><th>Ustekinumab, 6 mg/kg (N=322)</th></tr><tr><td>Clinical Remission</td><td>5.3</td><td>15.6</td><td>15.5</td></tr><tr><td>Endoscopic Improvement</td><td>13.8</td><td>26.3</td><td>27.0</td></tr><tr><td>Clinical Response</td><td>31.3</td><td>51.3</td><td>61.8</td></tr><tr><td>Histo-Endoscopic Mucosal Healing</td><td>8.9</td><td>20.3</td><td>18.4</td></tr></table> <i>Id.</i> at 8 (annotated).	Outcome Measure	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)	Clinical Remission	5.3	15.6	15.5	Endoscopic Improvement	13.8	26.3	27.0	Clinical Response	31.3	51.3	61.8	Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4
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Induction Study - Number of Participants With Endoscopic Healing [Time Frame: Week 8] Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1.	“Major secondary end points at week 8 were endoscopic improvement (<i>defined as a Mayo endoscopic subscore of 0 or 1</i>)” and “Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1.” Ex. 1031 at 3, 8.  <table><tr><th>Outcome Measure</th><th>Placebo (N=319)</th><th>Ustekinumab, 130 mg (N=320)</th><th>Ustekinumab, 6 mg/kg (N=322)</th></tr><tr><td>Clinical Remission</td><td>5.3</td><td>15.6</td><td>15.5</td></tr><tr><td>Endoscopic Improvement</td><td>13.8</td><td>26.3</td><td>27.0</td></tr><tr><td>Clinical Response</td><td>31.3</td><td>51.3</td><td>61.8</td></tr><tr><td>Histo-Endoscopic Mucosal Healing</td><td>8.9</td><td>20.3</td><td>18.4</td></tr></table> <i>Id.</i> at 8 (annotated).	Outcome Measure	Placebo (N=319)	Ustekinumab, 130 mg (N=320)	Ustekinumab, 6 mg/kg (N=322)	Clinical Remission	5.3	15.6	15.5	Endoscopic Improvement	13.8	26.3	27.0	Clinical Response	31.3	51.3	61.8	Histo-Endoscopic Mucosal Healing	8.9	20.3	18.4
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NCT-236 (Ex. 1003) Outcome Measures	Sands (Ex. 1301) Results																								
Induction Study - Mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score [Time Frame: Week 8]	“Major secondary end points at week 8 were . . . <i>change from baseline in the IBDQ score.</i>” Ex. 1031 at 3. “Through week 8, the median changes from baseline in the IBDQ score were significantly greater in both ustekinumab groups than in the placebo group.” <i>Id.</i> at 8.																								
Maintenance Study - Number of Participants with Clinical Response Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Through Week 44] Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to ($\geq$) 30 percent (%) and ≥ 3 points, with either a decrease from Induction baseline in the rectal bleeding subscore ≥ 1 or rectal bleeding subscore = 0 or 1.	“Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.” Ex. 1031 at 8. <table><thead><tr><th>Outcome</th><th>Placebo (N=175)</th><th>Ustekinumab, 90 mg every 12 wk (N=172)</th><th>Ustekinumab, 90 mg every 8 wk (N=176)</th></tr></thead><tbody><tr><td>Clinical Remission</td><td>24.0</td><td>38.4</td><td>43.8</td></tr><tr><td>Maintenance of Clinical Response through Wk 44</td><td>44.6</td><td>68.0</td><td>71.0</td></tr><tr><td>Endoscopic Improvement</td><td>28.6</td><td>43.6</td><td>51.1</td></tr><tr><td>Corticosteroid-free Remission</td><td>23.4</td><td>37.8</td><td>42.0</td></tr><tr><td>Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial</td><td>38 (N=45)</td><td>65 (N=40)</td><td>58 (N=38)</td></tr></tbody></table> <i>Id.</i> at 9.	Outcome	Placebo (N=175)	Ustekinumab, 90 mg every 12 wk (N=172)	Ustekinumab, 90 mg every 8 wk (N=176)	Clinical Remission	24.0	38.4	43.8	Maintenance of Clinical Response through Wk 44	44.6	68.0	71.0	Endoscopic Improvement	28.6	43.6	51.1	Corticosteroid-free Remission	23.4	37.8	42.0	Remission through Wk 44 among Those in Remission at Wk 0 in Maintenance Trial	38 (N=45)	65 (N=40)	58 (N=38)
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NCT-236 (Ex. 1003) Outcome Measures	Sands (Ex. 1301) Results
Maintenance Study - Number of Participants with Clinical Remission Among those who Achieved Clinical Remission at Maintenance Study Baseline [Time Frame: Through Week 44] “For the US Clinical remission is defined as absolute stool number ≤ 3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.”	“An alternative primary end point of clinical remission that excluded the subscore on the physician’s global assessment component of the Mayo scale was also prespecified to support the FDA submission. This definition required an absolute stool number of 3 or fewer (average daily stool number during 3 days before a visit), a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1.” Ex. 1031 at 3. “Among patients in clinical remission at baseline in the maintenance trial, the percentage who had maintenance of clinical remission through week 44 was not significantly higher among those receiving 90 mg of ustekinumab every 8 weeks than among those receiving placebo; <i>when the alternative definition of clinical remission was used, the percentage was significantly higher in both ustekinumab groups than in the placebo group.</i>” <i>Id.</i> at 9.
Maintenance Study - Number of Participants with Clinical Remission and not Receiving Concomitant Corticosteroids Among those Receiving Concomitant Corticosteroids at Maintenance Baseline [Time Frame: Week 44]	“Among patients <i>receiving corticosteroids at baseline</i>, the percentages of those who <i>discontinued corticosteroid use at least 90 days before week 44 were higher in the groups</i> that received 90 mg of <i>ustekinumab</i> every 12 weeks (67% [55 of 82 patients]) or every 8 weeks (77% [71 of 92]) <i>than in the placebo group</i> (44% [40 of 91]); 97.2% of patients in clinical remission at week 44 (both definitions) (139 of 143) were corticosteroid-free at week 44.” Ex. 1031 at 9.

148. Second, a POSA would have looked at other clinical trials for UC and FDA guidance. In order to evaluate the effectiveness of ustekinumab on UC, a

POSA would have turned to the endpoints reflected in FDA industry guidance set out in an August 2016 for phase 3 UC clinical trials. Ex. 1029 (Clinical Trial Endpoints) at 11-12. Other phase three clinical studies for drugs treating UC such as Remicade (infliximab), Humira (adalimumab), and Entyvio (vedolizumab) included identical or similarly defined outcomes. Ex. 1060 (Remicade Study); Ex. 1061 (Humira Study); Ex. 1062 (Entyvio Study). The Remicade Phase 3 study defined the “Primary Outcome Measures” as of March 6, 2008 to be “[t]he proportion of patients with clinical response, defined as a decrease from baseline in the Mayo score by = 30% and = 3 points, with a decrease in the rectal bleeding subscore of = 1 or a rectal bleeding subscore of 0 or 1, at week 8,” and “Secondary Outcome Measures” were defined as “Achievement of clinical remission defined as a Mayo score of = 2 points, with no individual subscore > 1 at week, [sic] Patients in remission will have a rectal bleeding subscore of either 0 or 1, patients who demonstrate mucosal healing at week 8.” Ex. 1060 at 1. The adalimumab and vedolizumab studies also defined primary outcomes based on Mayo scores and clinical remission. *See* Ex. 1061 at 1 (Humira Study disclosing a primary outcome measure as “Proportion of Participants Who Achieved Clinical Remission Per Mayo Score at Week 8”); Ex. 1062 (Entyvio Study disclosing a primary outcome measure as “Clinical response is defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from Baseline with an accompanying decrease in rectal

bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.”). 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 overlapping pathways.

149. Third, a POSA would have looked at other publications detailing the use of STELARA® for UC, such as Ochsenkühn. The fact that Ochsenkühn successfully treated UC patients, explicitly referenced the STELARA® clinical trials, and ultimately concluded “[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 given a POSA further assurance that the NCT-236 trial was likely to be successful. Ex. 1005 (Ochsenkühn) at 2; *see also* Ex. 1033; Ex. 1034, Ex. 1035; Ex. 1070.

150. In my opinion, a POSA’s reasonable expectation of success is also confirmed by PO’s admissions. In its Clinical Protocol, submitted to the FDA on April 20, 2016,¹⁵ PO stated that “[d]ata from completed Phase 2 studies of ustekinumab in Crohn’s disease, *along with the shared biology and the similar*

¹⁵ While Ex. 1027 does not appear to have been public as of April 20, 2016, I understand that it can be used as an admission by Patent Owner.

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 (Phase 3 Clinical Protocol) 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, 134-35.¹⁶ 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 (emphasis added).

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

151. Each of the independent claims recite limitations related to an actual treatment regimen. The treatment regimen in each of these claims, however, was

¹⁶ The '307 itself notes “biologic therapies that are currently approved for the treatment of UC have also demonstrated efficacy in Crohn's disease” and “[m]ultiple lines of evidence suggest that inflammatory bowel disease (UC and Crohn's disease) is mediated by TH1 or Th17 cells with strong contributions from the proinflammatory cytokines, IL-12, and IL-23” Ex.1001 at 2:38-45.

well-known and expressly disclosed in NCT-236 alone, as well as by the combination of NCT-236 in view of Ochsenkühn and Stelara-PI(2017).

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

152. Each independent claim of the '307 Patent recites the same preamble: “A method of treating moderately to severely active ulcerative colitis (UC) in a subject in need thereof, comprising.” In my opinion, this preamble language is disclosed by NCT-236, *see* Section VIII.A.1.a.

153. Ochsenkühn likewise discloses this preamble in its title, “[U]stekinumab as [a] rescue *treatment* in therapy-refractory or -intolerant [ulcerative colitis].” Ex. 1005 (Ochsenkühn) at 2. 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*.” *Id.* at 2. Accordingly, a POSA would understand that the common preamble of the independent claims is satisfied under this Ground 2.

b. administering a “pharmaceutical composition” comprising specific dosages (claim elements 1[a], 19[a], 33[a][c][d], 34[a][b])

154. In my opinion, all three references under Ground 2—NCT-236, Ochsenkühn, and/or Stelara-PI(2017)—independently and in combination disclose

and teach the claimed methods of administration of the independent claims. *See* Section VIII.A.1.b.

155. The four independent claims recite “administering to the subject an anti-IL-12/IL-23p40 antibody” in varying but substantially overlapping ways: claim 1 recites “administering to the subject a pharmaceutical composition comprising ... [an] amount of an anti-IL-12/IL-23p40 antibody,” claims 19 and 33 recite “intravenously administering to the subject an anti-IL-12/IL-23p40 antibody in a first pharmaceutical composition,” and claim 34 recites “intravenously administering to the subject an anti-IL-12/IL-23p40 antibody.” Ex. 1001 (’307 Patent) at 119:35-38, 121:38-46, 123:8-16, 124:12-23. In addition, while claim 1 does not contain specific dosage requirements, claim elements 19[a], 33[a], and 34[a] recite the following specific dosage limitations:

19[a]	33[a]	34[a]
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	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	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 ...	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 ...	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,
	33[c]	34[b]
	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,	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
	33[d]	
	and wherein the maintenance therapy is provided for 44 weeks	

156. Claim elements 19[a], 33[a][c][d], and 34[a][b]—and, therefore, also the more general “administering” limitation in claim 1—are met by NCT-236, Ochsenkühn, and/or Stelara-PI(2017). Claim elements 19[a], 33[a], 34[a] are disclosed as follows:

Claim Limitation (19[a], 33[a], 34[a])	NCT-236, Ochsenkühn, Stelara-PI(2017)
a. intravenously	NCT-236 (Ex. 1003)

administering to the subject an anti-IL-12/IL-23p40 antibody in a first pharmaceutical composition at <i>a dosage of about 6.0 mg/kg body weight</i> of the subject or 130 mg per administration <i>at week 0</i> of the treatment, and	Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive <i>ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0</i> . Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.											
	Ochsenkühn (Ex. 1005) All patients received ustekinumab as approved for Crohn’s disease (<i>6 mg/kg body weight as an infusion</i> and 90 mg ustekinumab as s.c. injection every 8 weeks).											
	Stelara-PI(2017) (Ex. 1004) 2.3 Crohn’s Disease Intravenous Induction Adult Dosage Regimen A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 [see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]. Table 1: Initial Intravenous Dosage of STELARA® <table><tr><th>Body Weight of Patient at the time of dosing</th><th>Dose</th><th>Number of 130 mg/26 mL (5 mg/mL) STELARA® vials</th></tr><tr><td>55 kg or less</td><td>260 mg</td><td>2</td></tr><tr><td>more than 55 kg to 85 kg</td><td>390 mg</td><td>3</td></tr><tr><td>more than 85 kg</td><td>520 mg</td><td>4</td></tr></table>	Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials	55 kg or less	260 mg	2	more than 55 kg to 85 kg	390 mg	3	more than 85 kg	520 mg
Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials										
55 kg or less	260 mg	2										
more than 55 kg to 85 kg	390 mg	3										
more than 85 kg	520 mg	4										
b. subcutaneously administering to the subject the anti-IL-12/IL-23p40 antibody in a second pharmaceutical composition at <i>a dosage of 90 mg per administration at week 8</i> of the treatment)	NCT-236 (Ex. 1003) Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44</i>.											

	<table><tr><th>Ochsenkühn (Ex. 1005)</th></tr><tr><td>All patients received ustekinumab as approved for Crohn’s disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).</td></tr></table>	Ochsenkühn (Ex. 1005)	All patients received ustekinumab as approved for Crohn’s disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).
	Ochsenkühn (Ex. 1005)		
	All patients received ustekinumab as approved for Crohn’s disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).		
<table><tr><th>Stelara-PI(2017) (Ex. 1004)</th></tr><tr><td><u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.</td></tr></table>	Stelara-PI(2017) (Ex. 1004)	<u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.	
Stelara-PI(2017) (Ex. 1004)			
<u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.			

Claim elements 33[c] and 34[b] are met as follows:

Claim Limitation (33[c], 34[b])	NCT-236, Ochsenkühn, Stelara-PI(2017)
followed by a maintenance therapy, wherein the maintenance therapy comprises subcutaneously administering to the subject the anti-IL-12/IL-23p40 antibody at <i>a dosage of 90 mg per administration, once every 8 weeks or once every 12 weeks</i>	NCT-236 (Ex. 1003)
	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w)
	Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks</i> , beginning Week 0 of Maintenance study through Week 44.
	Ochsenkühn (Ex. 1005)
	All patients received ustekinumab as approved for Crohn’s disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).

	<table><tr><th colspan="2">Stelara-PI(2017) (Ex. 1004)</th></tr><tr><td></td><td><u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.</td></tr></table>	Stelara-PI(2017) (Ex. 1004)			<u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
Stelara-PI(2017) (Ex. 1004)					
	<u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.				

157. For claim element 33[d], NCT-236 discloses maintenance therapy:

Claim Limitation (33[d])	NCT-236, Ochsenkühn, Stelara-PI(2017)
<i>wherein the maintenance therapy is provided for 44 weeks</i>	NCT-236 (Ex. 1003)
	Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.</i>

A POSA would understand that a maintenance dose as described in Ochsenkühn and Stelara-PI(2017) is to be continued indefinitely, provided there are no adverse events or other changes necessitating cessation of treatment. Accordingly, it is my opinion that NCT-236, Ochsenkühn, and Stelara-PI(2017) disclose the administering limitations in each of the independent claims—1[a], 19[a], 33[a][c][d], 34[a][b]—including the specific dosage claim elements 19[a], 33[a][c][d], and 34[a][b].

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

158. As I explain above, a POSA understood by September 24, 2018 that ustekinumab is an anti-IL-12/IL-23p40 antibody with an amino acid sequence that contains all of the SEQ IDs recited in claim elements 1[a], 19[a], 33[a], 34[a]. *See supra* Section IV.C and Section VII.A.1.c. Both NCT-236 and Ochsenkühn recite administering ustekinumab to treat UC. Ex. 1003; Ex. 1005. Thus, in my opinion, a POSA would understand that this Ground satisfies all limitations reciting an anti-IL-12/IL-23p40 antibody having the claimed SEQ IDs.

d. “clinically proven safe... amount” (claim 1[a])

159. In my opinion, a POSA would understand that the treatment regimen in NCT-236, Ochsenkühn, and Stelara-PI(2017) is “a clinically proven safe... amount of an anti-IL-12/IL-23p40 antibody” as recited in claim 1.

160. As explained in Section VIII.B.4.b, Ochsenkühn, and Stelara-PI(2017) disclose the same dosages as NCT-236. Therefore, as I discussed above in Section VIII.A.1.d, a POSA would consider the treatment regimen disclosed in NCT-236, Ochsenkühn, and Stelara-PI(2017) to be “clinically proven safe.”

e. “clinically proven effective amount” (claim 1[a])

161. NCT-236 alone discloses this limitation. *See supra* VIII.A.1.d. According to the '307 Patent, the term “clinically proven effective” “refer[s] to the effectiveness of a particular dose, dosage or treatment regimen” as measured, for

example, by “administer[ing] [ustekinumab] to a subject in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated.” Ex. 1001 (’307 Patent) at 9:11-38. Under this definition, a POSA would have reasonably expected that the treatment regimen in NCT-236, Ochsenkühn, and Stelara-PI(2017) would be “clinically proven effective” because Ochsenkühn expressly discloses that “[u]stekinumab was effective” in patients. Indeed, 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. 1001 (’307 Patent) at 9:11-38; Ex. 1005 (Ochsenkühn) at 2. Moreover, Ochsenkühn concludes, “It seems possible that large ongoing trials will confirm our findings and ustekinumab could become a new therapeutic option for refractory UC.” Ex. 1005 (Ochsenkühn) at 2.

162. In addition, my opinion is further supported by my analysis of the “responder” limitations below. *See* Section VIII.B.4.f. The ’307 Patent states that an “improvement” that shows “clinically proven effectiveness” “can be indicated by an improvement in an index of disease activity, by amelioration of clinical symptoms *or by any other measure of disease activity.*” Ex. 1001 at 9:36-38. As discussed for the “responder” limitations below, the disclosures in NCT-236,

Ochsenkühn, and Stelara-PI(2017) support a reasonable expectation that at least some patients that are given the treatment regimen described in the three references will show improvement based on one or more of the Seven Claimed Measures of Response. Under the '307 Patent's own definition, this is enough to show a reasonable expectation that the treatment regimen is "clinically proven effective."

(1) A POSA would have had a reasonable expectation of "clinically proven effective"

163. As discussed in Section VII, the patent also includes language suggesting "clinically proven effective" may be understood to require successful results from an approved trial. Ex. 1001 ('307 Patent) at 10:34-42 ("clinically proven' ... shall mean that it has been proven by a clinical trial wherein the clinical trial has met the approval standards [of a] . . . national regulatory agency"). Even assuming this interpretation were adopted, it is my opinion that a POSA would have had a reasonable expectation of successful clinical trial results for the claimed dosing regimen in treating UC.

164. As described in Section VIII.A.1.d, a POSA would have understood, prior to engaging in any human clinical trial, the researchers would have had sufficient data and analysis to support a belief that the trial will be successful. In that regard, the existence of the NCT-236 trial in and of itself is supportive of a belief that the treatment regimen could be successful. In my own experience, clinicians who are aware of clinical trials for an off-label use of a drug that is

already known to be safe and effective (as is the situation for ustekinumab for the treatment of UC in NCT-236) rely on the *existence* of the clinical trial itself, not the results ultimately found, in order to recommend the treatment option to their own patients. The fact that NCT-236 was a direct-to-Phase 3 clinical trial, in an advanced stage without having been stopped for futility or safety by September 24, 2018, and that the exact same Induction-Maintenance dosing regimen as was already approved for treating Crohn's (which shares the same underlying IL-12/IL-23p40 mechanism treated by ustekinumab), all support the reasonable expectation a POSA would have had that NCT-236 would meet its defined endpoints. A POSA would have therefore understood that the dosage disclosed in NCT-236, Ochsenkühn, and Stelara-PI(2017) was a "clinically proven effective amount."

165. In this instance a POSA would not only have been aware of the NCT-236 trial, but would also have been aware of Ochsenkühn's success in treating UC patients using the same claimed treatment regimen being tested in the trial. This additional data strongly bolsters a reasonable expectation that the NCT-236 trial would reach its defined endpoints. Indeed, the Ochsenkühn authors seem to have come to this conclusion: "It seems possible that large ongoing trials will confirm our findings and ustekinumab could become a new therapeutic option for refractory UC." Ex. 1005 (Ochsenkühn) at 2. Based on my understanding that the NCT-236 was the only FDA trial evaluating the efficacy of ustekinumab to treat

UC, 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 and therefore be “clinically effective.”

166. My analysis here is further supported by my analysis of the “responder” limitations below.

(2) The dependent claims support the conclusion that the regimen is safe and effective

167. As I discussed above in Section VIII.A.1.d, claim 7 is dependent on claim 6 and (through claim 4) dependent on independent claim 1:

4. The method of any one of claims 1-3...

6. The method of claim 4, wherein the antibody is administered intravenously to the subject at week 0 of the treatment, at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.

7. The method of claim 6, wherein the antibody is further administered subcutaneously to the subject at week 8 of the treatment, at a dosage of about 90 mg per administration.

Ex. 1001 ('307 Patent) at claims 4, 6 and 7.

168. The administration of ustekinumab taught by NCT-236, Ochsenkühn, and Stelara-PI(2017) satisfies dependent claims 6 and 7, as follows:

6. The method of claim 4, wherein the antibody is administered intravenously to the subject at week 0 of the treatment, at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.

NCT-236 (Ex. 1003)

Experimental: Induction Study - Ustekinumab 6 mg/kg IV

Participants will be randomized to receive ***ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0.*** Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.

Ochsenkühn (Ex. 1005)

All 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).

Stelara-PI(2017) Ex. (1004)

2.3 Crohn's Disease

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 [see *Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)*].

Table 1: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

7. The method of claim 6, wherein the antibody is further administered subcutaneously to the subject at week 8 of the treatment, at a dosage of about 90 mg per administration.	NCT-236 (Ex. 1003) Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8 or Week 16</i>) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.</i>
	Ochsenkühn (Ex. 1005) All patients received ustekinumab as approved for Crohn's disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).
	Stelara-PI(2017) (Ex. 1004) <u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

169. The administration methods taught by NCT-236, Ochsenkühn, and Stelara-PI(2017) disclose the same administration recited in claims 6 and 7. Accordingly, to the extent that the administration in claims 6 and 7 is considered “a clinically proven safe and clinically proven effective amount of an anti-IL-12/IL-23p40 antibody,” the administration in NCT-236, Ochsenkühn, and Stelara-PI(2017) must also be considered “a clinically proven safe and clinically proven

effective amount of an anti-IL-12/IL-23p40 antibody” as recited in claim element 1[a].

- f. “the subject is a responder to treatment by at least one measure of response to treatment selected from the group consisting of [the Seven Claimed Measures of Response]” (claim elements 1[c], 19[c], 33[e], 34[c])**

170. Claim elements 1[c], 19[c], 33[e], 34[c] recite that “[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” the following “Seven Claimed Measures of Response”):

- (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 $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.” (1[d])

See Ex. 1001 ('307 Patent) at 119:52-65 (1[b]), 121:59-122:17 (19[b]), 123:38-124:7 (33[b]), 124:31-47 (34[b]). Each of the Seven Claimed Measures of Response were set forth in NCT-236 as either Primary or Secondary Outcome Measures, and therefore this limitation is inherently disclosed by NCT-236. *See* Section VIII.A.1.e. As described below, it is also obvious in view of NCT-236.

171. Ochsenkühn also discloses that the aim was “[t]o assess the clinical outcomes achieved with ustekinumab as rescue treatment in therapy-refractory or -intolerant UC,” that the “primary outcome was achievement of clinical remission at 3 and 6 months,” found 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,” and concluded that “Ustekinumab was effective as rescue medication in therapy-refractory or -intolerant UC in a large IBD referral center.” Ex. 1005 (Ochsenkühn) at 2. Ochsenkühn’s finding thus provides additional support that each of the Seven Claimed Measures of Response were obvious.

172. In the following sections, I provide my analysis as to why a POSA would reasonably expect that within the NCT-236 clinical trial there would be responders that meet each of the Seven Claimed Measures of Response.

173. First, I explain why a POSA would have had a reasonable expectation that at least some patients would have responded with clinical remission as the Primary Outcome Measure of NCT-236 after both Induction and Maintenance. As

explained in detail below, clinical remission was not only the Primary Outcome Measure that NCT-236 was intended to establish at a clinical trial level, it was also the primary outcome demonstrated in Ochsenkühn. This strongly supports a reasonable expectation that UC patients treated with STELARA® (ustekinumab) according to the administration method of NCT-236, Ochsenkühn, and Stelara-PI(2017) would have responded to treatment with clinical remission.

174. Second, I explain why a POSA would have reasonably expected that at least some UC patients treated with STELARA® (ustekinumab) according to the administration method of NCT-236, Ochsenkühn, and Stelara-PI(2017) would have responded to treatment under the Secondary Outcome Measures in NCT-236. As set forth above, A POSA would have understood that the expectation of success that at least some patients would achieve clinical remission means that those same patients would also be expected to satisfy the Secondary Outcome Measures of NCT-236 because the Secondary Outcome Measures are either subparts of the Primary Outcome Measure for clinical remission (and hence would be met by clinical remission) and/or would reasonably be expected to correlate with clinical remission.

175. Accordingly, a POSA would have reasonably expected that at least some UC patients treated with ustekinumab would have been responders to treatment under the Primary Outcome Measures of NCT-236 and would therefore

also meet the Secondary Outcome Measures of NCT-236. Moreover, because a POSA would have recognized that the Secondary Outcome Measures of NCT-236 are lower thresholds of response in comparison to the Primary Outcome Measures of clinical remission, a POSA would have expected the number of UC patients meeting the Secondary Outcome Measures to be greater than the number that satisfied the Primary Outcome Measure of Clinical Remission.

176. In my opinion, the following analysis shows that a POSA would have had a reasonable expectation that the administration of STELARA® (ustekinumab) to UC patients according to the teachings of NCT-236, Ochsenkühn, and Stelara-PI(2017) would achieve responses that satisfy each of the Seven Claimed Measures of Response.

(1) A POSA would have reasonably expected responders with the clinical remission response measure in (i) of the independent claims

177. The first of the Seven Claimed Measures of Response is “(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.” A POSA would have understood that the highest threshold measure of response and the most favorable clinical outcome measure of treatment is clinical remission. Primary Outcome Measures “represent

the main reason the trial is being conducted.”¹⁷ Since one of the Primary Outcome Measures in NCT-236 included patients achieving clinical remission as a response to treatment both after Induction at week 8 and after Maintenance at week 44, and these results are expressly supported by the results of Ochsenkühn, a POSA would have expected such results:

	NCT-236 (Ex. 1003)
(i) [having a] 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,	Induction Study - Number of Participants With <i>Clinical Remission</i> [Time Frame: Week 8] The global definition of <i>Clinical remission is defined as Mayo score less than or equal to ($\leq$) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States (US). For the US, Clinical remission is defined as absolute stool number ≤ 3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.</i> Maintenance Study - Number of Participants with <i>Clinical Remission</i> Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44] The global definition of <i>Clinical remission is defined as Mayo score less than or equal to ($\leq$) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States (US). For the US Clinical remission is defined as absolute stool number ≤ 3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.</i>

¹⁷ Ex. 1030 (Smith) at 7-8.

	Ochsenkühn (Ex. 1005) The primary outcome was achievement <i>of clinical remission at 3 and 6 months</i>. <i>[C]linical remission was achieved in 65% (11/17) at 1, 3, and 6 months</i>, whereas only 35% (6/17) of patients were in remission at the start of the study. Conclusions: Ustekinumab was effective as rescue medication in therapy-refractory or -intolerant UC in a large IBD referral center.
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178. A POSA would have understood that the Primary Outcome Measures of the phase 3 NCT-236 clinical trial had been proposed and approved for evaluation by the FDA with a reasonable expectation that there would be at least some patients that satisfied the Outcome Measures, particularly considering the Outcome Measures in NCT-236 are standard measures used in clinical trials for UC. Ex. 1003 (NCT-236) at 1-2; Ex. 1029 (Clinical Trial Endpoints). As shown in the above chart, NCT-236 defines clinical remission according to the same measure recited in the claims: “The global definition of Clinical remission is defined as Mayo score less than or equal to ($\leq$) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States (US). For the US, Clinical remission is defined as absolute stool number ≤ 3 , a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.” Ex. 1003 (NCT-236) at 1-2.

179. A POSA would have understood that the primary outcome measures of a clinical trial “are the most important outcomes of the study, the ones that determine its design and the study size” and that “[t]hey represent the main reason the trial is being conducted.” Ex. 1030 (Smith) at 7-8. Clinicaltrials.gov further explains that the Primary outcome measure “is the most important for evaluating the effect of an intervention/treatment.” Ex. 1044, Glossary of Common Site Terms, ClinicalTrials.gov (Oct. 2021) at 14; *see also* Ex. 1045, Outcome Measure Considerations for Clinical Trials Reporting on ClinicalTrials.gov, Harvard Catalyst (July 11, 2018). A POSA would have understood that a Phase 3 clinical trial, such as NCT-236 would not have been proposed, pursued, and approved if there was not an expectation that at least some patients would achieve the Primary Outcome Measures.

180. Here, the Primary Outcome Measures of NCT-236 are identifying the number of patients with clinical remission after Induction at week 8 and at week 44 of Maintenance: “Induction Study - ***Number of Participants With Clinical Remission*** [Time Frame: Week 8]” and “Maintenance Study - ***Number of Participants with Clinical Remission*** Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44].” Ex. 1003 (NCT-236) at 1-2. A POSA would have understood from NCT-236 that the sponsor and the FDA proposed the “number of patients with clinical remission” because there

was a reasonable expectation that at least some number of patients receiving ustekinumab according to the treatment arm of the trial would achieve clinical remission. Or, put conversely, a POSA would have known that the Primary Outcome Measures of the Phase 3 NCT-236 clinical trial would not have been proposed and approved if there was no expectation that any patients would have achieved clinical remission after Induction and Maintenance. A POSA would have therefore inferred, based on the fact NCT-236 was an expensive, wide ranging, and substantial Phase 3 trial (as opposed to a preliminary investigational, Phase 1, or Phase 2 study), that there was a reasonable expectation by both the sponsor and the FDA that the Primary Outcome Measures would have been met by at least some patients.

181. In addition to the reasonable expectations arising from the outcomes proposed and approved for NCT-236 (and the advanced status of the NCT-236 trial as of September 24, 2018, as discussed below), Ochsenkühn's reported results would have further bolstered a POSA's confidence that patients would have been responders to treatment according to the Primary Outcome Measures. Ochsenkühn reported that the primary outcome of treatment of UC patients with ustekinumab was "clinical remission at 3 and 6 months." Ex. 1005 (Ochsenkühn) at 2; *see also id.* ("Including the three drop-outs, 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.”). Ochsenkühn’s reported data of clinical remission would have been another strong indicator that a POSA would have reasonably concluded that patients in NCT-236 were likewise achieving clinical remission under the definition set forth as the Primary Outcome Measure.

182. A POSA would have recognized that the patients in Ochsenkühn included patients that were refractory or intolerant to other forms of treatment: “All patients were intolerant or refractory to purine-analogues, TNF-antibody therapy, and the anti-integrin vedolizumab.” Ex. 1005 (Ochsenkühn) at 2; *see also id.* (“All patients (17/17) previously had been steroid-refractory or -dependant and had recently failed all of the following drugs: purine-analogues, anti-TNF-antibodies and anti-integrin-antibodies. Of those, 41% (7/17) had failed infliximab and either golimumab or adalimumab, and 29% (5/17) had also failed i.v. ciclosporine.”). As such, a POSA would have viewed Ochsenkühn’s conclusion that “[u]stekinumab was effective as rescue medication in therapy-refractory or -intolerant UC in a large IBD referral center,” as a powerful indicator of a significant patient response because UC patients refractory to available treatments are generally patients that are the least susceptible to responding to new and other treatments, particularly considering many treatments are—like ustekinumab—directed to disruption of the same IL-12/IL-23p40 pathway.

183. Ochsenkühn's measure of clinical remission also supports the reasonable expectation of success of UC patients receiving the same treatment under the Primary Outcome Measure of clinical remission in NCT-236. Ochsenkühn reports that clinical remission in his study was defined as "as score of ≤ 5 points in the modified Truelove and Witts colitis activity index (CAI)." Ex. 1005 (Ochsenkühn) at 2. Under this index, Ochsenkühn noted that "the CAI at the start of the therapy ranged between 1 and 11 with a median of 8" and that "[m]edian CAI at 4 weeks was 5 points (range 1–8)," "[m]edian CAI at 3 months was 4.5 points (range 0–9)," and "[m]edian CAI at 6 months was 2 points (range 0–7)." *Id.* A POSA reviewing this data would have recognized a strong initial response to IV Induction infusion as shown by the substantial drop in the initial median CAI score of 8 and the 4-week median CAI score of 5, thus further bolstering a POSA's reasonable expectation that at least some UC patients would have achieved the Primary Outcome Measure of clinical remission in NCT-236 after IV Induction infusion at week 8.

184. The further CAI scores at 3 months and 6 months reported by Ochsenkühn show a trend that a POSA would have understood was very typical of Induction-Maintenance treatments. The overall median CAI scores reported by Ochsenkühn were: 8 (week 0)→5 (week 4)→4.5 (3 months)→2 (6 months). The trend in median CAI score shows, as mentioned in the previous paragraph, a

substantial response of the patients to the IV Induction infusion of 6 mg/kg body weight ($\Delta = -3$), an intermediate period through 3 months with modest further improvement after Induction ($\Delta = -0.5$), and a substantially greater improvement to maintenance at 6 months ($\Delta = -2.5$). In my experience, the data disclosed in Ochsenkühn is consistent with the Induction-Maintenance responses observed in other UC successful treatments, as they also demonstrated a strong initial improvement response to the immediate IV Induction infusion dose followed by longer timeframes for further improvements over time with ongoing Maintenance dosing. Accordingly, evaluation of the median CAI scores of Ochsenkühn, which show an ongoing improvement over 6 months, would have also led a POSA to understand that the patients had continued responses to Maintenance dosing as shown by the median CAI of 2 after 6 months (i.e., 24 weeks). This also supports a POSA's reasonable expectation of success that at least some UC patients would meet the Primary Outcome Measure of clinical remission in NCT-236 after ongoing subcutaneous Maintenance injections at week 44.

185. In my opinion, that Ochsenkühn used the modified Truelove and Witts colitis activity index (CAI) as the basis for determining clinical remission would not impact a POSA's reasonable expectation of success that at least some UC patients treated with ustekinumab would have met the Primary Outcome Measure of clinical remission under NCT-236. The Primary Outcome Measures of

clinical remission in NCT-236 are based on either: (1) Mayo scores and subscores (Global definition); or (2) absolute stool number, Mayo subscores for rectal bleeding and endoscopy (US definition).

186. The modified Truelove and Witts CAI (also known as the Lichtiger Index), is a symptom-based measure of UC patients' response to treatment. Ex. 1042, D'Haens et al., *A Review of Activity Indices and Efficacy End Points for Clinical Trials of Medical Therapy in Adults With Ulcerative Colitis*, *Gastroenterology*, 132:763-86 (2007) ("D'Haens") at 3. It is based on 8 variables that include diarrhea (number of daily stools), nocturnal stools, visible blood in stool (percentage of movements), fecal incontinence, abdominal pain/cramping, general well-being, abdominal tenderness, and need for antidiarrheals. *Id.* The Mayo score is based on the total of four subscores: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy (endoscopy), and a Physicians General Assessment (PGA). *Id.* at 5. Although the modified Truelove and Witts measure used in Ochsenkühn does not include a direct input of endoscopic evaluation, a POSA would have known that there is overlap between the inputs to the modified Truelove and Witts measure (e.g., stool frequency and blood in the stool) and the Global definition of clinical remission (Mayo score: includes stool frequency and rectal bleeding) and the US definition of clinical remission (absolute stool number, Mayo subscore for rectal bleeding) of the Primary Outcome Measure of clinical

remission in NCT-236. Based on these shared inputs, a POSA would have expected similar response to treatment demonstrated by Ochsenkühn using the modified Truelove and Witts measure to also be reflected in the Primary Outcome Measures of NCT-236 under the Global and US definitions of Mayo-score-based clinical remission.

187. The advanced stage of the ongoing NCT-236 as of September 24, 2018 would have further bolstered a POSA's reasonable expectation that UC patients being treated with ustekinumab in NCT-236 were responders according to the Primary Outcome Measures of Clinical Remission after Induction and Maintenance therapy.

188. A POSA would have known that patient recruitment in NCT-236 began in October of 2015 and was closed by September 8, 2017, culminating with a total enrollment of 966 patients. *See* Ex. 1046 (History of Changes for Study NCT02407236); Ex. 1047 (History of Changes for Study 2 NCT02407236). Based on these dates and considering the trial testing protocol was at week 8 after Induction and after week 44 for Maintenance, a POSA would have recognized that the majority (if not all) of the 966 patients in the NCT-236 clinical trial would have already completed the 8-week Induction Study and the vast majority would have already completed the 44-week Maintenance Study portion of the trial by September 24, 2018. Accordingly, the fact that the NCT-236 had not been ceased

due to futility based on a lack of efficacy or for safety reasons as of September 24, 2018 would have further enhanced a POSA's confidence and reasonable expectation that at least some statistically significant number of patients evaluated under NCT-236 had satisfied the Primary Outcome Measure of clinical remission after both the IV Induction and subcutaneous Maintenance administrations of ustekinumab in comparison to placebo.

(2) A POSA would have reasonably expected responders with the response measure in (ii) of the independent claims

189. The Secondary Outcome Measure in NCT-236—endoscopic healing with a Mayo endoscopy subscore of 0 or 1—is identical to the claimed measure of response (ii):

Claim Limitation	NCT-236 (Ex. 1003)
(ii) [having an] endoscopic healing with a Mayo endoscopy subscore of 0 or 1,	Induction Study - Number of Participants With <i>Endoscopic Healing</i> [Time Frame: Week 8] Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be <i>defined as Mayo endoscopic subscore = 0 or 1.</i>
	Maintenance Study - Number of Participants with <i>Endoscopic Healing</i> Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44] Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be <i>defined as Mayo endoscopic subscore = 0 or 1.</i>

190. As noted above, a POSA would have reasonably expected that at least some patients would achieve clinical remission under the Primary Outcome Measure of NCT-236 and at least these patients would also satisfy the measure of “endoscopic healing with a Mayo endoscopy subscore of 0 or 1.” Ex. 1003 (NCT-236). The global definition of clinical remission includes a requirement of “no individual subscore greater than ($>$) 1” and the US definition requires “a Mayo endoscopy subscore of 0 or 1.” *Id.* Thus, a POSA would understand that, based on the definitions of clinical remission and endoscopic healing in the Outcome Measures of NCT-236, that the expectation that UC patients would have achieved clinical remission would necessarily require that the expectation for those same patients would necessarily include “endoscopic healing with a Mayo endoscopy subscore of 0 or 1.” Thus, the reasonable expectation of success set forth above with respect to clinical remission based on the Primary Outcome Measures also apply to the reasonable expectation of success in achieving the Secondary Outcome Measure of “endoscopic healing with a Mayo endoscopy subscore of 0 or 1.”

191. The absence of endoscopic scoring in Ochsenkühn’s results would not detract from or otherwise refute the reasonable expectation a POSA would have had for at least some UC patients achieving (or the Primary Outcome Measures of clinical remission in NCT-236). Although responses to individual scoring inputs

may vary with any individual given patient, a POSA would have generally expected that the strong symptom-based response reported by Ochsenkühn would also generally (though not absolutely) correlate with endoscopic improvement in the mucosa and with respect to the extent of active inflammation and healing. (See Ex. 1043, Dhanda et al., *Can Endoscopy Be Avoided in the Assessment of Ulcerative Colitis in Clinical Trials?*, *Inflamm Bowel Dis* 18(11):2056-62 (Nov. 2012) (“Dhanda”) at 4 (“[T]he endoscopic component of the Mayo score does not contribute additional information to the score, probably because the endoscopic appearance is tightly related to other components of the Mayo score.”); Ex. 1051 (Higgins) at 1 (“The endoscopy items in the invasive indices correlate with stool frequency and stool blood items.”); Ex. 1048, Kim et al., *Correlation between Histological Activity and Endoscopic, Clinical, and Serologic Activities in Patients with Ulcerative Colitis*, *Gastroenterology Research & Practice* (2016) (“Kim”) at 1-3, 6; Ex. 1056, Nakov et al., *Correlation between Ulcerative Colitis Endoscopic Index of Severity, Lichtiger Index and Fecal Calprotectin in Ulcerative Colitis Patients*, *Intern Med* (2017), at 3 (“[I]n our study the Lichtiger Index demonstrated a very good correlation with FC levels and endoscopic activity.”). Indeed, as I note above in Section IV.B, based on my experience during the relevant time period, a POSA would expect that at least 15-20% of the patients who experienced symptom-based responses in Ochsenkühn would also eventually experience

endoscopic and mucosal improvement, consistent with the results later reported in Sands. Moreover, a POSA would understand that for at least some of those patients the endoscopic and mucosal improvement would occur contemporaneously with symptom-based responses. Consequently, it is my opinion that Ochsenkühn's reported successful response of refractory UC patients with moderately to severely active disease to treatment with ustekinumab at 1, 3 and 6 months solidified a POSA's reasonable expectation that at least some UC patients treated with ustekinumab would have "endoscopic healing with a Mayo endoscopy subscore of 0 or 1" within the recited timeframe as well as clinical remission according to the Primary Outcome Measures of NCT-236.

(3) A POSA would have reasonably expected responders with the response measure in (iii) of the independent claims

192. NCT-236 includes a secondary outcome measure for "Number of Participants With Endoscopic Healing," and describes "[e]ndoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1." Ex. 1003 at 2. This claimed measure of response would also be necessarily satisfied by the reasonable expectation that at least some patients would have met the clinical remission Primary Outcome Measures of NCT-236 (*see supra* Section VIII.B.4.f(1)) and would have also thereby met the Secondary Outcome Measure of "endoscopic healing with a Mayo

endoscopy subscore of 0 or 1.” As noted, both clinical remission and endoscopic healing in NCT-236 are defined by a Mayo endoscopy subscore of 0 or 1. The patient entry conditions into NCT-236 required “a Screening endoscopy subscore of the Mayo score greater than or equal to ($\geq$) 2.” Ex. 1003 (NCT-236) at 4. Thus, the patients under study in NCT-236 had an initial Mayo endoscopy subscore of 2 or 3 prior to treatment and the reasonable expectation of having a “clinical response based on the Mayo endoscopy subscore” would necessarily be met by patients reasonably expected to satisfy clinical remission and endoscopic healing with a Mayo endoscopy subscore of 0 or 1 because both of those measures of response include an improvement in the endoscopy subscore (initial patient Mayo subscore: 2 or 3; response based on clinical remission or endoscopic healing with Mayo subscore: 0 or 1).

193. A POSA would have also reasonably expected that there would be at least some additional patients showing clinical response based on the Mayo endoscopy subscore that may not have achieved clinical remission or a Mayo subscore of 0 or 1 in response to treatment. In this regard, clinical response based on the Mayo endoscopy subscore would include patients within the trial that had an initial Mayo endoscopy subscore of 3 and, after treatment, had a Mayo endoscopy subscore of 2. Those additional patients would have “a clinical response the Mayo endoscopy subscore.” Accordingly, a POSA would have reasonably expected,

based on NCT-236, the status of the ongoing trial as of September 24, 2018, and the strong responses of UC patients to treatment with ustekinumab in Ochsenkühn, a larger pool of at least some patients responding to treatment based on a showing of “clinical response based on the Mayo endoscopy subscore” in comparison to clinical remission or endoscopic healing based on a Mayo endoscopic subscore of 0 or 1.

(4) A POSA would have reasonably expected responders with the response measure in (iv) of the independent claims

194. NCT-236 discloses the Secondary Outcome Measure of “Mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score [Time Frame: Week 8]” similar to claimed measure of response (iv):

Claim Limitation	NCT-236 (Ex. 1003)
(iv) [having] improvements from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score,	Induction Study - <i>Mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score</i> [Time Frame: Week 8] The IBDQ is a 32-item questionnaire for participants with Inflammatory Bowel Disease (IBD) that will be 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). The total score ranges from 32 to 224 with higher scores indicating better quality of life.

195. A POSA would have reasonably expected at least some UC patients to have an improvement in the baseline IBDQ score upon treatment with STELARA® (ustekinumab). The IBDQ, as described in NCT-236, is “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. 1003 (NCT-236) at 2.

196. As noted above, a POSA had a reasonable expectation of success that at least some patients would have achieved clinical remission under the Primary Outcome Measure of NCT-236. *See supra* Section VIII.B.4.f(1). The definition of clinical remission includes symptom-based measures that, with improvement, a POSA would have reasonably expected to correlate with improvements in the baseline IBDQ scores because clinical remission under the Primary Outcome Measures of NCT-236 has the same inputs as the IBDQ with respect to the functioning of the bowel (i.e., frequency of stools and bloody stools). It would be merely a matter of common sense that improvements in symptoms would correlate with improvements in the IBDQ.

197. Furthermore, Ochsenkühn’s successful treatment of patients and achievement of clinical remission under the symptom-based modified Truelove and Witts scores would also have given a POSA a reasonable expectation of

improvement in at least some UC patients' IBDQ scores after being treated with STELARA® (ustekinumab). Ochsenkühn showed that the overall median scores improved both from baseline (score: 8) after Induction (score: 5) and Maintenance at 6 months (score: 2). *See* Ex. 1005 (Ochsenkühn) at 2. The strong improvements in the symptoms of a UC patient after being treated with STELARA® (ustekinumab) in Ochsenkühn would be expected to directly correlate with the quality-of-life assessment measured by an IBDQ. This is especially true considering the IBDQ has some of the same inputs as the modified Truelove and Witts score in Ochsenkühn. Accordingly, in my opinion, a POSA would have reasonably expected success in achieving an improvement in the IBDQ scores for at least some UC patients.

(5) A POSA would have reasonably expected responders with the response measure in (v) of the independent claims

198. A POSA would have reasonably expected that at least some UC patients treated with STELARA® (ustekinumab) would have responded to treatment with mucosal healing. As previously noted, a POSA would have reasonably expected at least some patients to have achieved the Primary Outcome Measures of clinical remission in NCT-236 after an IV Induction infusion and/or after subcutaneous Maintenance injections every 8 weeks through week 44. *See supra* Section VIII.B.4.f(1). As previously noted, a POSA would have reasonably

expected at least some patients to have responded to treatment by having endoscopic healing. *See supra* Section VIII.B.4.f(2). A POSA would have reasonably expected that a patient response of clinical remission and endoscopic healing (i.e., an endoscopic improvement in the appearance of the mucosa) would reasonably indicate mucosal healing, as demonstrated by the Secondary Outcome Measure of NCT-236:

Claim Limitation	NCT-236 (Ex. 1003)
(v) [having a] mucosal healing,	Endoscopic healing is <i>improvement in the endoscopic appearance of the mucosa</i> . It will be defined as Mayo endoscopic subscore = 0 or 1.

199. Although mucosal healing can be also assessed by histological analysis, a POSA would have reasonably expected that, in addition to endoscopically observed mucosal healing (as described in NCT-236), a POSA could also determine that mucosal healing occurred based on relieved clinical symptoms (i.e., according to Ochsenkühn). A POSA would have understood that both endoscopic and clinical measures of response observed in patients would generally be correlated with the histological activity associated with inflammation of the mucosa, such that a POSA would reasonably expect mucosal healing to be present in UC patients showing endoscopic and clinical improvements upon treatment:

Histological scores exhibited strong correlation with endoscopic subscores...

Histological activity was closely correlated with the endoscopic, clinical, and serologic UC activities.

[M]ucosal healing is reported to be associated with sustained clinical remission, decreased need for surgery

Several studies have already demonstrated that endoscopic findings are correlated with clinical and serologic disease activities [14-17].

Our results indicate that histological activity was most closely correlated with endoscopic activity in patients with UC.

In addition, we found a significant correlation between the Mayo endoscopic subscore and histological activity, with excellent specificity and sensitivity for a Mayo endoscopic subscore cut-off value of 1.

In conclusion, our results demonstrated that the histological activity exhibited strong correlation with the endoscopic activity and moderate correlation with the clinical and serologic activities in patients with UC.

Ex. 1048 (Kim) at 1-3, 6.

200. Since a POSA would have reasonably expected at least some UC patients to be responders to treatment with clinical remission under the Primary Outcome Measures of NCT-236 and clinical remission according to the symptom-based measure used in Ochsenkühn, a POSA would have reasonably expected at least some UC patients to also satisfy the claimed measure of mucosal healing.

(6) A POSA would have reasonably expected responders with the response measure in (vi) of the independent claims

201. A POSA would have had a reasonable expectation that at least some UC patients treated with STELARA® (ustekinumab) would have shown “a

decrease from baseline in the Mayo score” (claimed measure of response vi). This is one of the more easily met of the seven measures of response in the claims and would therefore necessarily have been satisfied by UC patients that had achieved clinical remission under the Primary Outcome Measures of NCT-236, patients with endoscopic healing, and patients who showed improvement of symptoms as reported by Ochsenkühn, as described above, since each of those measures would correlate with a decrease in the baseline Mayo score with treatment. *See supra* Sections VIII.B.4.f, VIII.B.4.f(1)-(2).

202. Indeed, a POSA would have understood that the data reported in Ochsenkühn *alone* would have correlated with a decrease from baseline in the Mayo score. As previously noted, Ochsenkühn reported significant clinical response by the 17 UC patients treated with ustekinumab, noting “achievement of clinical remission at 3 and 6 months” based on a “score of ≤ 5 points in the modified Truelove and Witts colitis activity index (CAI).” Ex. 1005 (Ochsenkühn) at 2. A POSA would have understood that a score of ≤ 5 points the Truelove and Witts CAI showed promising responsiveness to treatment and translated effectively to a reduced Mayo score from baseline.

203. The modified Truelove and Witts CAI score (also referred to as the “Lichtiger Index”) has eight input parameters: “diarrhea (number of daily stools), nocturnal stools, visible blood in stool (percentage of movements), fecal

incontinence, abdominal pain/cramping, general well-being, abdominal tenderness, and need for antidiarrheals.” Ex. 1042 (D’Haens) at 3. Ochsenkühn shows that the median score of the patients decreased substantially from a median of 8 at the start of treatment to median values of 5, 4.5, and 2 after 1, 3, and 6 months, respectively. Ex. 1005 (Ochsenkühn) at 2. Based on the substantial decrease in the median scores reported by Ochsenkühn, a POSA would have understood that the patients had achieved improvement in their symptoms, including the number of stools and blood in the stool.

204. A POSA would have also understood that the decrease in the modified Truelove and Witts CAI score correlates with a reduction in the baseline Mayo score because both share the same input parameters of stool frequency and rectal bleeding/bloody stool. The Mayo score is the sum of 4 subscores—each individually rated on a scale of 0-12—of stool frequency, rectal bleeding, findings of endoscopy, and a physician’s global assessment. Ex. 1001 (’307 Patent) at 9:39-44; Ex. 1043 (Dhanda) at 2, Table 1. In my opinion, a POSA would have also reasonably expected that the responders in Ochsenkühn, who had a substantial decrease in the modified Truelove and Witts CAI score, would also have had a reduction in their baseline Mayo score.

(7) A POSA would have reasonably expected responders with the response measure in (vii) of the independent claims

205. The Secondary Outcome Measures of Clinical Response at week 8 after IV Induction infusion and at week 44 after subcutaneous Maintenance injections in NCT-236 is defined identically to the claimed “clinical response” measure of the claims (vii):

Claim Limitation	NCT-236 (Ex. 1003)
(vii) [in] clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.	Induction Study - Number of Participants with <i>Clinical Response</i> [Time Frame: Week 8] <i>Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to ($\geq$) 30 percent (%) and ≥ 3 points, with either a decrease from induction baseline in the rectal bleeding subscore ≥ 1 or rectal bleeding subscore = 0 or 1.</i>
	Maintenance Study - Number of Participants with <i>Clinical Response</i> Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Through Week 44] <i>Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to ($\geq$) 30 percent (%) and ≥ 3 points, with either a decrease from Induction baseline in the rectal bleeding subscore ≥ 1 or rectal bleeding subscore = 0 or 1.</i>

206. As noted above, a POSA would have reasonably expected that at least some patients would achieve clinical remission under the Primary Outcome Measures of NCT-236 after Induction (week 8) and Maintenance (week 44). A

POSA would have understood that the defined “clinical response” is a lower threshold measure than “clinical remission” according to the Primary Outcome Measures of NCT-236. Thus, at least those patients that would have been reasonably expected to be responders with clinical remission would satisfy the measure of “clinical response as determined by a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points and a decrease from baseline in the rectal bleeding subscore ≥ 1 points or a rectal bleeding subscore of 0 or 1.”

207. A POSA would have further understood that the NCT-236 clinical trial was designed such that patients would only enter the Maintenance study if they demonstrated a clinical response to Induction treatment at week 8 (or week 16 for “delayed-responders”):

Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w)
Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.

Ex. 1003 (NCT-236) at 3 (annotated).

208. A POSA would have understood, based on the design of NCT-236, that there was a reasonable expectation that at least some patients receiving an IV Induction infusion would have responded with a clinical response. A POSA would have further reasonably expected that patients in NCT-236 would have a clinical response to IV Induction infusion of ustekinumab based on the effective treatment

results reported by Ochsenkühn at week 4. As Ochsenkühn noted for the 17 treated patients (11 of which had moderately to severely active UC), the modified Truelove and Witts score went from a median baseline score of 8 to a median baseline score of 5 at week 4 (i.e., 4 weeks after infusion). A POSA would have reasonably expected that the improvement in the scores reported by Ochsenkühn was a strong indication of clinical response, thereby bolstering the reasonable expectation that at least some patients would have had a clinical response to Induction treatment at week 8 (or a delayed-response at week 16) according to the Secondary Response Measure of NCT-236 (i.e., claimed response vii).

209. Ochsenkühn's results also would also have further supported a POSA's reasonable expectation of at least some UC patients satisfying the Secondary Outcome Measure of clinical response to Maintenance treatment at week 44 in NCT-236. Ochsenkühn disclosed a median baseline score of 8 and a median score of 2 at 6 months for patients receiving Maintenance therapy. Ex. 1005 (Ochsenkühn) at 2. The substantial improvement shown by Ochsenkühn at 6 months relative to baseline would have further supported a POSA's reasonable expectation that at least some UC patients treated with Maintenance therapy would have met the clinical response Secondary Outcome Measure outcome measure after 44 weeks of treatment.

210. In sum, it is my opinion that a POSA as of September 24, 2018 would have had a reasonable expectation that there would be at least some UC patients with moderately to severely active disease treated with STELARA® (ustekinumab) according to the Induction-Maintenance method of NCT-236, Ochsenkühn, and Stelara-PI(2017) that would have been responders to treatment according to each of the seven measures of response recited in the independent claims of the '307 Patent.

- g. “the subject . . . had previously failed or was intolerant of at least one therapy selected from the group consisting of: an anti-TNF, vedolizumab, corticosteroids, azathioprine (AZA), and 6 mercaptopurine (6 MP), or the subject had demonstrated corticosteroid dependence” (claim element 19[d])**

211. Claim element 19[d] is disclosed by NCT-236. See supra Section VIII.A.1.f.

212. I also note that Ochsenkühn expressly stated that “[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 (Ochsenkühn) at 2.

213. It is thus my opinion that Ground 2 satisfies claim element 19[d]. Accordingly, a POSA would consider claim 19 obvious in view of Ground 2.

5. Dependent Claims 2-3, 20-21

214. In my opinion, a POSA would have understood that the amino acid sequences recited in claims 2-3 and 21-22 are sequences within ustekinumab, and that those sequences were publicly known as of the priority date. *See supra* Section IV.C; *see also* Appendix I, Sections C-F. In my opinion, these claims are inherently disclosed by NCT-236, *see* Section VIII.A.2.

6. Dependent Claims 4 and 22

215. In my opinion, this claim is inherently disclosed by NCT-236, which discloses (via incorporation by reference) that the ustekinumab used was STELARA®. Because the formulation of STELARA® was known, *see* Stelara-PI(2017), NCT-236 discloses these claims. *See* Section VIII.A.3. Additionally, even if NCT-236 does not expressly disclose that the ustekinumab used was STELARA®, these claims would have also been obvious because they recite a formulation that was already known and disclosed for STELARA® (ustekinumab) in Stelara-PI(2017). Should the Board find that NCT-236 does not teach the use of STELARA® either by incorporation or inherently, a POSA would nevertheless find it obvious to use STELARA® as the form of ustekinumab used to treat UC as STELARA® was the only commercially available ustekinumab, was manufactured

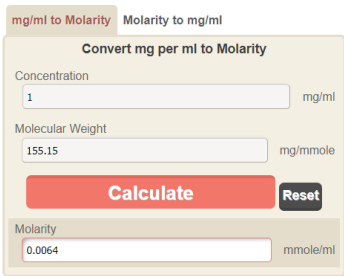
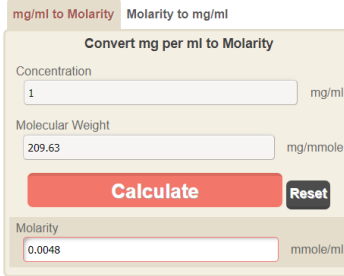
by NCT-236's sponsor, Janssen, and was the only FDA approved formulation of ustekinumab for IV administration. *See* Section VIII.A.3.

7. Dependent Claims 5 and 23

216. Claims 5 and 23 depend from claims 1-3 and 22, respectively, which, as I explained above, are anticipated and/or rendered obvious by NCT-236, Ochsenkühn, and Stelara-PI(2017). *See* Sections VIII.A and VIII.B. Claim 5 depends on the method of any one of claims 1-3, and claim 23 depends on claim 22, and both recite, “wherein the [antibody is in a]/[] pharmaceutical composition for subcutaneous administration [comprising]/[further comprises] a solution comprising 6.7 mM L-histidine, 7.6% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0,” respectively. Ex. 1001 ('307 Patent) at claims 5, 23.

217. Stelara-PI(2017) discloses “STELARA® for Subcutaneous Use” available as 90 mg of ustekinumab in 1 mL supplied in a single-dose prefilled syringe with the composition: “L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).” Ex. 1004 at 16. A POSA administering STELARA® to UC patients according to the treatment regimen disclosed in Stelara-PI(2017) for Crohn's patients would naturally have used the readily available composition disclosed in that label and already clinically proven to be safe. Further, NCT-236 discloses the same subcutaneous dosage as Stelara-PI(2017), *see* Sections VIII.A.1.b and VIII.B.4.b, therefore a POSA would

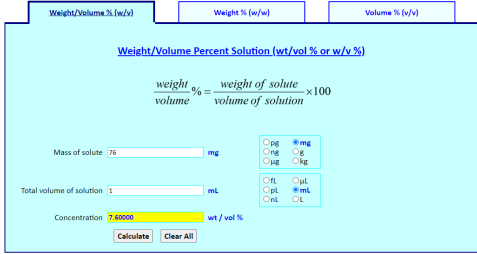
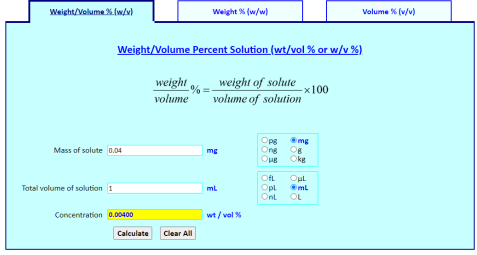
be motivated to use the same or a similar formulation. Simple math shows that this formulation discloses the same ingredients as claims 5 and 23 and in the same amounts, except for L-histidine, which Stelara-PI(2017) teaches at a range of 4.8 to 6.4 mM.¹⁸ Ex. 1004 at 16:

STELARA® IV Infusion – Histidine: mg/ml to mM					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ¹⁹
L-histidine	1	1	1	155.15	 0.0064 M = 6.4 mM
L-histidine hydrochloride monohydrate	1	1	1	209.63	

¹⁸ Stelara-PI(2017) does not disclose the relative proportions of L-histidine and L-histidine monohydrochloride monohydrate. For this reason, I calculate the mM of total L-histidine, assuming all L-histidine is in one form or the other, and therefore mathematically the final molarity will fall between the two values.

¹⁹ <https://www.easycalculation.com/chemistry/mg-per-ml-to-molarity.php> (mg/mL to M).

STELARA® IV Infusion – Histidine: mg/ml to mM					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ¹⁹
					0.0048 M = 4.8 mM
L-histidine (range)					4.8- 6.4 mM

STELARA® Label (mg)	Concentration – Calculated (1 ml)	Claims 5 and 23
sucrose (76 mg) ²⁰		7.6% (w/v) sucrose
Polysorbate 80 (0.04 mg) ²¹		0.004% (w/v) polysorbate 80

²⁰ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v).

²¹ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v)

218. In my experience, a range of 4.8 - 6.4 mM L-histidine, as taught by Stelara-PI(2017), renders obvious the claimed 6.7 mM L-histidine. The '307 explains that, "histidine and histidine monohydrochloride hydrate" are "buffering components" which are "preferably added to provide improved pH control," and states that "[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. Stelara-PI(2017) also discloses a "pH of 5.7-6.3." Ex. 1004 at 16. Since the patent 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 as POSA would be able to determine an optimized pH and L-histidine concentration through known routine optimization methods.

219. My conclusion is further bolstered by other formulations of the same anti-IL-12/IL-23p40 antibody in the prior art that disclose a range of L-histidine encompassing the claimed amount. I understand that the U.S. Patent Publication No. US 2009/0181027, titled "Anti-IL-12/23p40 Antibodies, Epitopes, Formulations, Compositions, Methods and Uses," and published July 16, 2009, and thus qualifies as prior art under 35 U.S.C. § 102(a)(1) because it was published prior to September 24, 2018. Ex. 1025 at 1. I further understand that the Examiner did not consider the '027-Publication during prosecution. The '027-Publication

shows on its face that the correspondence address is Johnson & Johnson, PO's parent organization. Ex. 1025 at 1. The '027-Publication discloses all Heavy and Light Chain CDR Sequences, as well as the Variable Region Sequence for both the Heavy and Light Chain of ustekinumab. *See* Appendix I. The '027-Publication also describes that "The invention provides pharmaceutical compositions comprising various formulations useful and acceptable for administration to a human or animal patient. Such pharmaceutical compositions are prepared using water at 'standard state' as the diluent and routine methods well known to those of ordinary skill in the art. For example, buffering components such as histidine and histidine monohydrochloride hydrate, may be provided first followed by the addition of an appropriate, non-final volume of water diluent, sucrose and polysorbate 80 at 'standard state.'" Ex. 1025 at [186]. The '027-Publication states "the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.'" Ex. 1025 at [177]. The '027-Publication therefore supports my opinion that a POSA would have optimized the formulation of Stelara-PI(2017) to reach the formulations of claims 5 and 23:²²

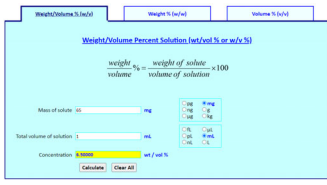
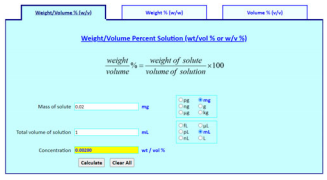
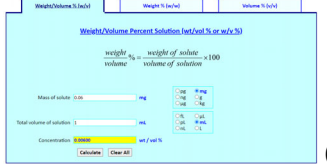
²² The same mathematical conversions as used in ¶230 were applied herein to

'027-Publication (Ex. 1025 at [0023])					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ²³
L-histidine	0.27 to about 0.80 mg per ml	1	0.27 to 0.80	155.15	mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 0.27 mg/ml Molecular Weight 155.15 mg/mmol Calculate Reset Molarity 0.0017 mmole/ml 0.0017 M = 1.7 mM mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 0.8 mg/ml Molecular Weight 155.15 mg/mmol Calculate Reset Molarity 0.0052 mmole/ml 0.0052 M = 5.2 mM
L-histidine hydrochloride monohydrate	0.69 to about 2.1 mg per ml	1	0.69 to 2.1	209.63	mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 0.69 mg/ml Molecular Weight 209.63 mg/mmol Calculate Reset Molarity 0.0033 mmole/ml 0.0033 M = 3.3 mM mg/ml to Molarity Molarity to mg/ml Convert mg per ml to Molarity Concentration 2.1 mg/ml Molecular Weight 209.63 mg/mmol Calculate Reset Molarity 0.01 mmole/ml 0.01 M = 10 mM

convert the disclosed mg to mM and %(w/v).

²³ <https://www.easycalculation.com/chemistry/mg-per-ml-to-molarity.php> (mg/mL to M).

'027-Publication (Ex. 1025 at [0023])					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ²³
L-histidine (total)					1.7 mM + 3.3 mM = 5.0 mM 5.2 mM + 10 mM = 15.2 mM

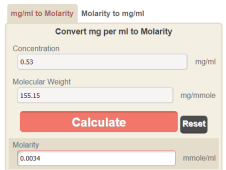
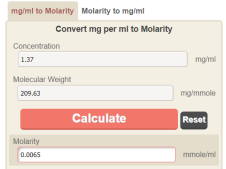
'027-Publication (Ex. 1025 at [0023])	Concentration – Calculated (1 ml)	Claims 5 and 23
sucrose (65 to about 87 mg) ²⁴	 6.5% (w/v)  8.7% (w/v)	7.6 % (w/v) sucrose
Polysorbate 80 (0.02 to about 0.06 mg) ²⁵	 0.002% (w/v)  0.006% (w/v)	0.004 (w/v) polysorbate 80

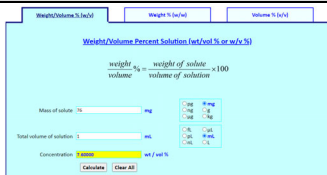
²⁴ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v).

²⁵ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

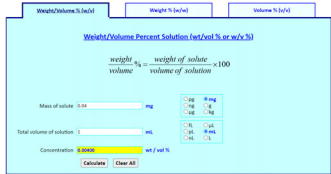
(mg/mL to w/v)

'027-Publication (Ex. 1025 at [0025])					
Component	Mass (mg)	Vol. (ml)	Conc (mg/ml)	MW (g/mol)	Molarity ²⁶
L-histidine	0.53 mg per ml	1	0.53	155.15	 0.0034 M = 3.4 mM
L-histidine hydrochloride monohydrate	1.37 mg per ml	1	1.37	209.63	 0.0065 M = 6.5 mM
L-histidine (total)					3.4 mM + 6.5 mM = 9.9 mM

'027-Publication (Ex. 1025 at [0025])	Concentration – Calculated (1 ml)	Claims 5 and 23
sucrose (76 mg) ²⁷	 7.6% (w/v)	7.6 % (w/v) sucrose

²⁶ <https://www.easycalculation.com/chemistry/mg-per-ml-to-molarity.php> (mg/mL to M).

²⁷ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html (mg/mL to w/v).

'027-Publication (Ex. 1025 at [0025])	Concentration – Calculated (1 ml)	Claims 5 and 23
Polysorbate 80 (0.04 mg) ²⁸	 0.004% (w/v)	0.004 (w/v) polysorbate 80

In summary, the formulations of claims 5 and 23 are rendered obvious by Stelara-PI(2017) and the '027-Publication as follows:

	Claims 5/23	Stelara-PI(2017)	'027-Publication [0023]	'027-Publication [0025]
L-histidine	6.7 mM L-histidine	4.8- 6.4 mM L-histidine	1.7 to 5.2 mM L-histidine 3.3 to 10 mM 0.69 L-histidine monohydrochloride monohydrate Total = 5-15.2 mM	3.4 mM L-histidine 6.5 mM L-histidine monohydrochloride monohydrate Total = 9.9 mM
sucrose	7.6% (w/v)	7.6% (w/v)	6.7-8.7% (w/v)	7.6% (w/v)
Polysorbate 80	0.004% (w/v)	0.004% (w/v)	0.002 to 0.006% (w/v)	0.004% (w/v)

220. Since the concentrations within the '027-Publication overlap with the concentrations claimed in the '307 Patent, they demonstrate that even if the ranges of Stelara-PI(2017) themselves do not render the concentrations of the '307 Patent

²⁸ https://www.physiologyweb.com/calculators/percent_solutions_calculator.html

(mg/mL to w/v)

obvious, a POSA would be able to determine similar concentrations through routine optimization.

8. Dependent Claim 6

221. In my opinion, this claim is disclosed by NCT-236, *see* Section VIII.A.4, as well as by Stelara-PI(2017) and Ochsenkühn:

6. The method of claim 4, wherein the antibody is administered intravenously to the subject at week 0 of the treatment, at a dosage of about 6.0 mg/kg body weight of the subject or 130 mg per administration.	NCT-236 (Ex. 1003) Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive <i>ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0</i>. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.												
	Ochsenkühn (Ex. 1005) All patients received ustekinumab as approved for Crohn’s disease (<i>6 mg/kg body weight as an infusion</i> and 90 mg ustekinumab as s.c. injection every 8 weeks).												
	Stelara-PI(2017) (Ex. 1004) 2.3 Crohn’s Disease <u>Intravenous Induction Adult Dosage Regimen</u> A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 [see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]. Table 1: Initial Intravenous Dosage of STELARA® <table><tr><th>Body Weight of Patient at the time of dosing</th><th>Dose</th><th>Number of 130 mg/26 mL (5 mg/mL) STELARA® vials</th></tr><tr><td>55 kg or less</td><td>260 mg</td><td>2</td></tr><tr><td>more than 55 kg to 85 kg</td><td>390 mg</td><td>3</td></tr><tr><td>more than 85 kg</td><td>520 mg</td><td>4</td></tr></table>	Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials	55 kg or less	260 mg	2	more than 55 kg to 85 kg	390 mg	3	more than 85 kg	520 mg	4
	Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials										
55 kg or less	260 mg	2											
more than 55 kg to 85 kg	390 mg	3											
more than 85 kg	520 mg	4											

9. Dependent Claim 7

222. In my opinion, claim 7 is disclosed by NCT-236, *see* Section VIII.A.5, as well as by Stelara-PI(2017) and Ochsenkühn. Dependent Claim 7:

7. The method of claim 6, wherein the antibody is further administered subcutaneously to the subject at week 8 of the treatment, at a dosage of about 90 mg per administration.	NCT-236 (Ex. 1003) Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (<i>at Week 8</i> or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to <i>receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.</i>
	Ochsenkühn (Ex. 1005) All patients received ustekinumab as approved for Crohn's disease (6 mg/kg body weight as an infusion and <i>90 mg ustekinumab as s.c. injection every 8 weeks</i>).
	Stelara-PI(2017) (Ex. 1004) <u>Subcutaneous Maintenance Adult Dosage Regimen</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

10. Dependent Claim 8

223. Claim 8 recites the same limitation as 19[d], which I discuss above in in Section VIII.B.4.g In my opinion, this claim is disclosed by NCT-236, *see* Section VIII.A.6, as well as by Ochsenkühn, *see* Section VIII.B.4.g.

11. Dependent Claim 9

224. In my opinion, claim 9 is disclosed by NCT-236, *see* Section VIII.A.7, as well as by Stelara-PI(2017) and Ochsenkühn. The dosage regimen of

Claim 9 was expressly disclosed in NCT-236, Ochsenkühn, and Stelara-PI(2017), and it is my opinion that a POSA would understand that at least some UC patients would be responders to treatment under this dosing regimen. Claim 9 recites “[t]he 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 (’307 Patent) at 120:62-65. 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 (Stelara-PI(2017)) at 4. Ochsenkühn similarly discloses that “All 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 (Ochsenkühn) at 2.

12. Dependent Claims 10, 12-16, 18

225. In my opinion, these claims are disclosed by NCT-236, *see* Section VIII.A.8, as well as by Ochsenkühn. A POSA would have understood claims 10, 12-16, and 18 to be obvious because they reflect what a POSA would have expected to see in patient responses through Maintenance therapy. Dependent claims 10, 12-16, 18 each recite that the subject is identified as having achieved each of the individual seven claimed measures, respectively, “continues/continuing at least 44 weeks after week 0.” Ex. 1001 (’307 Patent) at 120:66-121:3, 121:7-23,

121:29-34. As I explain above in Section VIII.B.3 with respect to a reasonable expectation that at least some UC patients would be responders to treatment and, in Section VIII.B.4.f 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 remission following the treatment disclosed in NCT-236. This expectation is supported by the Primary and Secondary Outcome Measures of NCT-236 and bolstered by Ochsenkühn's demonstrated effectiveness of ustekinumab by achieving and teaching 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" for UC patients that were refractory to other therapies. Ex. 1005 (Ochsenkühn) at 2. In my opinion, given the success of treating Crohn's patients with ustekinumab, a POSA would have understood that Crohn's patients had experienced remissions lasting at least through 44 weeks of treatment.

13. Dependent Claim 11

226. In my opinion this claim is disclosed by NCT-236, *see* Section VIII.A.9, as well as by Ochsenkühn. NCT-236 and Ochsenkühn both disclose the patient population identified in claim 11. Claim 11 recites "[t]he method of claim 9, wherein the subject is in corticosteroid-free clinical remission at least 44 weeks after week 0." Ex. 1001 ('307 Patent) at 121:4-6. A POSA would have known that corticosteroid-free clinical remission at week 44 was a Secondary Outcome

Measures for the Maintenance Study of NCT-236 and the patient inclusion criteria included patients that were corticosteroid intolerant and Ochsenkühn treated patients that were steroid refractory:

11. The method of claim 9, wherein the subject is in corticosteroid-free clinical remission at least 44 weeks after week 0.	
	NCT-236 (Ex. 1003)
	Maintenance Study - <i>Number of Participants with Clinical Remission and not Receiving Concomitant Corticosteroids</i> Among those Receiving Concomitant Corticosteroids at Maintenance Baseline [Time Frame: <i>Week 44</i>]
	Inclusion Criteria: a. Inadequate response to or <i>failure to tolerate current treatment with oral corticosteroids</i> or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]) OR b. <i>History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids</i> or immunomodulators (6-MP or AZA).
	Ochsenkühn (Ex. 1005)
	RESULTS: A total of 17 UC patients were treated with ustekinumab. <i>All patients (17/17) previously had been steroid refractory</i> or -dependent and had recently failed all of the following drugs: purine-analogues, anti-TNF-antibodies and anti-integrin-antibodies.

227. As stated in NCT-236 and Ochsenkühn, a POSA would have found it obvious to identify and treat UC patients with ustekinumab that were corticosteroid intolerant or dependent. Based on the results of clinical remission reported by Ochsenkühn and as I set forth above in Section VIII.B.4.f, a POSA would have had

a reasonable expectation that at least at least some UC patients would be in clinical remission by week 44 and would also be corticosteroid-free. In my opinion this claim is disclosed by NCT-236, *see* Section VIII.A.9, as well as by Ochsenkühn.

14. Claims 17, 30

228. NCT-236 alone renders this claim anticipated. *See supra* Section VIII.A.10. Nevertheless, these claims would have been obvious to a POSA. Claims 17 and 30 recite: “wherein the subject is identified as having a normalization of one or more biomarkers selected from the group consisting of C-reactive protein, fecal lactoferrin and fecal calprotectin [continuing at least 44 weeks after week 0]/[by week 16 of the treatment]” respectively. 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, 13. To the extent NCT-236 does not anticipate claims 17 and 30, it renders them obvious as a POSA would have understood that “Sponsors 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. 1029 (Clinical Trial Endpoints) at 14. In my opinion, these claims are disclosed or rendered obvious by NCT-236.

15. Dependent Claims 24-29, 31

229. In my opinion this claim is disclosed by NCT-236, *see* Section VIII.A.11, as well as by Ochsenkühn. Dependent claims 24-29, 31 each recite that the subject is identified as having achieved each of the individual seven claimed measures, respectively, “by week 16 of the treatment.” Ex. 1001 (’307 Patent) at 122:37-56, 122:62-67.

230. NCT-236 discloses each of these limitations in the Primary and Secondary Outcome Measures and teaches measurement of responses after induction at week 8 and Ochsenkühn showed that there was a strong response by UC patients to treatment after IV Induction infusion (“clinical remission was achieved in 65% (11/17) at 1 [month]”). Ex. 1003 at 1-2, Ex. 1005 (Ochsenkühn) at 2. Thus, for the reasons I have stated above in Sections VIII.B.3 and VIII.B.4.f, a POSA would reasonably have expected to see responders that satisfy each of response limitations of dependent claims 24-29, 31. A POSA would have reasonably expected that at least some patients with moderately to severely active UC treated with the claimed ustekinumab dosing regimens would respond according to the measures of response recited in these dependent claims.

16. Dependent Claim 32

231. In my opinion, these claims are disclosed by NCT-236. *See* Section VIII.A.11.b. NCT-236 identifies the patient population described in claim 32.

Specifically, claim 32 recites “[t]he 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 (’307 Patent) at 123:1-4. I note that 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 (NCT-236) at 3.

IX. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

232. As noted above, I understand that certain objective factors called “secondary considerations” should also be considered when determining whether a claimed invention is non-obvious. I understand that these “secondary considerations” may be utilized to guard against a hindsight bias in consideration of the prior art, which include: (a) commercial success of a product due to the merits of the claimed invention; (b) a long-felt, but unsatisfied need for the invention; (c) failure of others to find the solution provided by the claimed invention; (d) copying of the invention by others; (e) unexpected results achieved by the invention; (f) praise of the invention by others skilled in the art; (g) lack of independent simultaneous invention within a comparatively short space of time; (h) teaching away from the invention in the prior art.

233. In my opinion, there are no secondary considerations here that would show that the Challenged Claims of the '307 Patent are non-obvious. To the extent Patent Owner identifies any additional secondary considerations, I reserve the right to respond to them.

234. ***No Unexpected Results.*** As I explain above, the fact of the phase 3 clinical study, which NCT-236 describes and Ochsenkühn acknowledges, indicates that clinicians expected the proposed method of treatment to work. Ex. 1005 (Ochsenkühn) at 2; Ex. 1003 (NCT-236). 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 (Ochsenkühn) at 2. Ochsenkühn further noted that “[p]re-approval trials are ongoing” 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.” *Id.* Janssen in fact admitted 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.” Ex. 1027 at 58; *see also* Sections VIII.B.3, VIII.B.4.e. In my opinion, the mere clinical approval based on NCT-236 was therefore not, as of September 24, 2018, and unexpected result.

235. *No Long-Felt But Unmet Need.* By 2018, the claimed method of treatment, including its specific dosing regimen and response criteria, was already publicly disclosed by Patent Owner itself. It is thus my opinion that any “unmet” need had already been fulfilled before the ’307 Patent was filed. NCT-236. Indeed, I note that other gastroenterologists had also been implementing methods like that claimed since before 2018. Ex. 1005 (Ochsenkühn) at 2.

236. *No Commercial Success.* As I have noted above, there is nothing patentably distinguishable in the ’307 Patent’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.

X. CONCLUSION

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

Executed on June 20, 2023.

By:

Michael Epstein, MD

Michael S. Epstein, M.D.

XI. APPENDIX I: SEQUENCE ANALYSIS

A. Heavy Chain CDR Sequences (SEQ ID NOS:1-3)

Source	Heavy Chain CDR Sequences																				
Ex. 1001 (’307 Patent)	<u>SEQ ID NO:1</u> Thr Tyr Trp Leu Gly (TYWLG)	<u>SEQ ID NO: 2</u> Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln (IMSPVDSDIRYSPSFQG)	<u>SEQ ID NO: 3</u> Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe (RRPGQGYFDF)																		
	<u>SEQ ID NO: 27</u> Thr Tyr Trp Leu Gly <210> 27 <211> 5 <212> PRT <213> Homo sapiens <400> 27 Thr Tyr Trp Leu Gly 1 5	<u>SEQ ID NO: 28</u> Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln <210> 28 <211> 16 <212> PRT <213> Homo sapiens <400> 28 Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln 1 5 10 15	<u>SEQ ID NO: 29</u> Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe <210> 29 <211> 10 <212> PRT <213> Homo sapiens <400> 29 Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe 1 5 10																		
Ex. 1052 (’035 Application) at 96	<u>SEQ ID NO 17</u> TYWLG (yellow highlighting added) <table><tr><th>SEQ ID NO</th><th>Description</th><th>Sequence</th></tr><tr><td>17</td><td>Unknown</td><td>EVQLVQSGAEVDPSSSLRLCDSDSYSP-TYWLGSRVQNPSSGLEWGLNGPVQDLPY</td></tr></table>	SEQ ID NO	Description	Sequence	17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- TYWLG SRVQNPSSGLEWGLNGPVQDLPY	<u>SEQ ID NO 17</u> IMSPVDSDIRYSPSFQG (yellow highlighting added) <table><tr><th>SEQ ID NO</th><th>Description</th><th>Sequence</th></tr><tr><td>17</td><td>Unknown</td><td>EVQLVQSGAEVDPSSSLRLCDSDSYSP-IMSPVDSDIRYSPSFQGLWGLNGPVQDLPY</td></tr></table>	SEQ ID NO	Description	Sequence	17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- IMSPVDS DIRYSPSFQGLWGLNGPVQDLPY	<u>SEQ ID NO 17</u> RRPGQGYFDF (yellow highlighting added) <table><tr><th>SEQ ID NO</th><th>Description</th><th>Sequence</th></tr><tr><td>17</td><td>Unknown</td><td>EVQLVQSGAEVDPSSSLRLCDSDSYSP-RRPGQGYFDFSRVQNPSSGLEWGLNGPVQDLPY</td></tr></table>	SEQ ID NO	Description	Sequence	17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- RRPGQGYFDF SRVQNPSSGLEWGLNGPVQDLPY
	SEQ ID NO	Description	Sequence																		
17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- TYWLG SRVQNPSSGLEWGLNGPVQDLPY																			
SEQ ID NO	Description	Sequence																			
17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- IMSPVDS DIRYSPSFQGLWGLNGPVQDLPY																			
SEQ ID NO	Description	Sequence																			
17	Unknown	EVQLVQSGAEVDPSSSLRLCDSDSYSP- RRPGQGYFDF SRVQNPSSGLEWGLNGPVQDLPY																			

[illegible]

Source	Heavy Chain CDR Sequences		
Ex. 1025 ('027-Publication) at 44	SEQ ID NO:1	SEQ ID NO:2	SEQ ID NO:3
	Thr Tyr Trp Leu Gly <210> SEQ ID NO 1 <211> LENGTH: 5 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 1 Thr Tyr Trp Leu Gly 1 5	Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln <210> SEQ ID NO 2 <211> LENGTH: 17 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 2 Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln 1 5 10 15 Gly	Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe <210> SEQ ID NO 3 <211> LENGTH: 10 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 3 Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe 1 5 10

B. Light Chain CDR Sequences (SEQ ID NOS:4-6)

Source	Light Chain CDR Sequences		
Ex. 1001 ('307 Patent)	<u>SEQ ID NO:4 (CDRL1)</u> Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala (RASQGISSWLA)	<u>SEQ ID NO: 5 (CDRL2)</u> Ala Ala Ser Ser Leu Gln Ser (AASSLQS)	<u>SEQ ID NO: 6 (CDRL3)</u> Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr (QQYNIYPYT)
Ex. 1053 ('841 Publ.) at 25 (citing SEQ ID Nos: 27-36); Ex. 1063 ('841 Publ. Sequence) at 31	SEQ ID NO: 30 Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala <210> 30 <211> 11 <212> PRT <213> Homo sapiens <400> 30 Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala 1 5 10	SEQ ID NO: 31 Ala Ala Ser Ser Leu Gln Ser <210> 31 <211> 7 <212> PRT <213> Homo sapiens <400> 31 Ala Ala Ser Ser Leu Gln Ser 1 5	SEQ ID NO: 32 Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr <210> 32 <211> 9 <212> PRT <213> Homo sapiens <400> 32 Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr 1 5
Ex. 1052 ('035 Application) at 96	<u>SEQ ID NO 18</u> RASQGISSWLA (yellow highlighting added) 18 Unikemmh LC C:QKQDFSLASVSRVYLLTASQGLSSKLANVQKFKAPRLTYAASLQDVPF RFSQSSSTDFLTLSLQDFDAFYCOQNIYPTFYQDCKLKRVAAPSVJFF SDQLKSGTASVYCLINFTFKRAKVNQVHQLQSHQSVYEQDSKSTVSLSTLT LSKADYKRMVYACVYTHQGLSDVYKSPNHSIC	<u>SEQ ID NO 18</u> AASSLQS (yellow highlighting added) 18 Unikemmh LC C:QKQDFSLASVSRVYLLTASQGLSSKLANVQKFKAPRLTYAASLQDVPF RFSQSSSTDFLTLSLQDFDAFYCOQNIYPTFYQDCKLKRVAAPSVJFF SDQLKSGTASVYCLINFTFKRAKVNQVHQLQSHQSVYEQDSKSTVSLSTLT LSKADYKRMVYACVYTHQGLSDVYKSPNHSIC	<u>SEQ ID NO: 18</u> QQYNIYPYT (yellow highlighting added) 18 Unikemmh LC C:QKQDFSLASVSRVYLLTASQGLSSKLANVQKFKAPRLTYAASLQDVPF RFSQSSSTDFLTLSLQDFDAFYCOQNIYPTFYQDCKLKRVAAPSVJFF SDQLKSGTASVYCLINFTFKRAKVNQVHQLQSHQSVYEQDSKSTVSLSTLT LSKADYKRMVYACVYTHQGLSDVYKSPNHSIC

Source	Light Chain CDR Sequences		
Ex. 1019 ('285 Patent) at 47-48; see also Ex. 1021 ('285 PTE Application) at 2, 117-118	<u>SEQ ID NO:4</u> Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala <400> SEQUENCE: 4 Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala 1 5 10	<u>SEQ ID NO: 5</u> Ala Ala Ser Ser Leu Gln Ser <400> SEQUENCE: 5 Ala Ala Ser Ser Leu Gln Ser 1 5	<u>SEQ ID NO: 6</u> Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr <400> SEQUENCE: 6 Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr 1 5
Ex. 1018 ('734 Patent) at 42; see also Ex. 1020 ('734 PTE Application) at 2, 103	<u>SEQ ID NO:4</u> Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala <210> SEQ ID NO 4 <211> LENGTH: 11 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 4 Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala 1 5 10	<u>SEQ ID NO: 5</u> Ala Ala Ser Ser Leu Gln Ser <210> SEQ ID NO 5 <211> LENGTH: 7 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 5 Ala Ala Ser Ser Leu Gln Ser 1 5	<u>SEQ ID NO: 6</u> Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr <210> SEQ ID NO 6 <211> LENGTH: 9 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 6 Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr 1 5
Ex. 1022 (PMDA Report) at 4	RASQGISSWLA (yellow highlighting added) Light Chain DIQMTQSPSS LSASVGRVT ITRASQGISSWLAWYQKPK EKAPKSLIYA ASSLSGQVPS 60	AASSLQS (yellow highlighting added) Light Chain DIQMTQSPSS LSASVGRVT ITRASQGISSWLAWYQKPK EKAPKSLIYA AASSLQSVPS 60	QQYNIYPYT (yellow highlighting added) Light Chain DIQMTQSPSS LSASVGRVT ITRASQGISSWLAWYQKPK EKAPKSLIYA ASSLSGQVPS 60 RPSGSGSGTD FTLTISLLQP EDPATYQQYNIYPYTPGQ GTKLEIKRTV AAPSVFIFFP 120

C. Heavy Chain Variable Region Sequence (SEQ ID NO:7)

Source	Sequence Compared
Ex. 1001 ('307 Patent)	SEQ ID NO:7 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser (EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRYSPSFQGGQVTMSVDKSITTAYLQWNSLKASDTAMYYCARRRPGQGYFDFWGQGTLVTVSS)

Source	Sequence Compared
Ex. 1053 ('841 Publ.) at 25 (citing SEQ ID Nos: 27-36); Ex. 1063 ('841 Publ. Sequence) at 31-32	SEQ ID NO: 33 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> 33 <211> 119 <212> PRT <213> Homo sapiens <400> 33 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr 20 25 30 Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile 35 40 45 Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr 65 70 75 80 Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115

Source	Sequence Compared					
Ex. 1052 (’035 Application) at 96	SEQ ID NO 17 EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRYSPSFQGGQV TMSVDKSITTAYLQWNSLKASDTAMYWCARRRPGQGYFDFWGQGTLVTVSS (yellow highlighting added)					
	<table><tr><th>SEQ ID NO</th><th>Description</th><th>Sequence</th></tr><tr><td>17</td><td>Ustekinumab HC</td><td>EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRYSPSFQGGQVTMSVDKSITTAYLQWNSLKASDTAMYWCARRRPGQGYFDFWGQGTLVTVSSS STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYCKKVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK</td></tr></table>	SEQ ID NO	Description	Sequence	17	Ustekinumab HC
SEQ ID NO	Description	Sequence				
17	Ustekinumab HC	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRYSPSFQGGQVTMSVDKSITTAYLQWNSLKASDTAMYWCARRRPGQGYFDFWGQGTLVTVSSS STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYCKKVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK				
Ex. 1019 (’285 Patent) at 42; see also Ex. 1021 (’285 PTE Application) at 2, 118	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr 20 25 30 Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile 35 40 45 Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr 65 70 75 80 Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115					

Source	Sequence Compared
Ex. 1018 ('734 Patent) at 42; <i>see also</i> Ex. 1020 ('734 PTE Application) at 2 (combining (A) FW1-FW4), 103	SEQ ID NO:7 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 7 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 7 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr 20 25 30 Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile 35 40 45 Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr 65 70 75 80 Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115
Ex. 1022 (PMDA Report) at 4	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDSDIRYSPSFQ GQVTMSVDKSITTAYLQWNSLKASDTAMYCYARRRPGQGYFDFWGQGTLVTVSS (yellow highlighting added, red color in original) Heavy Chain EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY 60 22-96 SPSFQGVQVTM SVDKSITTAY LQWNSLKASD TAMYCYARRR PGQGYFDFWG QGTLVTVSSS 120

Source	Sequence Compared
Ex. 1025 ('027-Publication) at 45	SEQ ID NO:7 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 7 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 7 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr 20 25 30 Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile 35 40 45 Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr 65 70 75 80 Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115

D. Light Chain Variable Region Sequence (SEQ ID NO:8)

Source	Sequence Compared
Ex. 1001 ('307 Patent)	SEQ ID NO: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg (DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGT DFTLTISLQPEDFATYYCQQYNIYPYTFGQGTKLEIKR)
Ex. 1053 ('841 Publ.) at 25 (citing SEQ ID Nos: 27-36); Ex. 1063 ('841 Publ. Sequence) at 32	SEQ ID NO: 34 <210> 34 <211> 108 <212> PRT <213> Homo sapiens <400> 34 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30 Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg 100 105

Source	Sequence Compared		
Ex. 1052 ('035 Application) at 96	SEQ ID NO 18		
	DIQMTQSPSSLSASVGDRVITITCRASQGIISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFGSGSGS GTDFTLTISSLQPEDFATYYCQQYNIYPYTFGQGTKLEIKR (yellow highlighting added)		
	18	Ustekinumab LC	DIQMTQSPSSLSASVGDRVITITCRASQGIISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFGSGSGSGTDFTLT TISSLQPEDFATYYCQQYNIYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEHKKVYACEVTHQGLSSPVTKSFNRGEC
Ex. 1019 ('285 Patent) at 43; see also Ex. 1021 ('285 PTE Application) at 2, 118-119	SEQ ID NO: 8		
	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg		
	<400> SEQUENCE: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30 Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg 100 105		

Source	Sequence Compared
Ex. 1018 ('734 Patent) at 42-43; see also Ex. 1020 ('734 PTE Application) at 2 (combining (B) FW1-FW4 and part of CK), 103-104	SEQ ID NO: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg <210> SEQ ID NO: 8 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30 Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg 100 105
Ex. 1022 (PMDA Report) at 4	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQYNIYPYTFGQGGTKLEIKR (yellow highlighting added, red color in original) Light Chain DIQMTQSPSS LSASVGDRVT ITCRASOGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS 60 23-88 RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP 120

Source	Sequence Compared
Ex. 1025 ('027-Publication) at 45	SEQ ID NO: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg <pre> <210> SEQ ID NO 8 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 8 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30 Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg 100 105 </pre>

E. Full Heavy Chain Sequence (SEQ ID NO:10)

Source	Sequence Compared
Ex. 1001 (307 Patent)	SEQ ID NO: 10 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ser Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys (EVQLVQSGAEVKKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDS DIRYSPSFQGGQVTM SVDKSITTAYLQWNSLKASDTAMYYCARRRPGQGYFDWFQGGLTVTVSSSSTKGPSVFPLAPSSKSTSGGT AALNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQK SLSLSPGK)

Source	Sequence Compared		
Ex. 1053 (‘841 Publ.) at 25 (citing SEQ ID Nos: 27-36); Ex. 1063 (‘841 Publ. Sequence) at 32-34	SEQ ID NO: 35		
	<210> 35 <211> 449 <212> PRT <213> Homo sapiens <400> 35 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr 20 25 30 Trp Leu Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Asp Trp Ile 35 40 45 Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Met Ser Val Asp Lys Ser Ile Thr Thr Ala Tyr 65 70 75 80 Leu Gln Trp Asn Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Arg Arg Pro Gly Gln Gly Tyr Phe Asp Phe Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser Ser Ser Thr Lys Gly Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175 Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190 Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro 195 200 205 Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys 210 215 220 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro 225 230 235 240 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser 245 250 255 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp 260 265 270 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn 275 280 285 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val 290 295 300	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu 305 310 315 320 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys 325 330 335 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr 340 345 350 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr 355 360 365 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu 420 425 430 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly 435 440 445 Lys
Ex. 1052 (‘035 Application) at 96	SEQ ID NO 17		
17	Ustekinumab HC	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWLGWVRQMPGKGLDWIGIMSPVDS DIRY SPSFQGGVTMSVDKSIITAYLQWNSL KASDTAMY YCARRRPGQGYFD FFWGQGTLVTVSSS STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	

Source	Sequence Compared
Ex. 1021 (285 PTE Application) at 2	The active ingredient in the approved product, ustekinumab, is comprised of 1,326 amino acids. The amino acid sequence for ustekinumab is as follows: (A) FW1 EVQLVQSGAEVKKPGESLKISCKGSGYSFT CDR1 TYWLG FW2 WVRQMPGKGLDWIG CDR2 IMSPVDS DIRYSPSFQG FW3 QVTMSVDKSITTAYLQWNSLKASDTAMYYCAR CDR3 RRPQGQYFDF FW4 WGQGT LVTVSS CH1 SSTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV HINGE EPKSCDKTHTCPPCPAPELLG CH2 GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK CH3 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
Ex. 1020 (734 PTE Application) at 2	The active ingredient in the approved product, ustekinumab, is comprised of 1,326 amino acids. The amino acid sequence for ustekinumab is as follows: (A) FW1 EVQLVQSGAEVKKPGESLKISCKGSGYSFT CDR1 TYWLG FW2 WVRQMPGKGLDWIG CDR2 IMSPVDS DIRYSPSFQG FW3 QVTMSVDKSITTAYLQWNSLKASDTAMYYCAR CDR3 RRPQGQYFDF FW4 WGQGT LVTVSS CH1 SSTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV HINGE EPKSCDKTHTCPPCPAPELLG CH2 GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK CH3 GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

Source	Sequence Compared
Ex. 1022 (PMDA Report) at 4	(red color in original) Heavy Chain EVQLVQSGAE VKKPGESLKI SCKGSGYSFT <u>TYWLGWVRQM</u> PGKGLDWIGI <u>MSPVDSDIRY</u> 60 22-96 <u>SPSFQGV</u>TM SVDKSITTAY LQWNSLKASD TAMYYCARRR <u>PGQGYFDFWG</u> QGTLVTVSSS 120 STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG 180 146-202 LYSLSSVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK ²²²SCDKTHT²²⁸CPP ²³¹CPAPELLGGP 240 LC HC HC N-Glycan SVFLFPPKPK DTLNISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300 263-323 TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 360 TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTTPVL DSDGSFFLYS KLTVDKSRWQ 420 369-427 QGNVFSCSVM HEALHNHYTQ KSLSLSPGK 449

F. Full Light Chain Sequence (SEQ ID NO:11)

Source	Sequence Compared											
Ex. 1001 (’307 Patent)	SEQ ID NO: 11											
	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNIYPYTFGGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC)											
Ex. 1053 (’841 Publ.) at 25 (citing SEQ ID Nos: 27-36); Ex. 1063 (’841 Publ. Sequence) at 30	SEQ ID NO: 36											
	<210> 36 <211> 214 <212> PRT <213> Homo sapiens <400> 36 <table><tr><td>Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15</td><td>Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95</td><td>Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175</td></tr><tr><td>Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30</td><td>Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala 100 105 110</td><td>Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr 180 185 190</td></tr><tr><td>Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45</td><td>Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly 115 120 125</td><td>Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser 195 200 205</td></tr><tr><td>Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60</td><td>Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala 130 135 140</td><td>Phe Asn Arg Gly Glu Cys 210</td></tr></table>	Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala 100 105 110	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr 180 185 190	Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly 115 120 125	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser 195 200 205	Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala 130 135 140
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Tyr 85 90 95	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175										
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp 20 25 30	Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala 100 105 110	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr 180 185 190										
Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile 35 40 45	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly 115 120 125	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser 195 200 205										
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala 130 135 140	Phe Asn Arg Gly Glu Cys 210										

Ex. 1052 (’035 Application) at 96	SEQ ID NO 18																		
	18	Ustekinumab LC	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPS RFSGSGSGTDFTLTISLQPEDFATYYCQQYNIYPYTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC																
Ex. 1021 (’285 PTE Application) at 2, 117	The active ingredient in the approved product, ustekinumab, is comprised of 1,326 amino acids. The amino acid sequence for ustekinumab is as follows: (B) <table><tr><td>FW1</td><td>DIQMTQSPSSLSASVGDRVTITC</td></tr><tr><td>CDR1</td><td>RASQGISSWLA</td></tr><tr><td>FW2</td><td>WYQQKPEKAPKSLIY</td></tr><tr><td>CDR2</td><td>AASSLQS</td></tr><tr><td>FW3</td><td>GVPSRFSGSGSGTDFTLTISLQPEDFATYYC</td></tr><tr><td>CDR3</td><td>QQYNIYPYT</td></tr><tr><td>FW4</td><td>FGQGTKLEIK</td></tr><tr><td>CK</td><td>RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC</td></tr></table>			FW1	DIQMTQSPSSLSASVGDRVTITC	CDR1	RASQGISSWLA	FW2	WYQQKPEKAPKSLIY	CDR2	AASSLQS	FW3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC	CDR3	QQYNIYPYT	FW4	FGQGTKLEIK	CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
FW1	DIQMTQSPSSLSASVGDRVTITC																		
CDR1	RASQGISSWLA																		
FW2	WYQQKPEKAPKSLIY																		
CDR2	AASSLQS																		
FW3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC																		
CDR3	QQYNIYPYT																		
FW4	FGQGTKLEIK																		
CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC																		
Ex. 1018 (’734 Patent) at 41; see also Ex. 1020 (’734 PTE Application) at 2, 102	The active ingredient in the approved product, ustekinumab, is comprised of 1,326 amino acids. The amino acid sequence for ustekinumab is as follows: (B) <table><tr><td>FW1</td><td>DIQMTQSPSSLSASVGDRVTITC</td></tr><tr><td>CDR1</td><td>RASQGISSWLA</td></tr><tr><td>FW2</td><td>WYQQKPEKAPKSLIY</td></tr><tr><td>CDR2</td><td>AASSLQS</td></tr><tr><td>FW3</td><td>GVPSRFSGSGSGTDFTLTISLQPEDFATYYC</td></tr><tr><td>CDR3</td><td>QQYNIYPYT</td></tr><tr><td>FW4</td><td>FGQGTKLEIK</td></tr><tr><td>CK</td><td>RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC</td></tr></table>			FW1	DIQMTQSPSSLSASVGDRVTITC	CDR1	RASQGISSWLA	FW2	WYQQKPEKAPKSLIY	CDR2	AASSLQS	FW3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC	CDR3	QQYNIYPYT	FW4	FGQGTKLEIK	CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
FW1	DIQMTQSPSSLSASVGDRVTITC																		
CDR1	RASQGISSWLA																		
FW2	WYQQKPEKAPKSLIY																		
CDR2	AASSLQS																		
FW3	GVPSRFSGSGSGTDFTLTISLQPEDFATYYC																		
CDR3	QQYNIYPYT																		
FW4	FGQGTKLEIK																		
CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC																		

Ex. 1022 (PMDA Report) at 4	(red color in original)									
	Light Chain									
	DIQMTQSPSS	LSASVGDRVT	IT	C	RASOGIS	SWLAWYQQKP	EKAPKSLIYA	ASSLOSGVPS	60	
	23-88									
	RFSGSGSGTD	FTLTISSLQP	EDFATYY	C	OO	YNIYPYTFGQ	GTKLEIKRTV	AAPSVFIFPP	120	
SDEQLKSGTA	SVV	C	LLNNFY	PREAKVQWKV	DNALQSGNSQ	ESVTEQDSKD	STYLSSTLT	180		
134-194										
LSKADYEKHK	VYA	C	EVTHQG	LSSPVT	KSFN	RGE	C	214		
HC										

XII. APPENDIX II: CURRICULUM VITAE OF DR. MICHAEL EPSTEIN

CURRICULUM VITAE
Michael S. Epstein, M.D., F.A.C.G., A.G.A.F., A.M.E.

Investigative Clinical Research
621 Ridgely Avenue, Suite 403
Annapolis, MD 21401

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michael@icrmd.com

EDUCATION AND TRAINING

- | | | |
|-------------|--|-------------------------|
| 1984 – 1986 | Fellowship in Gastroenterology and Hepatology
Veterans Administration Medical Center
Director: Leonard B. Seef, M.D. | <i>Washington, D.C.</i> |
| 1981-1984 | Internship and Residency Program
George Washington University Hospital and School of Medicine
Director: Gorge G. Rios, M.D. | <i>Washington, D.C.</i> |
| 1977-1981 | Doctor of Medicine
Robert Wood Johnson School of Medicine, New Jersey College of
Medicine and Dentistry | <i>Newark, NJ</i> |
| 1973-1977 | Bachelor of Arts with Distinction
University of Colorado
Molecular, Cellular, Developmental Biology | <i>Boulder, CO</i> |

CURRENT STATUS

- | | |
|--------------|---|
| 2010-Present | Founder and President , Investigative Clinical Research, <i>Annapolis, MD</i> |
| 2009-Present | Member , IRB Company |
| 2007-Present | Aviation Medical Examiner , FAA |
| 2006-Present | Special Government Employee and Consultant , Gastrointestinal Drugs
Advisory Committee |
| 2006-Present | Fellow , American Gastroenterology Association |
| 1995-Present | Fellow , American College of Gastroenterology |
| 1993-Present | Founder and President , Maryland Diagnostic & Therapeutic Endo
Center (MDTEC), <i>Annapolis, MD</i> |
| 1990-Present | Principal Physician , Digestive Disorders Associates, <i>Annapolis, MD</i> |
| 1990-Present | Staff Gastroenterologist , Anne Arundel Medical Center, <i>Annapolis, MD</i> |
| 1986-Present | Assistant Professor of Medicine , Uniformed Services of Health Science,
<i>Bethesda, MD</i> |

2020-Present **Clinical Internal Medicine Residency Instructor**, Luminis Health,
Annapolis, MD

CURRENT LICENSURE

Maryland license number D0034426, September 1986

BOARDS CERTIFICATION

1987 American Board of Internal Medicine, subspecialty of Gastroenterology
1984 American Board of Internal Medicine

PREVIOUS PROFESSIONAL POSITIONS

2006-2009 **Member**, Gastrointestinal Drugs Advisory Committee of the FDA
1988-2007 **Member**, American Gastroenterology Association
1996-2007 **Vice President and Medical Director**, AmeriTrial OTC Research Inc.
2003-2006 **Acting Medical Director**, First Circle Medical
2000-2004 **Member**, Board of Trustees, Anne Arundel Medical Center
2002-2004 **Member**, FDA Gastrointestinal and Urologic Device Panel
2000-2002 **President**, Medical Staff of Anne Arundel Medical Center
1999-2001 **President**, Medical Board Executive Committee, AAMC, *Annapolis, MD*
1998-2000 **Vice President**, Medical Board Executive Committee, Anne Arundel
 Medical Center *Annapolis, MD*
1998-2000 **Vice President**, Anne Arundel County Medical Society
1997-1999 **Secretary/Treasurer**, Medical Board Executive Committee, AAMC
1997-1998 **Secretary**, Anne Arundel County Medical Society
1995-1998 **President**, Maryland Ambulatory Surgery Association
1995-1999 **Chairman**, Anne Arundel Medical Center Institutional Review Board
1988-1995 **Member**, American College of Gastroenterology
1994-1995 **Member at Large**, Medical Executive Board, AAMC, *Annapolis, MD*
1990-1992 **Board Member**, Anne Arundel Medical Center, *Annapolis, MD*
1990-1992 **President**, Medical Staff, Anne Arundel Medical Center, *Annapolis, MD*
1989-1990 **IRB Chair**, Anne Arundel Medical Center, *Annapolis, MD*
1986-1990 **Staff Gastroenterologist**, Malcolm Grow USAF Medical Center,
 Andrews Air Force Base, *Largo, MD*

AWARDS

2009 **US FDA Advisory Committee Service Award**
1992 **Meritorious Service Medal USAF**
1992 **AMA Physicians Recognition Award**

CONSULTING CLIENTS (Partial List)

Pharmaceutical Corporations

- Proctor and Gamble Pharmaceutical
- Given Imaging
- Anesta Corporation
- McNeil Pharmaceutical
- Merck and Co. Inc.
- Roche Pharmaceutical
- Sucampo
- Allergan
- Abbott (Abbvie) Pharmacheticals
- Zx Pharmaceuticals
- Eli Lilly
- Vertice Pharmaceuticals
- Ferring Pharmaceuticals
- Otsuka America Pharmaceuticals
- Knsyl Pharmaceuticals

Device Manufacturers

- Proteus Biomedical
- Ethicon Endosurgical
- Medigus
- Betastim Ltd. Life Sciences
- GI View Ltd.
- EVASC Medical Systems
- Precision Endoscopic Therapeutics

Legal Firms

- Baker, Donelson, Bearman, Caldwell, & Berkowitz, PC, *Jackson, MS*
- Nutter, McClennen, & Fish, LLP, *Boston, MA*
- Lisa S. Levine, P.A., *Weston, FL*
- Frommer Lawrence & Huang, LLP, *New York, NY*
- Dickstein Shapiro, *New York, NY*
- Hogan & Harston, *Washington, D.C.*
- Keating Jones Hughes, PA, *Portland, OR*
- Latham Watkins, LLP, *Washington D.C. & San Francisco, CA*

PERSONAL DATA

Born: December 30, 1955, Ft. Meade, Maryland
Children: Lauren J. Epstein, October 17, 1986
Stephen D. Epstein, October 1, 1989
Rachelle A. Epstein, August, 9, 1991
Hobbies: Water skiing, skiing, aviation

PUBLICATIONS

1. **Epstein, M.**, Johnson, D., Hawes, R., Schmulewitz, N., Vanagunas, A., Gossen, R., Eaton, S., Robieson, W., Dubow, J., Chatamra, K., & Benesh, J. Gastrointestinal safety of levodopa-carbidopa intestinal gel system in advanced Parkinson's Disease. *Movement Disorders*. (in press)
2. Cash, B. D., **Epstein, M. S.**, & Shah, S. M. (2016). A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. *Digestive Diseases and Sciences*, 61(2), 560-571.
3. Cash, B. D., **Epstein, M. S.**, & Shah, S. M. (2016). Patient Satisfaction with IBS Symptom Relief Using a Novel Peppermint Oil Delivery System in a Randomized Clinical Trial and in the General Population. *International Journal of Digestive Diseases*, 2(2), 227.
4. **Epstein, M.**, Johnson, D. A., Hawes, R., Schmulewitz, N., Vanagunas, A. D., Gossen, E. R., Robieson, W.Z., Eaton, S., Dubow, J., Chatamra, K., & Benesh, J. (2016). Long-term PEG-J Tube safety in patients with advanced Parkinson's disease. *Clinical and Translational Gastroenterology*, 7(3), e159.
5. **Epstein, M.S.**, Ehrenpreis, E.D., & Kulkarni, P.M. (2014). Biosimilars: the need, the challenge, the future: the FDA perspective. *The American Journal of Gastroenterology*, 109(12), 1856-1859.
6. McLemore, E.C., Rai, R., Siddiqui, J., Basu, P., Tabbba, M., & **Epstein M.S.** (2012). Novel endoscopic delivery modality of infrared coagulation therapy for internal hemorrhoids. *Surgical Endoscopy*, 26(11), 3082-3087.
7. Au-Yeung, K.Y., Moon, G.D., Robertson, T., DiCarlo, L.A., **Epstein, M.S.**, Weis, S.E., Reves, R.R., & Engel, G. (2011). Early clinical experience with networked system for promoting patient self-management. *American Journal of Managed Care*, 17(7), e277-e287.
8. Jacobson, I. M., Brown, R. S., Freilich, B., Afdhal, N., Kwo, P. Y., Santoro, J., Becker, S., Wakil, A.E., Pound, D., Godofsky, E. Strauss, R., Bernstein, D., Flamm, S., Pauly, M.P., Mukhopadhyay, P., Griffel, L.H., & Brass, C.A. (2007). Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: A randomized trial. *Hepatology*, 46(4), 971-981.
9. **Epstein, M.S.** (1995). Munchausen syndrome: Case reports and literature overview. *Maryland Medical Journal*, 44(1), 39-43.
10. Devaney, K., Goodman, Z.D., **Epstein, M.S.**, Zimmerman, H.J., & Ishak, K.G. (1993). Hepatic sarcoidosis: clinicopathologic features in 100 patients. *The American Journal of Surgical Pathology*, 17(12), 1272-1280.

11. **Epstein, M.S.**, Ingram, C.W., Borts, F.W., Korman, L.Y., & Seef, L.B. (1986). Retrospective and prospective analysis of focal defects demonstrated by computerized tomography. *Gastroenterology*, 90(5), 1724.

ABSTRACTS

1. Bertiger, G., **Epstein, M.**, Marshall, D., & Dahdal, D. (2016). A low-volume sodium picosulfate and magnesium citrate bowel preparation has no effect on cardiovascular parameters in patients preparing for colonoscopy. Seattle, WA.
2. Draganov, P., **Epstein, M.**, Hawes, R. Johnson, D., Vanagunas, A., Robieson, W.Z., Chatamra, K., Benesh, J.A., & Eaton, S. (2016). Short- and long-term safety of PEG-J used for continuous infusions of levodopa-carbidopa intestinal gel. Vancouver, BC, Canada.
3. **Epstein, M.S.**, Clayton, L., Ng, R., & DeMicco, M. (2016). Efficacy and safety of the novel 1L PEG and ascorbate bowel preparation NER1006 versus standard 2L PEG with ascorbate in overnight or morning split-dosing administration: results from the phase 3 study. San Diego, CA.
4. **Epstein, M.**, Willey, R., Almansa, C., & Dahdal, D. Efficacy, safety and patient-reported tolerability of sodium picosulfate plus magnesium citrate in patients with previous bowel preparation experience. San Antonio, TX.
5. **Epstein, M.S.**, Clayton, L., Ng, R., & DeMicco, M. (2016). Efficacy and safety of the novel 1L PEG and ascorbate bowel preparation NER1006 versus trisulfate solution in overnight split-dosing administration: results from the phase 3 study NOCT. Vienna, Austria.
6. Poordad, F., Sedghi, S., Pockros, P.J., Ravendrhan, N., Reindollar, R, Lucey, M.R., **Epstein, M.**, Bank, L., Bernstein, D., Trinh, R., Krishnan, P., Piolot-Matias, T., Polepally, A.R., Pothacamury, R.K., Rajvineeth, K., Martinez, M., & Nelson, D.R. (2016). GEODE-II: Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin QD in patient with genotype 1a chronic hepatitis C virus infection without cirrhosis. Paris, France.
7. Poordad, F., Sedghi, S., Pockros, P.J., Ravendrhan, N., Reindollar, R, Lucey, M.R., **Epstein, M.**, Bank, L., Bernstein, D., Trinh, R., Krishnan, P., Piolot-Matias, T., Polepally, A.R., Pothacamury, R.K., Rajvineeth, K., Martinez, M., & Nelson, D.R. (2016). GEODE-II: Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin QD in patient with genotype 1a chronic hepatitis C virus infection without cirrhosis. Boston, MA.
8. Bertiger, G., **Epstein, M.**, Hutson-Walker, A., Almansa, C., & Dahdal, D.N. (2016). Comparison of bowel preparation quality scales used in randomized controlled trials of patients undergoing colonoscopy. Las Vegas, NV.
9. Vanagunas, A., Draganov, P., Schmulewitz, N., **Epstein, M.**, Hawes, R., Johnson, D., Benesh, J.A., Chatamra, K., Easton, S., Facheris, M.F., Hall, C.M., & Robieson, W.Z. (2016). Multi-year safety and durability of PEG-J used for continuous infusion of levodopa-carbidopa intestinal gel in ambulatory Parkinson's disease patients: year 2 and beyond. Las Vegas, NV.

10. **Epstein, M.S.,** Cash, B.D., & Shah, S.M. (2015). Targeted delivery of peppermint oil to the small intestine provide significant improvement in the syndrome of symptoms associates with irritable bowel syndrome. Presented at Digestive Disorders Week, Washington, D.C.
11. Cash, B.D., **Epstein, M.S.,** & Shah, S.M. (2015). IBgard®, a novel targeted delivery system of peppermint oil, results in significant improvement in the Total IBS Symptom Score and individual IBS symptoms. Results from the US based, 4-week, randomized, placebo controlled, multi-center IBREST™ trial. Presented at Digestive Disorders Week, Washington, D.C.
12. **Epstein, M.S.,** Cash, B. D., & Shah, S. M. (2015). 24-Hour Results From a Placebo-Controlled Trial, to Evaluate a Novel Peppermint Oil Delivery System, Targeting Release in the Small Intestine. Results From the US Based, 4-Week, Randomized, Placebo Controlled, Multi-Centered IBREST™ Trial. *Gastroenterology*, 148(4), S-69.
13. **Epstein, M.S.,** Cash, B.D., & Shah, S.M. (2015). 24 hour results form a US based, randomized, placebo-controlled, multi-centered trial, to evaluate a novel peppermint oil delivery system: Results from the IBREST™ Trial. Presented at Digestive Disorders Week, Washington, DC.
14. **Epstein, M.,** & Shah, S. (2015). A novel formulation containing a L-Menthol and peppermint oil blend (LPB) reduces symptom intensity and frequency in Irritable Bowel Syndrome (IBS). Presented at James W. Freston Conference, AGA Institute, Chicago, IL.
15. Dragov, P., **Epstein, M.,** Robieson, W.Z., Chatamra, K., Benesh, J.A., & Easton, S. (2015). Short- and long-term safety of PEG-J used for continuous infusion of levodopa-carbidopa intestinal gel. Presented at ACG, Honolulu, HI.
16. Johnson, D., **Epstein, M.,** Hawes, R., Draganov, P., Schmulewitz, N., Vanaguna, A., Hall, C.M., Robieson, W.Z., Chatamra, K., Benesh, J.A., & Eaton, S. (2015). Devices complaints and longevity of PEG-J used for continuous infusion of levodopa-carbidopa intestingal gel in ambulatory patients with Parkinson's disease. Presented at ACG, Honolulu, HI.
17. **Epstein, M.,** Cash, B., & Shah, S. (2015). Rapid relief of Irritable Bowel Syndrome (IBS) symptoms with targeted delivery of L-Menthol to the small intestine: results form 2 clinical trials and a patient survey. Presented at ACG, Honolulu, HI.
18. **Epstein, M.,** Cash, B., & Shah, S. (2015). Patient satisfaction with IBS symptom relief using a novel peppermint oil delivery system in a randomized clinical trial and by the general patient population. Presented at ACG, Honolulu, HI.
19. Cash, B.D., **Epstein, M.,** & Shah, S. (2015). Successful management viscerosensory symptoms in patients with IBS-M and IBS-D using a targeted delivery system of peppermint oil (PO-SST). Presented at ACG, Honolulu, HI.
20. **Epstein, M.,** Johnson, D., Hawes, R., Schmulewitz, N., Vanagunas, A., Gossen, R., Widnell, K.L., Eaton, S., Robieson, W.Z., Chatamra, K., & Benesh, J. (2014). Gastrointestinal safety of the levodopa-carbidopa intestinal gel delivery system in treating advanced Parkinson's patients (MDS Encore). Presented at American Academy of Neurology Annual Meeting, Philadelphia, PA.
21. **Epstein, M.,** Johnson, D., Hawes, R., Schmulewitz, N., Vanagunas, A., Gossen, R., Widnell, K.L., Eaton, S., Robieson, W.Z., Chatamra, K., & Benesh, J. (2013). Gastrointestinal safety of the levodopa-carbidopa intestinal gel delivery system in treating advanced Parkinson's patients. Sydney, Australia.

22. **Epstein, M.**, Johnson, D., Hawes, R., Schmulewitz, N., Vanagunas, A., Gossen, R., Eaton, S., Robieson, W.Z., Chatamra, K., & Benesh, J. (2013). Gastrointestinal safety of the long-term PEG-J used for continuous infusion of levodopa-carbidopa intestinal gel. Berlin, Germany.
23. **Epstein, M.**, Johnson, D., Hawes, R., Schmulewitz, N., Vanagunas, A., Zadikoff, C., Gossen, R., Eaton, S., Robieson, W.Z., Chatamra, K., & Benesh, J. (2013). PEG-J administration of therapeutic agents for neurological disorders: levodopa-carbidopa intestinal gel for advanced Parkinson's disease. San Diego, CA.
24. Johnson, D., **Epstein, M.**, Hawes, R., Schmulewitz, N., Vanaguna, A., Gossen, R., Eaton, S., Robieson, W.Z., Chatamra, K., & Benesh, J. Durability of the PEG-J system in long-term studies of levodopa-carbidopa intestinal gel infusion in advanced Parkinson's disease patients. San Diego, CA.
25. **Epstein, M.**, Grandhi, N., Katz, P., & Joseph, R. (2013). Diabetes controlled hypertension and obesity have little effect on the safety and tolerability of day before sodium picosulfate and magnesium citrate bowel preparation. *American Journal of Gastroenterology*, 108, S581.
26. **Epstein, M.**, Grandhi, N.K., Katz, P.O., & Rex, D.K. (2013). Colon cleansing in patients with predictors of a poor bowel preparation: an analysis of the See Clear II study. Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting, Baltimore, MD.
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CLINICAL RESEARCH STUDIES

1. Clinical Validation of An Optimized Multi-Target Stool DNA (mt-sDNA 2.0) Test, for Colorectal Cancer Screening “Blue-C” 2019-01. Principal Investigator, 2020
2. BLOOD COLLECTION SUB-STUDY OF EXACT SCIENCES PROTOCOL 2019-01: “CLINICAL VALIDATION OF AN OPTIMIZED MULTI-TARGET STOOL DNA (mt-sDNA 2.0) TEST, FOR COLORECTAL CANCER SCREENING BLUE-C” 2019-01B. Principal Invesitgator, 2020

3. Ironwood, Protocol C3718-302: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Oral IW-3718 Administered to Patients with Gastroesophageal Reflux Disease while receiving Proton Pump Inhibitors. Principal Investigator, 2019.
4. Exact Sciences, Protocol 2018-10B: Blood Collection Sub-Study of Exact Sciences Protocol 2018-10: “An Evaluation of a Multi-target Stool DNA (mt-sDNA) Test, Cologuard, for CRC Screening in Individuals Aged 45-49 and at Average Risk for Development of Colorectal Cancer: Act Now”. Principal Investigator, 2019.
5. Exact Sciences, Protocol 2018-10: An Evaluation of a Multi-target Stool DNA (mt-sDNA) Test, Cologuard, for CRC Screening in Individuals Aged 45-49 and at Average Risk for Development of Colorectal Cancer. Principal Investigator, 2019.
6. Gilead, Protocol GS-US-418-4279: A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Testicular Safety of Filgotinib in Adult Males with Moderately to Severely Active Ulcerative Colitis. Principal Investigator, 2018.
7. Sebel, Protocol SEB-ECP-202: A Randomized, Investigator- and Colonoscopist-blinded, Phase 2 Study of the Efficacy and Safety of ECP (polyethylene glycol 3350 [PEG 3350]) Colon Prep Kit Compared with Moviprep® Split-dose for Colonoscopy Preparation. Principal Investigator, 2017.
8. Allergan, Protocol CMO-US-GI-0429: A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF). Principal Investigator, 2017
9. Gilead, Protocol GS-US-419-3895: Combined Phase 3, Double-blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Crohn’s Disease. Principal Investigator, 2017
10. Gilead, Protocol GS-US-419-3896: A Long Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Crohn’s Disease. Principal Investigator, 2017
11. Gilead, Protocol GS-US-418-3898: Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis. Principal Investigator, 2017
12. Gilead, Protocol GS-US-418-3899: A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Ulcerative Colitis. Principal Investigator, 2017
13. AbbVie Clinical Study Protocol M14-327: A Phase 2, Multicenter, Open-Label Extension (OLE) Study to Evaluate the Long-Term Efficacy, Safety, and Tolerability of Repeated Administration of ABT-494 in Subjects with Crohn's Disease. Principal Investigator, 2016
14. Colanary Concepts, Protocol: C Bar 001 An Exploratory Study Evaluating the use of C-Bar in the Treatment of Chronic Idiopathic Constipation Principal Investigator, 2016
15. Intercept, Protocol 747-303: A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis. Principal Investigator, 2016

16. Synergy, Protocol SP304203-05 Second Phase 3 Randomized, 12-Week, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C). Principal Investigator, 2016
17. AbbVie, Clinical Study Protocol M14-172: A Single Arm, Open-label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1). Principal Investigator, 2016
18. Ironwood, Protocol ICP-3718-202: A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Trial of IW-3718 Administered Orally for 8 Weeks to Patients with Symptomatic Gastroesophageal Reflux Disease Not Completely Responsive to Proton Pump Inhibitors. Principal Investigator, 2015
19. Ardelyx, Protocol TEN-01-302: A 26-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C). Principal Investigator, 2015
20. AbbVie, Clinical Study Protocol M15-582: An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Low-Dose Ribavirin QD in Subjects with Genotype 1a Chronic Hepatitis C Virus Infection (GEODE II). Principal Investigator, 2015
21. Biomecrite, LLC, Protocol BM-1001: Metagenomic Signature Discovery. Principal Investigator, 2015
22. Synergy, Protocol SP304203-05: Second Phase 3 Randomized, 12-Week, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C). Principal Investigator, 2015
23. AbbVie, Clinical Study Protocol M13-740: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Anti-TNF Therapy. Principal Investigator, 2014
24. Norgine, Protocol NER1006-01/2014 (NOCT): A Multicenter Randomized Parallel Group Phase III Study Comparing the Bowel Cleansing Efficacy, Safety and Tolerability of NER 1006 (a Low Volume Bowel Cleansing Solution using a 2-Day Split-Dosing Regime in Adults. Principal Investigator, 2014
25. Hologic, Protocol P10433-HCVQPS-CSP-01: Collection of Plasma and Serum Samples From Individuals Initiating Therapy With Sofosbuvir for Chronic Hepatitis C Virus Infection for the Clinical Evaluation of the Aptima HCV Quant DX Assay. Principal Investigator, 2014
26. Redhill, Protocol RHB-105-01: A Randomized Placebo-controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed *Helicobacter pylori* (*H. pylori*) Infection in Dyspepsia Patients. Principal Investigator, 2014
27. Robarts, Clinical Trials Inc. Protocol No. RP1202: A Cluster Randomized Controlled Trial of an Enhanced Treatment Algorithm for the Management of Crohn's Disease. Principal Investigator, 2014
28. AbbVie, Clinical Study Protocol F12-119: A Multicenter Study Evaluating a PRactical IndEx Score for Subjects with Crohn's Disease Assessing the Absence of Mucosal UlCeraTion (PREDICT). Principal Investigator, 2014

29. AbbVie, Clinical Study Protocol M14-347 A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease. Principal Investigator, 2014
30. AbbVie, Clinical Study Protocol M14-115 A Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Two Adalimumab Induction Regimens in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration. Principal Investigator, 2014
31. Takeda, Protocol ROF-NASH-205: A Randomized, Double-Blind, Controlled, Multi-Center Phase 2 Study to Evaluate the Effect of Roflumilast Plus Pioglitazone on Liver Enzymes and Liver Fat Content in Subjects with Nonalcoholic Steatohepatitis A Phase 2 Study of Roflumilast plus Pioglitazone in Subjects with Nonalcoholic Steatohepatitis. Principal Investigator, 2013
32. Ventrus, Protocol VEN307-AF-001: A Phase 3B, Randomized, Double-Blind, Placebo Controlled, Parallel-Treatment Group, Multicenter Efficacy and Safety Study of Topical Diltiazem Hydrochloride 2% Cream in Subjects with Anal Fissure. Principal Investigator, 2013
33. Salix, Protocol RNLC 2131: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study to Assess the Efficacy and Safety of Rifaximin Soluble Solid Dispersion (SSD) Tablets for the Prevention of Complications in Subjects with Early Decompensated Liver Cirrhosis. Principal Investigator, 2013
34. AbbVie, Registry Protocol P11-282: A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis (UC). Principal Investigator, 2013
35. Redhill, Protocol RHB-104: A Phase III Randomized, Double Blind, Placebo-controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease. Principal Investigator, 2013
36. Ardelyx, Protocol No. D5612C00001: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of AZD1722 for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C). Principal Investigator, 2013
37. AbbVie, Clinical Study Protocol M13-102: A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection. Principal Investigator, 2013
38. AbbVie, Clinical Study Protocol M13-098: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II). Principal Investigator, 2013
39. Ferring Pharmaceuticals, Protocol 000110: Renal Function Assessment in Subjects Undergoing Colon Cleansing with Prepopik™ or HalfLytely® in Preparation for Colonoscopy: A Retrospective Analysis. Principal Investigator, 2013
40. Salix, Protocol RFIB3053: A Study to Assess Repeat Treatment Efficacy and Safety of Rifaximin 550 mg TID in Subjects with Irritable Bowel Syndrome with Diarrhea (IBS-D). Principal Investigator, 2012

41. Idenix, Protocol IDX-08C-008: An Open-Label Study to Evaluate the Safety and Efficacy of IDX184 in Combination with Telaprevir and Ribavirin for 12 Weeks in Subjects with Genotype 1 Chronic Hepatitis C Infection. Principal Investigator, 2012
42. Abbott, Protocol M13-393: A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 with Ritonavir (ABT 450/r) and ABT-267 in Adults with Chronic Hepatitis C Virus Infection (PEARL-I). Principal Investigator, 2012
43. Cubist, Protocol LCD-CDAD-11-06: A Randomized, Double-Blinded, Active-Controlled Study of CB-138,315 in Patients with Clostridium difficile Associated Diarrhea. Principal Investigator, 2012
44. Furiex, Protocol 27018966IBS3001: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients With Diarrhea-Predominant Irritable Bowel Syndrome. Principal Investigator, 2012
45. Abbott, Protocol M13-101: An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DDA) Treatment in Combination with Peginterferon a-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous Abbott DDA Combination Study. Principal Investigator, 2012
46. Abbott, Protocol M13-386: An Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ABT-267 in HCV Infected Subjects. Principal Investigator, 2012
47. Santarus, Protocol C2011-0401: A randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Budesonide MMX® 9mg Extended-release Tablets as Add-on Therapy in Patients with Active, Mild or Moderate Ulcerative Colitis not Adequately controlled on a Background Oral 5-ASA Regimen. Principal Investigator, 2012
48. Pharmasset, Protocol P2938-0721: QUANTUM: An International, Multi-center, Blinded, Randomized Study to Investigate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Administration of Regimens Containing PSI-352938, PSI-7977, and Ribavirin in Patients with Chronic HCV Infection. Principal Investigator, 2011
49. Abbott, Protocol M11-652: A Randomized, Open-Label, Multicenter Study to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics, of ABT-450 with Ritonavir (ABT-450/r) in Combination with ABT-267 and/or ABT-333 With and Without Ribavirin (RBV) for 8, 12 or 24 Weeks in Treatment-Naïve and Null Responder Subjects with Genotype 1 Chronic Hepatitis C Virus Infection. Principal Investigator, 2011
50. Pfizer, Protocol B0151005: A Multicenter Open-Label Extension Study for Subjects Who Participated in Study B0151003 (Andante II). Principal Investigator, 2011
51. Ardelyx, Protocol No. RDX5791-201: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of RDX5791 for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C). Principal Investigator, 2011
52. Pharmasset, Protocol P7977-0724: The ATOMIC Study: A Multicenter, Open-label, Randomized, Duration Finding Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 in Combination with Pegylated Interferon and Ribavirin in Treatment-Naïve Patients with Chronic HCV Infection Genotype 1, 4, 5, or 6. Principal Investigator, 2011

53. NovoNordisk, Protocol NN8555-3797: A randomized, double-blind, parallel-group, placebo-controlled, induction trial to assess clinical efficacy and safety of NNCO142-0000-0002 in subjects with moderately to severely active Crohn's disease. Principal Investigator, 2011.
54. Pfizer, Protocol B3041001: A Phase 2, randomized, double-blind, placebo-controlled, parallel-group, Multi-Center Study to investigate the safety and efficacy of Multistem in subjects with moderate to severe Ulcerative Colitis. Principal Investigator, 2011
55. Pfizer, Protocol B0151003: A double-blind, randomized, placebo-controlled, dose ranging study to evaluate the efficacy and safety of PF-04236921 in subjects with Crohn's Disease who are anti-TNF inadequate responders (ADANTE). Principal Investigator, 2011
56. Merck and Co., Protocol 3415A 001-00: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to Clostridium difficile toxin A), MK-6072 (Human Monoclonal Antibody to Clostridium difficile toxin B), and MK-3415A (Human Monoclonal Antibodies to Clostridium difficile toxin A and B) in Patients Receiving Antibiotic Therapy for Clostridium difficile Infection. Principal Investigator, 2010
57. Shire Development Inc., Protocol SPD476-409: A Phase 3b/4, Open-label, Multicenter, Prospective Study to Evaluate the Effect of Remission Status on the Ability to Maintain or Achieve Clinical and Endoscopic Remission During a 12-Month, Long Term Maintenance Phase with 204g/day MMX Mesalamine/mesalazine Once Daily in Adult Subjects with Ulcerative Colitis. Principal Investigator, 2010
58. Ferring Pharmaceuticals, Protocol 2009-02: A randomized, Assessor-Blinded, Multi-Center Study Investigating the Efficacy, Safety and Tolerability of "Day Before" PicoPrep for Oral Administration Versus Halflytely for Colon Cleansing in Preparation for Colonoscopy. Principal Investigator, 2010
59. Pfizer, Protocol A4091032: A Phase 3, Multicenter, Randomized, Long Term Study of the Safety of the Subcutaneous Administration of Tanezumab in Patients with Osteoarthritis of the Knee. Principal Investigator, 2010
60. Pfizer, Protocol A4091027: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Analgesic Efficacy and Safety of Subcutaneous Administration of Tanezumab in Patients with Osteoarthritis of the Knee. Principal Investigator, 2010
61. Tioga Pharmaceuticals, Inc., Protocol ASMP3001: A 12-Week, Randomized, Double Blind, Placebo-Controlled Study of Asimadoline in Subjects with Diarrhea Predominant Irritable Bowel Syndrome. Principal Investigator, 2010
62. Nabi Pharmaceuticals, Protocol Nabi-4515: A second Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Assess Efficacy, Immunogenicity and Safety of 3'-aminomethylnicotine-P. aeruginosa r-Exoprotein A Conjugate Vaccine as an aid to Smoking Cessation. Principal Investigator, 2010
63. Prometheus Laboratories Inc., Protocol 08IBS04: Sub Study Collection of Blood Samples from IBD and Celiac Disease Control Subjects. Principal Investigator, 2009
64. Prometheus Laboratories Inc., Protocol 08IBS04: Collection of Blood Samples for the discovery of Biomarkers Associated with Irritable Bowel Syndrome. Principal Investigator, 2009

65. Sanofi Aventis, Protocol ACT11286: A Randomized double-blind, placebo controlled study of the effect of a single injection of SAR164877 (REGN475) on reduction of pain from chronic pancreatitis. Principal Investigator, 2009
66. Xenport Inc., Protocol XP-B-078: A Dose Response Efficacy and Safety Study of Arbaclofen Placarbil (XP 19986) as Adjunctive Therapy in Subjects with Gastroesophageal Reflux Disease (GERD) who are Incomplete Responders to a Proton Pump Inhibitor (PPI). Principal Investigator, 2009
67. Gilead Sciences, Inc., Protocol GS-US-227-0106: A Phase 2b, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of GS-9450 in Adults with Chronic Hepatitis C Virus Infection. Principal Investigator, 2009
68. SECURE, Protocol C87075: A Non-Interventional Long-term Post-Marketing Registry of Patients treated with Certolizumab Pegol (Cimzia) for Crohn's Disease. Principal Investigator, 2009
69. Ironwood Pharmaceuticals, Protocol, MCP-103-302: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 26 Weeks in Patients with Irritable BOWEL Syndrome with Constipation. Principal Investigator, 2009
70. Cosmo Technologies Ltd., Protocol CB -01-02/04: Randomized, Double-Blind, Multi-Centre, 12 Month Extension Study to Evaluate the Safety and Efficacy of Daily Budesonide MMXtm 6 mg VS Placebo in the Maintenance of Remission in Subjects with Ulcerative Colitis. Principal Investigator, 2009
71. Cosmo Technologies Ltd., Protocol CB-01-02/01: Efficacy and safety of New Oral Budesonide-MMXtm (CB-01-02) 6 mg and 9 mg Extended Release Tablet Formulations in Patients with Mild to Moderate, Active Ulcerative Colitis. A Multicentre, Randomized, Double-Blind, Double Dummy Comparative Study Versus Placebo, with and Additional Reference Arm Evaluating Asacol 2400mg. Principal Investigator, 2009
72. Proctor and Gamble Pharmaceuticals. Protocol 2007003: A Phase II, Randomized, Multicenter, Placebo-controlled Study of ATI-7505 in Patients with Chronic Idiopathic Constipation. Medical Monitor, 2008
73. Proctor and Gamble Pharmaceuticals. Protocol 2007033: A Phase II, Randomized, Adaptive Design, Multicenter, Parallel Group, Placebo-controlled, 58-day, Dose-ranging Study of ATI-7505 in Patients with Postprandial Distress Syndrome. Medical Monitor, 2008
74. Ironwood Pharmaceuticals, Protocol, MCP-103-305: An Open-label, Long-term Safety Study of Oral Linaclotide Administered to Patients with Chronic Constipation. Principal Investigator, 2008
75. Ironwood Pharmaceuticals, Protocol, MCP-103-303: A Phase 3, Randomized, Double-Blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered orally for 12 Weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Chronic Constipation. Principal Investigator, 2008
76. Colotech, Protocol Colo-CP-01-US: Chemoprevention of Colorectal Adenomas – An international, multi-center, randomized, parallel group prospective, double blind, placebo controlled clinical trial evaluating the efficacy and safety of a combination treatment administered over three years in patients at risk of experiencing recurrence of colorectal adenomas. Principal Investigator, 2008

77. Tioga, Protocol AST014: A Double-Blind, Randomized, Placebo-Controlled Multicenter Study to assess the safety and efficacy of AST-120 in Patients with Non-Constipating Irritable Bowel Syndrome. Principal Investigator, 2008
78. Eisai, Protocol E3810-G000-305: A Randomized, Double-Blind Parallel Study of Rabeprazole Extended Release 50 mg versus Ranitidine 150 mg for Maintenance of Healed Erosive Gastroesophageal Reflux Disease (GERD). Principal Investigator, 2008
79. Eisai, Protocol E3810-G001-303: A Randomized Double-Blind Parallel Study of Rabeprazole ER 50 mg versus Esomeprazole 40 mg for Healing and Symptomatic Relief of Mild to Moderate Erosive Gastroesophageal Reflux Disease (GERD). Principal Investigator, 2008
80. Eisai, Protocol E3810-G001-301: A Randomized Double-Blind Parallel Study of Rabeprazole ER 50 mg versus Esomeprazole 40 mg for Healing and Symptomatic Relief of Moderate to Severe Erosive Gastroesophageal Reflux Disease (GERD). Principal Investigator, 2008
81. UCB, Protocol C87088: A phase 3B, multinational, open-label, follow-on trial to C87085 designed to assess the long-term safety of Certolizumab Pegol, a pegylated Fab' fragment of a humanized anti-TNF-alpha monoclonal antibody, administered at weeks 0, 2, and 4, and every 4 weeks thereafter, in subjects with moderately to severely active Crohn's disease who have participated in study C87085. Principal Investigator, 2008
82. UCB, Protocol C87085: A Phase 3B, Multinational, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Efficacy and Safety of Certolizumab Pegol, A Pegylated Fab' Fragment of a Humanized Anti-TNF-Alpha Monoclonal Antibody, Administered Subcutaneously at Weeks 0, 2, and 4 in Subjects with Moderately to Severely Active Crohn's disease. Principal Investigator, 2008
83. Proteus, Proteus Emitter 1.0 (Event Marker Ingested to Trigger Event Recorder 1.0): A Non-Significant Risk Feasibility Study of the Raisin Ingestible Marker System. Principal Investigator, 2008
84. Abbott, Protocol PO6-134: A 5-Year Registry Study of Humira (Adalimumab) in Subjects With Moderately to Severely Active Crohn's disease (CD). Principal Investigator, 2008
85. Roche, Protocol 3-MV21542: Prophesys - A Prospective observational study on predictors of early on-treatment response and sustained virological response in a cohort of treatment naïve HCV-infected patients treated with pegylated interferons. Principal Investigator, 2008
86. Abbott Protocol M10-223: A Multicenter, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects with Ulcerative Colitis. Principal Investigator, 2008
87. AGI Therapeutics Research Ltd., Protocol AG1003-007: Open-Label Safety Study of AG1003 Averapamil. Principal Investigator, 2007
88. AGI Therapeutics Research Ltd., AG1003-003: A Randomized, Double-Protocol Blind, Placebo-Controlled, Study of AGI-003 Arverapamil in the treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D). Principal Investigator, 2007
89. ProStrakan Ltd, Protocol REC-C-001: A Randomized, Double-Blind, Placebo-Controlled, Multinational Study to determine the effect of Cellegesic nitroglycerin

- ointment 0.4% (Cellestic) on the pain associated with a chronic anal fissure. Phase III A. Principal Investigator, 2007
90. Alizyme, Protocol ATL 1251/052/CL: A Phase III, Multicenter, Open-Label, Extension Study to Evaluate the long-term safety of renzapride 4 mg daily in women with Constipation-Predominant Irritable Bowel Syndrome. Principal Investigator, 2007
 91. Alizyme, Protocol ATL 1251/038/CL: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of renzapride in women with Constipation-Predominant Irritable Bowel Syndrome. Principal Investigator, 2007
 92. Shire, Protocol SPD476-404: A Phase IV, Multicenter, Open-Label Study to assess clinical recurrence related to compliance with treatment with MMX mesalamine 2.4 g/day given once daily for the maintenance of quiescent ulcerative colitis. Principal Investigator, 2007
 93. Abbott, Protocol MO6-827: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis. Principal Investigator, 2007
 94. UCB, Protocol C87065 Cospar 2: An Open-Label, Multicenter Trial to examine the long-term safety, efficacy, and corticosteroid-sparing effect of certolizumab pegol in patients with moderate to severe Crohn's disease who have failed tapering of corticosteroids, needed corticosteroids after completion of tapering, or have successfully completed the trial of Cospar 1. Principal Investigator, 2007
 95. UCB, Protocol C87059 (Cospar 1): A Phase 3B Multicenter, Double-Blind, Placebo-Controlled, Randomized Trial to examine the corticosteroid-sparing effect of certolizumab pegol in patients with moderate to severe Crohn's disease. Principal Investigator, 2007
 96. Tioga, Protocol ASMP 2003: A 12-Week, Randomized, Double-Blind, Dose-Blind, Dose-Ranging, Placebo-Controlled Study of Asimadoline in Subjects with Irritable Bowel Syndrome. Principal Investigator, 2006
 97. Abbott, Protocol MO6-808: A Multicenter, Open-Label Treatment Protocol of the Human Anti-TNF Monoclonal Antibody Adalimumab in Patients with Moderate to Severe Crohn's Disease with Previous Exposure to Infliximab. Principal Investigator, 2006
 98. UCB, Protocol CDP870-033: A Phase III Multinational, Multicenter, Open-Label 52-week Safety Study to assess the safety of chronic therapy with the humanized anti-TNF PEG conjugate CDP870 400 mg sc, (dosed 4-weekly to week 48), in the treatment of patients with active Crohn's disease who have previously completed studies CDP870-031 or CDP870-032. Principal Investigator, 2005
 99. Colon Cleansing Efficacy and Safety of New Microcrystalline Cellulose Free Formulation of Sodium Phosphate Tablets (INKP-102) compared to Visicol Tablets (INKP-101): An Investigator-Blind, Randomized, Multiple Center Trial. Principal Investigator, 2004
 100. Phase II, Parallel-Group, Open-Label, Prospective, Comparative Study of JTK-003 400 mg co-administered with PEG-INF-2a versus ribavirin co-administered with PEG-INF-2a in genotype 1 HCV patients refractory to ribavirin co-administered with either PEG-INF-2a or PEG-INF-2b treatment. Approximately 18 US sites will enroll 100 treatment refractory patients. Patient participation consists of a 4-week Pre-treatment Screening

Phase, a 12-week Treatment Phase, and an 8-week Follow-up Phase for a total of 24 weeks. Principal Investigator, 2004

101. Vertex: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. The treatment period is comprised of two phases: the Core Study and the Rollover Phase. During the Core Study the subject will be randomized in a 1:1:1 ratio to 24 weeks of treatment in one of three groups. Principal Investigator, 2004
102. A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm Study of the Efficacy and Safety of OPC-6535 tablets in the Treatment of Subjects with Active Ulcerative Colitis. Sub-principal Investigator, 2004
103. ITONUD01-02: A Multicenter, Randomized, Open-Label Extension Phase Study of itopride to evaluate the long-term safety and efficacy in patients suffering from functional dyspepsia. Sub-principal Investigator, 2004
104. ITONUD01-01: Clinical Efficacy and Safety of Itopride versus Placebo in the treatment of Functional Dyspepsia: A Multicenter, Double-Blind, Randomized, Placebo-Controlled and Parallel Group Study. Sub-principal Investigator, 2004
105. D9770C00012: A Randomized, Double-Blind, Multicenter, Dose-Finding Phase IIb Study for up to 8 weeks treatment with AZD0865 25, 50, 75 mg and esomeprazole 40 mg given orally once daily for healing of Erosive Esophagitis in adults with GERD with erosive esophagitis according to the LA Classification. Principal Investigator, 2004
106. D9770C00011: A 4-week, Randomized, Double-Blind, Multicenter, Dose-Finding, Phase IIb Study with AZD0865 25, 50, 75 mg and esomeprazole 20 mg given orally once daily for the treatment of GERD without erosive esophagitis according to the LA Classification in adult subjects. Principal Investigator, 2004
107. 308180 (NOVEL 3): Phase III Randomized, Double-Blind, Placebo-Controlled, Multicenter Retreatment Study of Sargramostim (Leukine®) in Patients with Active Crohn's disease and Prior Treatment Response to Sargramostim. Principal Investigator, 2004
108. 197-02-220-OPC-6535-A: Phase III, Multicenter, Randomized, Double-Blind, Parallel Arm, 52-week dose comparison study of the efficacy and safety of 25 mg q.d. and 50 mg q.d. of OPC-6535 oral tablets and 800 mg b.i.d. of Asacol in the maintenance of remission in subjects with UC. Sub-principal Investigator, 2004
109. Dipentum (olsalazine sodium) in the management of UC in Remission: A Multicenter, Open-Label, Post Marketing Clinical Experience Study. Sub-principal Investigator, 2004
110. UCB, Protocol Precise 1-CDP870-031: A Phase III, Multinational, Multicenter, Double-Blind, Placebo-Controlled, Parallel group, 26-week study to assess the safety and efficacy of the humanized anti-TNF PEG conjugate, CDP-870, 400 mg (dosed at weeks 0, 2, 4, then 4-weekly to week 24, in the treatment of patients with active Crohn's disease. Sub-principal Investigator, 2003
111. An Open Label, Multicenter, efficacy and safety study of Pegasys® plus ribavirin in patients with chronic HCV infection who are unable to tolerate or who do not respond to 12 weeks of therapy with PEG-Intron® plus ribavirin (ML 16965). Principal Investigator, 2003
112. Open Label Trial of Leukin (sargramostim), a Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), in Active Crohn's disease. Principal Investigator, 2003

113. ISIS 2302-CS20: Phase III Double-Masked, Placebo-Controlled study of Alicaforsen (ISIS 2302), an Antisense Inhibitor of ICAM-1, for the Treatment of Patients with Active Crohn's Disease. Principal Investigator, 2003
114. Remission Rates for Once Daily Treatment with Esomeprazole 20 mg and Lansoprazole 15 mg for 6 months in Patients Whose Erosive Esophagitis Has Been Healed. Principal Investigator, 2003
115. Efficacy of 8 week with Esomeprazole Magnesium 40 mg qd to Lansoprazole 30 mg qd for the Healing of Erosive Esophagitis in Patients with Moderate or Severe Erosive Esophagitis, 2003
116. Randomized, Stratified, Double-Blind, Placebo-Controlled Phase 2 Study of the Steroid-Sparing Properties of Sargramostim (Leukine) Therapy in Patients with Corticosteroid-Dependent Crohn's Disease. Principal Investigator, 2003
117. A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study with PRN BID and Fixed Dosing Regimens of Alosetron in Female Subjects with Severe Diarrhea-Predominant Irritable Bowel Syndrome Who Have Failed Conventional Therapy. Principal Investigator, 2003
118. Phase II Randomized, Double-Blind, Placebo-Controlled, Multicenter Dose Ranging Study of IV daclizumab in Patients with Moderate to Severe Ulcerative Colitis. Principal Investigator, 2003
119. Esomeprazole 20 mg qd to Placebo qd for the resolution of Upper Abdominal Pain in Patients with Symptomatic Gastroesophageal Reflux Disease. Principal Investigator, 2003.
120. Abbott: Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Maintenance of Clinical Remission in Subjects with Crohn's Disease. Principal Investigator, 2003
121. Mesalamine Rectal Gel vs. Placebo in the treatment of Mild to Moderate Distal Ulcerative Colitis: A Multi-center, Double-Blind, Randomized, and Parallel Groups Study. Principal Investigator, 2003
122. Abbott: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Crohn's Disease. Principal Investigator, 2002
123. Pegylated Interferon ALFA 2B Plus Ribavirin on the Response of Genotype 1 Hepatitis C infected African American and Caucasian Patients. Principal Investigator, 2002
124. PEG-Intron + Ribavirin for Genotype 1 Hepatitis C Patients with Normal Aminotransferase Levels. PING. Principal Investigator, 2002
125. Merck Research Laboratories (084): A Consumer Use Study of OTC MEVACOR™ (Custom): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System. Sub-Investigator of Toll Free Medical Response Center, 2002
126. Safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet) for the treatment of mildly to moderately active ulcerative colitis. Principal Investigator, 2001
127. McNeil Consumer Healthcare (97-005): A Randomized, Open-Label, Multicenter Trial to Evaluate and Compare the Efficacy and Safety of Nicotrol Inhaler as part of an OTC Intervention Package or a Prescription as an Aid for Smoking Cessation. Principal Investigator, 2002

128. A Twelve week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging, Phase II Study to Assess the Clinical Efficacy of Alosetron (GR68755) in Male Subject with Irritable Bowel Syndrome. Principal Investigator, 1999
129. A Twelve week, Randomized, Double-Blind, Placebo-Controlled Study of Alosetron in Female Subjects with Alternating Diarrhea/Constipation Irritable Bowel Syndrome. Principal Investigator, 1999
130. Randomized, Controlled, Long-Term Trial of Interferon Alone Versus Interferon and Low-Dose Ribavirin in Patients with HCV Hepatitis Fibrosis who Failed Interferon and Ribavirin Treatment (Long Term Maintenance Trial). Principal Investigator, 1999
131. A Comparative Efficacy and Safety Study of H 199/18 (40mg) and Omeprazole (20 mg) in Study Subjects with Erosive Esophagitis. Principal Investigator, 1999
132. Pilot Study of the Safety and Activity of Interleukin-10 (rHuIL-10) in the prevention of Acute Pancreatitis following Endoscopic Retrograde Cholangiopancreatography (ERCP). Principal Investigator, 1999
133. BioClinical Partners, Inc. Protocol #007: Evaluation of Biomarkers for the Diagnosis and Management of Acute and Chronic Viral Hepatitis. Clinical samples collection protocol. 100 samples. Principal Investigator, 1999
134. BioClinical Partner, Inc. Protocol #005 : Evaluation of Biomakers for the Diagnosis and Management of Gastrointestinal Disorders and Patients with H. Pylori. Clinical Samples collection protocol. Principal Investigator, 1999
135. A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multi-Center Trial to Assess the Effect of Lexipafant on the Incidence of Acute Pancreatitis in Patients Undergoing an Endoscopic Retrograde Cholangiopancreatography (ERCP). Principal Investigator, 1999
136. Merck Research Laboratories, (081): A Multicenter, Open-Label, Storefront, Observational Use Study to Evaluate the Ability of Patients to Appropriately Self-Select Lovastatin 10 mg Utilizing an Enhanced Label and Additional Label-Reinforcement Tools. Principal Co-Investigator, 1999
137. Efficacy of INFERGEN for Chronic Hepatitis C in patients who are non-responders and relapsers to combination therapy with Intron-A + Ribavirin. A Multi-Center Trial. Investigator, 1998
138. Treatment of Chronic Hepatitis C with a Combination of Interferon Plus Ribavirin for Patients who are Treatment Naïve. Principal Investigator, 1998
139. A Phase II, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Clinical Trial to Evaluate the Safety and Efficacy of Two Doses of SYNORB Cd ®(8g/day, 16g/day) for the Treatment of Recurrent Clostridium Difficile-Associated Disease (CDAD).” Principal Investigator, 1998
140. A Multicenter, Randomized, Double-Blind, Parallel-Group Comparison Study of the Safety and Efficacy of a 7-Day Treatment of Pantoprazole Plus Selected Antibiotics in the Eradication of Helicobacter Pylori Infection. Sub-Investigator, 1998
141. J&J Merck Consumer Products Company: A Single-Dose, Randomized, Pilot Evening Heartburn Study Comparing Famotidine, Famotidine/Antacid Combination, Antacid, and Placebo. Principal Investigator, 1998
142. Merck Research Laboratories, (076): A Multicenter, Open-Label Study to Evaluate Compliance and Persistence in Patients Who Self-select to Receive Lovastatin 10 mg for

- Treatment of Moderate Primary Hypercholesterolemia (Total Cholesterol 200 to 240 mg/dl). Principal Investigator of Toll Free Medical Consultation Center, 1997-1998
143. An Open-Label Trial Assessing the Efficacy of Rimantadine in the Treatment of Patients Who Have Failed or Are Unable to Tolerate Interferon Therapy for Hepatitis C. Sub-Investigator, 1997
 144. A Double-Blind, Placebo-Controlled, Dose-Response, Parallel-Group, Randomized Study of Anxiolysis, Sedation, Safety, and Tolerance of Oral Transmucosal Etomidate in Patients Undergoing Diagnostic Fiberoptic Flexible Sigmoidoscopy. Principal Investigator, 1997
 145. Merck Research Laboratories: A Single-Dose, Randomized, Pilot Evening Heartburn Study Comparing Famotidine, Famotidine/Antacid Combination, Antacid, and Placebo. Principal Investigator, 1997
 146. Merck Research Laboratories: A Double-Blind, Randomized, Parallel-Group Study, Comparing the Onset and Duration of Symptom Relief with Famotidine/Antacid Combination, Famotidine 10 mg, Antacid 21mEq, and Placebo in Patients with Frequent Heartburn. Principal Investigator, 1997
 147. Intron® A+ Ribavirin for Treatment of Patients with Chronic Hepatitis C not previously Treated with Interferon. Co-Principal Investigator, 1997
 148. Merck Research Laboratories, (079): A Multicenter, Open Label, Storefront Study to Evaluate Compliance and Persistence of Lovastatin 10 mg in Patients Who are Qualified by a Telephone Label Reinforcement Service for Treatment of Moderate Primary Hypercholesterolemia (Total Cholesterol $\leq$ 240 mg/dl, LDL $\geq$ 130 mg/dl).
 149. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of Healing and Relapse Rates following Oral GR122311X Compared with GR88502X, Ranitidine and Placebo in Patients with Duodenal Ulcer. Clinical Investigator.
 150. A Multicenter Randomized, Double-Blind, Placebo-Controlled Evaluation of Healing and Relapse Rates following Oral GR122311X in Combination with Clarithromycin Compared to GR122311X Clarithromycin, and Placebo in Patients with Duodenal Ulcer. Clinical Investigator.
 151. Nizatidine vs Placebo- Preventing GU Relapse in Long-term NSAID Users. Clinical Investigator.
 152. A Randomized Open-Label Multicenter Trial to Evaluate and Compare Efficacy and Safety of Nicotrol ® Gum as an Aid in Smoking Cessation. Principal Investigator.
 153. A Multicenter, Open-Label, Long Term Safety Study of H 199/18 40 mg in Subjects with Healed Erosive Esophagitis. 1997.
 154. A Multicenter, Randomized, Double-Blind, Eight Week Comparative Efficacy and Safety Study of H 199/18 20mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis. Principal Investigator, 1997
 155. Washington-Metropolitan Area Multicenter Investigator Initiated Trial of Chronic Hepatitis C Patients Using Combination of Interferon Alpha 2b (Intron A) and Ribavirin for Patients with Previous Non-Sustained or Non-Response to Interferon Alone. Co-Principal Investigator, 1997
 156. A Multi-center, Double-Blind, Randomized Study to Evaluate the Effects of a Ten Day Regimen of Omeprazole 20 mg B.I.D., Clarithromycin 500 mg B.I.D. and Amoxicillin 1 gr B.I.D. on Eradication of H. Pylori and Duodenal Ulcer Healing in Patients with Acute Duodenal Ulcer and H. Pylori Infection. Principal Investigator, 1996

157. Anesta Corp.: A Multicenter, Open-Label, Cross-Over Comparative Study of Safety and Preferences for Three Smoking Cessation Products- Oral Transmucosal Nicotine (OTNC), Nicotine Polacrilex Gum, or Nicotine Transdermal Patches, in Smokers Attempting to Quit. Principal Investigator, 1996
158. McNeil Consumer Products Company: Randomized Open-Label Multicenter Trial to Evaluate and Compare the Efficacy and Safety of Nicotrol ®Patch versus Nicorette® as an Aid in Smoking Cessation. Principal Investigator, 1996
159. Clinical Evaluation of Propulsid 7 (Cisapride) Tablets, 20 mg B.I.D., in the Treatment of Subjects with Symptoms of Chronic Gastroesophageal Reflux Disease. Principal Investigator, 1995
160. McNeil Nicotrol ®Patch: Prospective OTC Switch Study of Nicotrol® Patch Physician Site vs. OTC Site. Chief Clinical Investigator, 1994
161. ELAN ProStep Patch: Prospective Double-Blind, Placebo-Controlled Study of 600 Subjects Comparing Placebo to Active Patch. Chief Clinical Investigator, 1993
162. A Multicenter Trial of Early Colorectal Cancer Detection Comparing Hemoccult, Hemoccult SENSE and HemeSelect for Detection of Occult Blood in the Stool. Investigator, 1985-1986