A U S T R A L I A

Patents Act 1990

IN THE MATTER of Australian Patent Application No. 2019346134 in the name of Janssen Biotech, Inc.

- and -

Opposition thereto by Samsung Bioepis AU Pty Ltd

DECLARATION

Declaration of: Matthew Aaron Ciorba

Address: 1 Ricardo Lane, St. Louis, MO 63124, United States of America

Occupation: Gastroenterologist and Professor of Medicine

Date: 14 January 2024

CONTENTS

3.	**Annexure MAC-3**, being a copy of a clinical trial record of the clinical trial titled "A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UNIFI)" and identifiable by ClinicalTrials.gov identifier NCT02407236, as published on the ClinicalTrials.gov website on 13 August 2018	136(i)	39
4.	**Annexure MAC-4**, being a copy of Ochsenkühn et al (2018) "P759 Ustekinumab as rescue treatment in therapy-refractory or –intolerant ulcerative colitis" 12(S1) *Journal of Crohn's and Colitis* S495 published on 16 January 2018	136(ii)	39
5.	**Annexure MAC-5**, being a copy of Ochsenkühn et al (2018) "Tu1713 Clinical outcomes with ustekinumab as recue [sic] treatment in therapy-refractory or -intolerant ulcerative colitis: real worl [sic] experience in a large single center cohort" 154(6;S1) *Gastroenterology* S-997 published in May 2018	136(iii)	39
6.	**Annexure MAC-6**, being a copy of a poster titled "Tu1713: Clinical outcomes with ustekinumab as rescue treatment in therapy-refractory or -intolerant ulcerative colitis: real world experience in a large single center cohort", allegedly presented at the AGA's annual conference, DDW, on 5 June 2018	136(iv)	39
7.	**Annexure MAC-7**, being a copy of the Product Information for Stelara® (ustekinumab) dated 27 February 2017	168	46
8.	**Annexure MAC-8**, being a copy of Australian Patent Application No. 2019346134 in the name of Janssen Biotech, Inc.	221	57

I, **Matthew Aaron Ciorba**, 1 Ricardo Lane, St. Louis, MO 63124, United States of America, do solemnly and sincerely declare as follows:

A BACKGROUND

1. I am a gastroenterologist, Professor of Medicine, and Director of Inflammatory Bowel Diseases (**IBD**s) Research at Washington University in St Louis, Missouri, in the United States. My clinical practice and research is primarily directed to advancing care for patients affected by Crohn's disease (**CD**), ulcerative colitis (**UC**), and colon cancer.

2. I have been asked by Davies Collison Cave Law Pty Ltd (**DCCL**) to provide independent expert evidence in this proceeding.

3. I have been informed by DCCL that my evidence will be used in an opposition by Samsung Bioepis AU Pty Ltd to an Australian patent application in the name of Janssen Biotech, Inc. (the **Opposed Application**). I have received research support from a number of pharmaceutical companies throughout my career, including Janssen Scientific Affairs, LLC. To the best of my knowledge, none of the support I received relates either directly or indirectly to the Opposed Application.

4. DCCL has informed me that 24 September 2018 is the Relevant Date of the Opposed Application (the **Relevant Date**). I have been instructed by DCCL that my evidence should be given based upon my knowledge that I had acquired prior to the Relevant Date and without regard to the knowledge that I had acquired after that date. In giving my evidence I have complied with this instruction.

5. In this declaration, I refer to documents in each case by a reference based on my initials, for example **Annexure** "**MAC-1**", "**MAC-2**", and so on. In each case, the particular document or item is produced and shown to me and marked as I have described at the time of making my declaration.

6. I have been provided with a copy of the Federal Court of Australia Expert Evidence Practice Note (GPN-EXPT) dated 25 October 2016 (**Practice Note**), including the Harmonised Expert Witness Code of Conduct (**Code of Conduct**) by DCCL. I have read these documents, and I agree to be bound by the Code of Conduct. I confirm that I have complied with the Code of Conduct when giving my evidence. **Annexure MAC-1** to this declaration is a copy of the Practice Note and Code of Conduct provided to me by DCCL. For the purpose of making this declaration, I have made all enquiries that I believe are desirable and appropriate and no matters of significance which I regard as relevant, have, to my knowledge, been withheld.

7. I make this declaration from my own knowledge. My opinions set out in this declaration are wholly or substantially based on my specialized knowledge and experience gained from the training, study and experience set out in **Part B**, below. I consider that my clinical and academic knowledge and experience renders me well-qualified to express the opinions I do in this declaration.

8. While, in some parts of my declaration below I have used the present tense and others the past tense, each of my comments below reflects my opinion as to what was known and understood by me as at the Relevant Date, unless I indicate otherwise.

9. This declaration adopts the following structure:

B QUALIFICATIONS AND EXPERIENCE

10. My curriculum vitae, which outlines my qualifications and experience, is provided as **Annexure MAC-2**.

B.1 Education

11. I obtained a Bachelor of Science in Exercise Science (with Honors) from the University of Iowa College of Liberal Arts in 1996. I subsequently undertook graduate studies at the University of Iowa College of Medicine, graduating with a Doctorate of Medicine with Alpha Omega Alpha Honors in 2001.

12. After graduating university, I commenced further postgraduate training. From 2001–2004, I undertook an Internship and Medicine Residency at the Washington University School of Medicine in St Louis, Missouri. In 2004, I was Chief Resident at the Washington University School of Medicine and John Cochrane VA Hospital. From 2004–2007, I continued at Washington University School of Medicine, completing a Gastroenterology and Hepatology Fellowship (through a National Institutes of Health T32 grant). In this time, I received subspecialty clinical training

in IBD under Christian Stone, MD as part of the Washington University Inflammatory Bowel Disease Program. In 2005, I participated in the American Gastroenterological Association / Abbott "Investing in the Future of IBD" program and the Annenberg "Mentoring in IBD" program. In 2007, I took part in the Shire IBD Mentoring Program. Finally, in 2007, I completed a Clinical Inflammatory Bowel Disease Fellowship (sponsored by the Crohn's and Colitis Foundation of America) under Maria T. Abreu, MD at the Inflammatory Bowel Disease Center of Mount Sinai Hospital in New York City, New York.

13. I also undertook post-doctoral research training at the Washington University School of Medicine from 2005–2010, under my primary mentor William F. Stenson, MD and an advising committee of Rodney D. Newberry, MD, Thaddeus S. Stappenbeck, MD, PhD, and Nicholas O. Davidson, MD, DSc.

B.2 Employment history

B.2.1 Academic employment history

14. I have held various academic positions at Washington University in St Louis since 2007. My key appointments have been:

    (a) Instructor of Medicine (2007–2010);

    (b) Assistant Professor of Medicine (2010–2017);

    (c) Associate Professor of Medicine (with tenure) (2017–2022); and

    (d) Professor of Medicine (investigator track with tenure) (2022–present).

15. In addition to these appointments, I have held a number of academic directorships at Washington University in St Louis, including:

    (a) Director of the Inflammatory Bowel Diseases Clinical Fellowship (2008–present);

    (b) Director of IBD Research for the Inflammatory Bowel Disease Program (2016–2017);

    (c) Associate Director of GI Fellowship Program and Fellow Research (T32) (2016–present);

    (d) Founding Director of the Inflammatory Bowel Diseases Research Program and the Lawrence C. Pakula, MD IBD Innovation and Education Fund (2017–present);

(e) Founding Director of the Inflammatory Bowel Disease Center of Excellence (2017–present);

(f) Associate Director of the Gastrointestinal Fellowship Program and Fellow Research (NIDDK T32) (2018–present);

(g) Founding Director of the Advanced Fellowship in Inflammatory Bowel Diseases (2019–present); and

(h) Co-Director, Precision Animal Models and Organoids Core (PAMOC), Washington University (P30 NIDDK) Digestive Diseases Research Cores Center (2019–present).

16. My academic research has been focused on advancing care for patients affected by IBDs, including CD and UC, and colon cancer. My basic-translational research program is dedicated to defining pathways and mechanisms of intestinal inflammation and the transition to colon cancer. My laboratory focuses largely on the epithelial response to inflammation, injury and repair. To date, my laboratory's investigations have spawned four ground-breaking bench-to-bedside clinical trials addressing unmet patient needs in colitis, enteritis and rectal cancer using probiotics, novel immunotherapies and manipulating bile acids. As Director of IBD Research for the Inflammatory Bowel Disease Program at Washington University in St Louis since 2016, I foster collaborative discovery between the university's scientific investigators and its affiliated clinical program.

17. A major focus of my academic research has been investigating the role of an enzyme, indoleamine-2,3-dioxygenase 1, as a regulator of the intestinal inflammatory response and as a modifier of colitis-associated cancer progression. Another focus of my academic research has been the role and mechanisms of probiotic bacteria in protecting the intestinal epithelium from injury during radiation therapy.

18. Furthermore, I have served as the Institutional Principal Investigator for 10 sponsored clinical trials of CD or UC treatments, including trials involving the monoclonal antibodies GS-5745 (andecaliximab), MLN0002 (vedolizumab), ABT-874 (briakinumab) and MDX-1100, the small molecule pan-Janus kinase inhibitor TD-1473 (izencitinib), and an electro-mechanical injection device for self-injection of certolizumab pegol.

B.2.2 Clinical employment history

19. Since 2007, I have been an Attending Physician: Internal Medicine & Gastroenterology at Barnes-Jewish Hospital, St Louis, the teaching hospital of the Washington University School of Medicine and the largest hospital in Missouri. Since 2015, I have also been an Attending Physician: Internal Medicine & Gastroenterology at Barnes-Jewish West County Hospital in western St Louis County, Missouri. At the Relevant Date, I also held (and continue to hold) a number of other hospital and committee appointments, a list of which is set out in my curriculum vitae at **Annexure MAC-2**.

20. My clinical expertise is in caring for patients with IBDs (particularly CD and UC) and preventing colon cancer. As the head of the Washington University School of Medicine in St Louis' IBD Center, I lead one of the largest clinical teams (14 clinicians) in the United States dedicated to providing comprehensive and cutting-edge clinical care to more than 8,000 patients affected by IBDs.

B.3 Publications

21. As at the Relevant Date, I was an author or co-author of over 50 peer-reviewed academic papers, in the form of both original research and review articles. I had also authored or co-authored 10 book chapters. These publications were predominantly on gastroenterology and IBDs, including in relation to the topics described at paragraphs 17 and 18 above. A full list of my publications is referred to in my curriculum vitae at **Annexure MAC-2**.

C SOURCES OF INFORMATION

22. DCCL asked me to outline the sources of information I regularly consulted to keep up to date with developments in relation to the diagnosis, treatment and management of IBDs (the **Field**) at the Relevant Date.

C.1 Literature

23. I subscribed to and/or regularly read peer-reviewed journals and industry publications, including the following:

    (a) Nature;

    (b) Nature Reviews Gastroenterology and Hepatology;

    (c) Science;

    (d) The New England Journal of Medicine;

(e) The Lancet;

(f) The Lancet Gastroenterology and Hepatology;

(g) Proceedings of the National Academy of Sciences;

(h) Gut;

(i) American Gastroenterological Association Journals (Gastroenterology, Cellular and Molecular Gastroenterology and Hepatology, and Clinical Gastroenterology and Hepatology);

(j) Journal of Crohn's and Colitis; and

(k) Inflammatory Bowel Diseases Journal.

24. I also held editorial positions for several academic journals, where part of my regular responsibilities was to review the latest research papers in the Field. At the Relevant Date, I was or had been:

(a) Section Editor of Current Opinion in Supportive and Palliative Care – Gastrointestinal Tract (2017);

(b) Editorial Board Member of Gastroenterology;

(c) Editorial Board Member of the Journal of Clinical Gastroenterology;

(d) Editorial Board Member of Translational Research;

(e) Contributing Editorial Board Member of Gastroenterology (Selected Summaries);

(f) Contributing Editorial Board Member of Gut;

(g) Ad Hoc Scientific Journal Reviewer of over 15 journals, including: Journal of Clinical Investigation; Gut; Journal of Immunology; American Gastroenterological Association Journals (Gastroenterology; Cellular and Molecular Gastroenterology and Hepatology; and Clinical Gastroenterology and Hepatology); Inflammatory Bowel Diseases Journal; Journal of Crohn's and Colitis; American Journal of Pathology; British Journal of Pharmacology; Journal of Gastroenterology and Hepatology; Digestive Diseases and Sciences; Radiation Research; Journal of Basic Microbiology; Hospital Practice; American Journal of Clinical Nutrition; and Nature Scientific Reports.

C.2 Professional meetings

25. I regularly attended international conferences including the Digestive Diseases Week (**DDW**; for which I have been a Moderator since 2010), Advances in Inflammatory Bowel Diseases, the Crohn's and Colitis Conference, and the Annual Meeting of the American College of Gastroenterology.

26. I also read papers published in the proceedings of conferences I did not attend, including the World Gastroenterology, IBD & Hepatology Conference and the European Crohn's and Colitis Organisation (**ECCO**) Congress.

27. Furthermore, I was the chair or an organizing committee member of the following professional meetings, courses and workshops:

    (a) Chair of the Crohn's and Colitis Foundation Mid America Patient Education Symposium (from April 2010 to 2017);

    (b) Chair of Washington University's Multidisciplinary Management of IBD Continuing Medical Education Course (from April 2018 to Present);

    (c) Course Organizer for the Crohn's and Colitis Foundation St Louis Patient and Provider Education Day (from April 2018); and

    (d) Organizer of the Washington University Organoid Workshop and Journal Club (from September 2018).

C.3 Other

28. As at the Relevant Date, I had been (and in some cases was still) an ad hoc member of nine National Institutes of Health scientific panels, as well as a member of a number of other national and international scientific panels (e.g., the Colitis Foundation of America and the American Gastroenterological Association).

29. I have held teaching, academic supervisory, and clinical mentorship roles since 2004. At the Relevant Date, I had various teaching responsibilities at the Washington University School of Medicine which required me to be up to date in my knowledge of the Field. Since 2006, I had been a small group leader in the course "Pathophysiology of Disease: Gastroenterology and Nutrition". I also had numerous duties as part of my Fellowship in Gastroenterology directorship positions, including responsibility over Gastrointestinal Fellows in each clinic, being part of education, mentoring and Fellowship selection committees, and in relation to IBD lecture series, Advanced Fellowship Training, and Journal Club. Furthermore, I had supervised numerous undergraduate students, postgraduate medical

students, PhD candidates and postdoctoral scholars, and regularly served on university thesis committees.

30. I undertook, and continue to undertake, invited professorships and lectureships on the topic of IBDs several times each year at universities, medical professional associations, conferences and companies, a full list of which can be found in my curriculum vitae at **Annexure MAC-2**.

31. From consulting the above sources of information and my discussions with other gastroenterologists, I believe my knowledge of IBDs was generally reflective of the knowledge of gastroenterologists working in the Field internationally at the Relevant Date and at that date (as it is now) the Field was an international field.

D COMMON GENERAL KNOWLEDGE

32. DCCL asked me to outline what I understood to be generally known and accepted by gastroenterologists working in the Field in relation to CD and UC as at or prior to the Relevant Date.

33. Each of the matters set out in this **Part D** of my declaration were known to me, and I believe were well known and generally accepted by other gastroenterologists working in the Field at the Relevant Date.

34. While both CD and UC are categorized as IBDs, they are distinct diseases. In the below paragraphs I address many of the differences between CD and UC, including in relation to their phenotype, pathogenesis and treatment options. In this declaration I sometimes refer to CD and UC collectively (e.g. CD and UC, CD and/or UC, etc.). This is for convenience of expression only and does not indicate that CD and UC are the same disease. Further, where I refer to both CD and UC, I refer to CD first and UC second. This is for consistency of expression and does not indicate anything regarding the relative importance or severity of the two diseases.

D.1 CD

35. CD is characterized by inflammation anywhere in the gastrointestinal (**GI**) tract, which runs from the mouth to the anus and comprises the esophagus, stomach, and bowel, including the small intestine and large intestine (colon). CD most commonly affects the ileum, which is the lower end of the small intestine where it connects to the colon. The rectum (the last six or so inches of the colon before the anal canal) is involved in only about 10% of CD cases. Commonly, inflammation due to CD appears in patches of the GI tract (or "skip lesions") and can affect the full thickness of the bowel wall, termed "transmural lesions".

36. Symptoms of CD tend to have an insidious onset. Patients with CD typically present with symptoms such as chronic diarrhea, abdominal pain and fatigue. Fever, weight loss and anemia are also common in patients with severe CD, as their ability to absorb nutrients may be affected by the inflammation. CD is also associated with bowel complications, such as fibrosis and strictures, fistulas and abscesses, and an increased risk of colorectal cancer. CD can also cause extra-intestinal manifestations, such as in the joints (e.g., swelling, pain), eyes (e.g., redness, itchiness, and pain), skin (e.g., bumps, rashes, ulcers) and kidneys (e.g., stones).

37. Patients with CD may present at any age, although the peak incidence of diagnosis is before the age of 30 years during a period of active disease. Patients typically experience relapsing and remitting disease activity, which involves periods of active disease ("flares") alternating with periods of remission in which symptoms are minimal or absent. Periods of remission can vary greatly between patients, lasting weeks, months or even years. However, some patients may experience continuous disease activity and never experience remission.

D.2 UC

38. UC is characterized by chronic inflammation and ulcers on the inner lining of the colon and rectum. Unlike CD, UC is a more superficial disease that does not penetrate the bowel wall, and inflammation usually begins in the rectum and spreads to the lower portion of the colon in a continuous pattern. In severe cases, inflammation may spread throughout the entire colon.

39. Patients with UC typically present with acute onset of symptoms of an inflamed rectum, such as rectal bleeding (bloody stools), urgent bowel movements (diarrhea) or a feeling of pressure or pain as though they need to have a bowel movement even though the bowel is empty (termed "tenesmus"). Extra-intestinal manifestations, such as in the joints, eyes, skin and kidneys, may also occur in patients with UC but are less common than in CD patients and may manifest differently. Patients with UC also have an increased risk of colorectal cancer, however other bowel complications (such as the strictures, fistulas and abscesses that are common in CD patients) are not typically seen in UC patients.

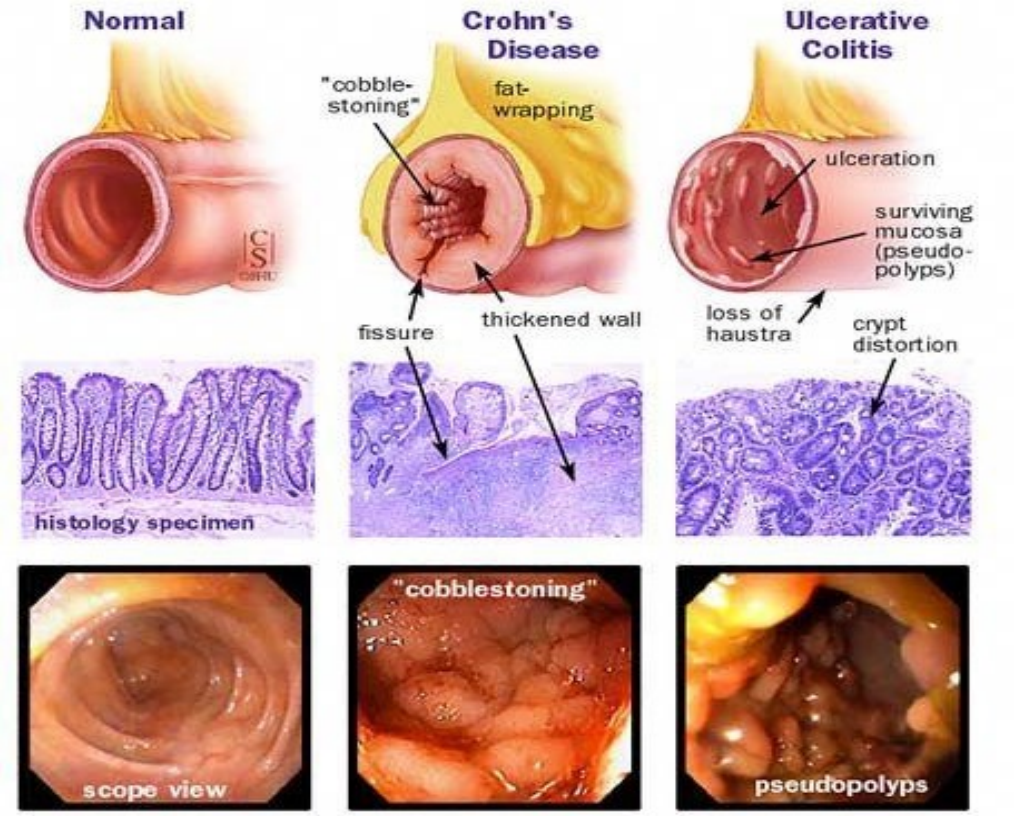
40. Patients with UC may present at any age, although the peak incidence of diagnosis is between the ages of about 15 and 30 years during a period of active disease. Patients typically experience relapsing and remitting disease activity, although some patients may experience continuous disease activity and never experience remission. Like CD, periods of remission can vary greatly among patients with UC.

D.3 Differing phenotypes of CD and UC

41. The differing phenotypes of CD and UC are shown in Figure 1 below. CD, which affects the full thickness of the bowel wall, typically presents very differently to UC. For example, CD results in thickening of the bowel wall with a "cobblestone" appearance of the inner lining and is commonly associated with fissure formation in the bowel wall. Fat wrapping or "creeping" is also common in CD, which occurs when mesenteric fat wraps around the intestines in an effort to protect the tissue, but ultimately exacerbates inflammation. CD is also associated with significant distortion of colonic crypts, the basic structural unit of the colonic epithelium.

42. In contrast, UC, which affects only the inner lining of the bowel, appears as ulcers and pseudopolyps in the surviving mucosal tissue. Chronic UC is also associated with loss of haustra, which are the saccules on the outer surface of the colon that are responsible for its segmented appearance. This loss of haustra causes the diseased segment of the colon to appear smooth-walled and cylindrical, leading to a "lead pipe" appearance of the colon, which can be visualized using imaging techniques such as radiography, barium enema, CT, or MRI. Loss of haustra is far less common with CD and typically does not occur throughout the entire colon.

Figure 1. Comparison of gross (top), histologic (middle) and endoscopic (bottom) appearance of normal colon with the colon of patients with CD or CD (adapted from https://www.hopkinsmedicine.org/health/conditions-and-diseases/crohns-disease)



D.4 Pathogenesis of CD and UC

43. CD and UC are referred to as "idiopathic" inflammatory diseases because their underlying causes are not fully understood. However, the distinct phenotypes of CD and UC discussed in **Part D.3** above are indicative of the underlying differences in their pathogenesis.

44. At the Relevant Date, CD and UC were generally thought to arise due to a dysfunctional immune response to certain environmental and/or genetic factors that disrupt the homeostasis of the intestinal mucosa. Certain aspects of this dysfunctional immune response had been characterized (although incompletely) as at the Relevant Date. For example, certain cell signalling proteins called "cytokines" (identified using Genome Wide Association Studies) and the cell types that secrete them were known in the Field to be associated with either CD or UC, or both. However, at the Relevant Date, there was a substantial amount that was not yet understood about the pathogenesis of CD and UC, and why an immune response leads to CD in some patients and UC in others. That lack of understanding persists today.

45. The association of certain altered cytokine profiles with CD and/or UC has been known since the 1980s. Since that time extensive research has been undertaken in an attempt to characterize the various immunological processes and inflammatory mediators implicated in CD and/or UC. As a result, various theories have been put forward in relation to the immunological processes leading to CD and UC. For example, prior to around the early 2000s, the prevailing theory was that CD was driven by a Th1 cytokine profile (e.g., IFN-γ, TNF-α, IL-2), whereas UC was driven by a Th2 cytokine profile (e.g., IL-5, IL-13). However, by around the mid-2000s, this theory had fallen out of favor with many researchers, at least in part because the roles of other effector T cell subsets, such as Th17, NKT and regulatory T (T_{Reg}) cells, were subsequently identified in CD and/or UC. Accordingly, it was identified that some cytokines were distinctly associated with either CD or UC, and others were common to both. Other theories contemplated a greater role of the intestinal epithelium, the constitution of the microbiota and/or other environmental factors (such as smoking, diet, infections) in the pathogenesis of CD and UC.

46. In the following paragraphs, I briefly touch on some of the immunological processes and inflammatory mediators that were known in the Field to be implicated to varying extents in CD and/or UC as at the Relevant Date.

47. Cytokines are small proteins – including interleukins (**IL**s), interferons (**IFN**s), tumor necrosis factor (**TNF**) and chemokines – that play an important role in regulating inflammation in the body. There are many different pro-inflammatory cytokines (e.g., IFN-γ, TNF-α, IL-6, IL-12, IL-13, IL-17, IL-23, and IL-33) and anti-inflammatory cytokines (e.g., IL-10, IL-22, TGF-β) involved in various immunological processes throughout the body. Cytokines also exhibit the properties of both pleiotropy (i.e., cytokines are capable of performing multiple biological functions) and redundancy (i.e., different cytokines share biological functions). Cytokines are secreted locally or systemically by almost all immune cells types, including T cells (e.g., Th1, Th2 and Th17), macrophages, dendritic cells, neutrophils, natural killer (**NK**) cells, $\mathbf{T_{Reg}}$ cells, and innate lymphoid cells (ILCs). Each immune cell type is associated with a different cytokine profile.

48. As I mentioned in paragraph 45 above, some of these cytokine profiles are unique to either CD or UC, and some of them are implicated in both diseases. Under normal conditions, local immune cells secrete a delicate balance of pro- and anti-inflammatory cytokines to maintain homeostasis in the intestinal mucosa. When the intestinal epithelium is compromised, these immune cells become activated and various pro-inflammatory cytokines become upregulated, driving the inflammatory response. Anti-inflammatory cytokines may also be upregulated in an attempt to bring the inflammation under control, but are insufficient to counteract the pro-inflammatory environment. The distinct and overlapping cytokine profiles associated with CD and UC are further complicated by the pleiotropic and redundant roles of cytokines. For example, the effect of any one cytokine can depend on the cell type and location where it is produced as well as the cell type receiving it, activating different gene expression networks. Further, when a particular cytokine is either up- or down-regulated, other cytokines may compensate to varying degrees for its altered expression. This may lead to a change in the cytokine profile associated with CD and UC as the respective diseases progress.

49. The complex network of inflammatory cytokines implicated in CD and/or UC act via a series of different cytokine-mediated intracellular signalling pathways involving Janus kinase (**JAK**) and signal transducer and activator of transcription (**STAT**) signalling cascades. At the Relevant Date, at least four different JAK molecules (JAK1, JAK2, JAK3, and TYK2) and several members of the STAT family (e.g., STAT1, STAT2, STAT3, etc.) were known. Each different cytokine signals through a different cell surface receptor. The binding of a cytokine to its specific receptor activates the corresponding JAK, resulting in the creation of a binding site for STATs, where they are phosphorylated by the JAK and dimerize. The dimerized

STATs then translocate into the cell nucleus, where they regulate the transcription of certain cytokines. Different combinations of cytokine receptor, JAK and STAT result in different cellular responses. Therefore, different cytokines result in different STAT/JAK activation patterns and the transcription of different cytokine profiles, which may be associated with CD or UC, or both.

50. The disruption of cytokine-mediated interactions in the intestinal mucosa also results in circulating immune cells (leukocytes) migrating to the site of inflammation as part of the body's immune response (a process termed "leukocyte trafficking"). This process is facilitated, for example, by the interaction of integrin molecules located on the surface of the leukocytes (e.g., α4β7 integrin) with cellular adhesion molecules, such as mucosal vascular addressin cellular adhesion molecule 1 (**MAdCAM-1**), expressed on the surface of endothelial cells lining the blood vessels along the GI tract. The complex process of leukocyte trafficking is also mediated by numerous other factors, including the binding of sphingosine-1-phosphate (**S1P**) to receptors on the surface of T cells.

D.5 Differential diagnosis of CD and UC

51. Patients are typically referred to a gastroenterologist like myself for assessment for IBD after presenting to their primary care physician with symptoms of persistent diarrhea (e.g., for at least 2 weeks), rectal bleeding, abdominal pain and/or changes in frequency of bowel movements. In some cases, patients present for the first time to a hospital emergency room with severe pain. Every patient presents differently, so my comments below represent generalizations about the diagnostic process and are not intended to be exhaustive.

52. When I assess a patient with a suspected IBD, I first obtain a full patient history to gauge whether their symptoms are consistent with CD or UC. In some cases, the symptoms described may be more consistent with an unresolved infection (e.g., if their symptoms have not exceeded 2 months, acute onset of symptoms, partial response to an initial course of antibiotics, or if there is recent history of travel), in which case I might first prescribe antibiotics to see if the infection resolves. If the symptoms described are more consistent with IBD (e.g., if the patient reports rectal bleeding or blood in their stools, or the symptoms do not resolve with antibiotics), I would typically send the patient for an endoscopy. I may also request cross-sectional imaging, e.g., a CT scan, at the same time. CT scans tend to be more useful for identifying complications of IBD, such as fistulas or strictures in patients with CD. Patients who present for the first time to a hospital emergency room will

usually get a CT scan in the first instance, and if a bowel abnormality is identified, they will then have an endoscopy.

53. Endoscopy uses a small camera affixed to a thin, flexible tube to visualize parts of the GI tract. The type of endoscopy may depend on the location of the symptoms. For example, in a colonoscopy the camera is inserted via the anus to visualize the rectum, colon and ileum. In a sigmoidoscopy, the camera is also inserted via the anus to visualize the rectum and sigmoid colon (this is less invasive than a colonoscopy). In an esophagogastroduodenoscopy, the camera is inserted via the mouth to visualize the esophagus, stomach and duodenum. During endoscopy, biopsy may be performed to remove a small portion of damaged tissue, which can be used to detect for cancer, pre-cancerous changes or inflammatory changes to the tissue. In addition to its usefulness in diagnosis, endoscopy is a key component in the monitoring of disease activity and progression, as well as response to therapy, in CD and UC.

54. Differential diagnosis usually requires a combination of patient history, physical examination, blood and stool testing, endoscopy, and/or biopsy. However, there are some clear signposts that aid in differentiating between CD and UC. For example, as discussed above, inflammation in UC typically occurs in a continuous pattern and is limited to the rectum and colon, whereas CD is patchier in appearance and can occur anywhere in the GI tract but does not typically involve the rectum. Therefore, involvement of the rectum is usually indicative of UC, whereas involvement of areas beyond the colon, such as the terminal ileum (part of the small intestine), is indicative of CD. Fistula formation, strictures or granulomas are also indicative of CD.

55. Given the distinct phenotypes of CD and UC (as discussed in **Part D.3** above), differential diagnosis is typically possible upon first presentation in over 90% of cases. When inflammation is confined to the colon but appears patchy, differential diagnosis may require further monitoring of disease progression. In this case, the patient is said to have "indeterminate colitis" until such time as a diagnosis of CD or UC can be made. For example, if signs of inflammation are subsequently observed in the GI tract beyond the colon (or in the perianal area), the patient will be diagnosed with CD. If the inflamed tissue becomes continuous and involves the rectum, the patient will be diagnosed with UC.

56. Blood tests can also be useful in the diagnosis and monitoring of disease progression in CD and UC. For example, fecal calprotectin, erythrocyte sedimentation rate (**ESR**) and C-reactive protein (**CRP**) are biomarkers of

inflammation that can be measured in serum. However, none of these biomarkers is specific to CD or UC and cannot form the basis for a definitive diagnosis (although the correlation between fecal calprotectin levels and remission tends to be greater in UC patients). Other routine blood tests may also be performed during diagnosis and monitoring of disease progression of CD and/or UC, such as complete blood count (CBC; which can be indicative of infection or anemia), electrolyte levels (which can drop due to diarrhea), and vitamin B12 (which can be deficient in patients with CD due to poor nutrient absorption).

D.6 Disease activity indices (DAIs)

57. Patients with CD or UC are typically classified as having mildly, moderately or severely active disease, or as being in remission. A number of disease activity indices (**DAI**s) have been developed to measure disease activity. While these DAIs were developed for use in clinical trials to help standardise the assessment of participants, most (if not all) gastroenterologists have familiarity with them and use one or more of them from time to time in clinical practice. Some of these DAIs were more widely used than others. For example, DAIs that incorporate objective measures of disease activity, particularly endoscopic assessment, tend to be favored over (or used in combination with) more subjective DAIs, both in clinical trials and by gastroenterologists.

58. DAIs are used to provide a moment-in-time assessment of disease activity and are useful for comparing disease activity at different points in time, or across multiple patients. In addition to disease activity, gastroenterologists are also concerned with disease severity, which is a measure of disease progression. Disease severity accounts for changes in disease activity over time as well as other longitudinal factors, such as patient history, that represent risk factors for more severe disease prognosis.

59. In clinical practice, disease activity is most commonly assessed using endoscopy, which provides the most reliable and objective measure of disease activity. Other objective measures of inflammation may also be used, including measuring the levels of certain biomarkers of inflammation in the blood, such as fecal calprotectin, ESR or CRP. However, as I mentioned above these biomarkers are not specific to CD or UC. There are also certain members of the population who have active CD or UC but do not have elevated levels of certain inflammatory biomarkers.

60. There have been a number of DAIs developed for CD or UC that involve quantitative and/or qualitative assessment of physical symptoms, as discussed below. In

addition, a patient's health-related quality of life can be an important factor in determining whether treatment is effective and whether surgical intervention would be appropriate. Therefore, clinical trials often also incorporate the Inflammatory Bowel Disease Questionnaire (**IBDQ**) as an indicator of disease severity. The IBDQ is a 32-item questionnaire that assesses a patient's health-related quality of life in four domains: bowel symptoms, emotional health, systemic systems and social function.

D.6.1 DAIs for CD

61. The most commonly used DAI for CD is the Crohn's Disease Activity Index (**CDAI**), which was developed for use in clinical trials. The CDAI involves providing a score for several variables across eight domains over a seven day period: number of liquid/soft stools per day, abdominal pain, general wellbeing, complications (arthritis/arthralgia, mucocutaneous lesions, iritis/uveitis, anal disease, external fistula and fever), antidiarrheal use, abdominal mass, deviation from normal hematocrit levels and deviation from standard weight (100 × (1 − [body weight divided by standard weight])). Scores in each domain are weighted and summed for a total score from 0 to 600. A score of < 150 is considered remission, 150 to 220 is considered mild, 221 to 450 is considered moderate and > 450 is considered severe.

62. There is also a simpler version of the CDAI available, the Harvey-Bradshaw index, which is limited to five domains: number of liquid/soft stools per day, abdominal pain, general wellbeing, complications and abdominal mass. Scores in each domain are weighted and summed for a total score of 0 to 16 or more, depending on the number of liquid/soft stools per day. A score of < 5 is considered remission, 5 to 7 is considered mildly active, 8 to 16 is considered moderately active and > 16 is considered severely active. There is also a pediatric version of the CDAI (the PCDAI), which assesses stool patterns, abdominal pain, weight, height and extra-intestinal manifestation (e.g., rash).

63. An endoscopy-based DAI specific to CD is the Simple Endoscopic Score for Crohn's Disease (SES-CD), which determines disease activity based on endoscopic assessment alone.

D.6.2 DAIs for UC

64. The most commonly used DAI for UC is the Mayo score (or full Mayo score), which involves providing a score from 0 to 3 for each of the following four domains over a seven day period: stool frequency, rectal bleeding, mucosal appearance at

endoscopy and a physician's global assessment (**PGA**), for a total score of 0 to 12. A score of ≤ 2 is considered remission, 3 to 5 is considered mildly active, 6 to 10 is considered moderately active and 11 or 12 is considered severely active. There are also modified versions of the Mayo score, for example, excluding the endoscopic assessment (partial Mayo score) or excluding the PGA (modified Mayo score).

65. In clinical trials, remission is commonly defined as a Mayo score ≤ 2, with none of the individual subscores for each of the four domains exceeding 1. In the US, the FDA recommends defining clinical remission in terms of the modified Mayo score, with an absolute stool number ≤ 3, a rectal bleeding subscore of 0 and an endoscopy subscore of 0 or 1.

66. Another endoscopy-based DAI specific to UC is Ulcerative Colitis Endoscopic Index of Severity (**UCEIS**), which determines disease activity based on endoscopic assessment alone.

67. Other DAIs specific to UC include the Simple Clinical Colitis Activity (**SCCA**), Seo Index, and the Lichtiger Index. Both the SCCA and Lichtiger Index are based on clinical symptoms alone and are therefore more subjective than the Mayo scoring system and UCEIS, which includes endoscopic assessment. The Seo Index combines clinical symptoms with biomarkers, but also does not involve endoscopic assessment. However, these DAIs tended to be less popular in the Field and in clinical trials than those involving endoscopic assessment.

D.7 Treatment of CD and UC

D.7.1 General approaches to treatment

68. There is no one-size-fits-all approach to treatment of CD or UC, and my comments below are generalizations only based on my experience and my understanding of the views shared by other gastroenterologists working in the Field as at the Relevant Date. I have formed this understanding from sources such as those identified in **Part C** above, and in my discussion with colleagues both locally and internationally.

69. There is presently no known cure for CD or UC. Once a patient presents with CD or UC, the objective of treatment is to have the patient achieve a significant reduction in disease activity and/or severity, preferably remission. In both CD and UC, remission may be described as clinical and/or endoscopic. In clinical remission, symptoms are minimal or absent. However, a proportion of patients in clinical remission may still have inflammation that can be seen on endoscopy.

70. Medications may control inflammation by supressing the immune system generally, or they may have a more targeted mechanism of action. For example, corticosteroids, such as prednisone/prednisolone and budesonide, help to control inflammation throughout the body by supressing the immune system via multiple pathways. Long term use of corticosteroids can have serious side effects. Because of this, they are typically only used short-term (e.g., days to weeks) to treat disease flares and induce remission in CD and UC. If administered by themselves, once treatment with corticosteroids is ceased, inflammation typically returns. Therefore, corticosteroids are usually administered together with another medication that is more suitable for long-term use. Provided inflammation remains under control once the patient ceases corticosteroid use, they then usually stay on the other medication long-term.

71. By the Relevant Date, there were also a number of medications available that specifically targeted inflammatory mediators associated with CD and UC in the gut. I consider these medications in more detail below. These medications could be used as a second line of treatment for CD and UC patients with mild disease activity who did not respond (i.e., were refractory) to the broader-acting medications mentioned above (i.e., corticosteroids and immunomodulators), or as a first line of treatment for patients with moderate-severe disease activity.

72. A number of the medications approved for treating one or both of CD and UC at the Relevant Date were biologics. Biologics include antibodies, typically monoclonal antibodies, which target specific parts of the immune system. Antibodies, also known as immunoglobulins (**Ig**s), are typically Y-shaped protein molecules that constitute an important part of the immune response. Their ordinary function is to bind to pathogens, marking them for destruction. In humans, there are five classes (isotypes) of immunoglobulins, namely IgG, IgA, IgM, IgD and IgE, which differ in their structural features and how they interact with other components of the immune system to have varied temporal and spatial functions during the immune response. IgG is the most abundant class of antibodies in serum.

73. Broadly speaking, an antibody molecule is made up of four polypeptide chains; two heavy chains and two light chains (colored blue and orange respectively, in Figure 2 below). The heavy chains are partially bound together in a "Y" shape, and each heavy chain is linked to a light chain by disulphide bonds.

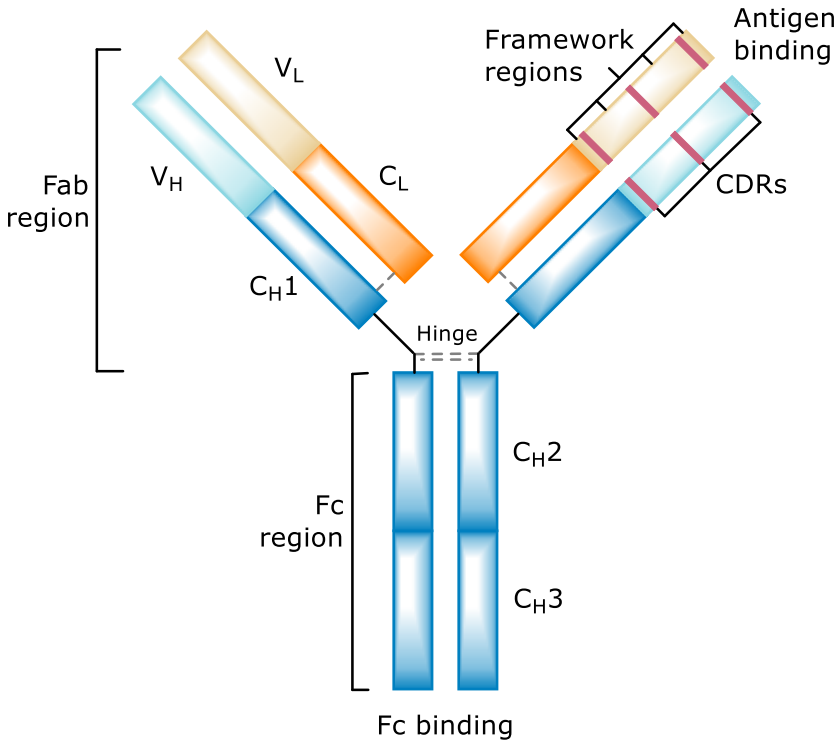


Figure 2. Typical structure of an antibody (image adapted from Hansel *et al.* 2010 *Nature Reviews Drug Discovery* 9, 325-338)

74. Each arm of the Y-shaped antibody structure is formed by the association of a light chain with the amino-terminal half of a heavy chain, to form the Fragment Antigen Binding (**Fab**) region that contains the antigen-binding site. The antigen binding site contains complementarity determining regions (**CDR**s), which are short stretches of amino acid sequences within the variable domains of the heavy chain and light chains (**VH** and **VL**, respectively), that come into contact with the antigen (i.e., a specific site on a target molecule). Generally speaking, the amino acid sequence of the CDRs informs the binding specificity and affinity of the antibody molecule. The stem of the Y-shaped antibody structure is the Fragment Crystallizable (**Fc**) region, formed by the constant regions of the heavy chains, and is responsible for antibody effector function, as the region interacts with Fc receptors and complement proteins. The Fc region is typically not important for targeting and neutralising soluble antigens, including soluble inflammatory cytokines. However, the Fc region can play a role in pharmacokinetics / bioavailability.

75. The medications that were approved by the US Food and Drug Administration (**FDA**) for treating either CD or UC, or both, before the Relevant Date are summarized in the table below. The green cells indicate the FDA approval date for the relevant indication. The yellow cells indicate that the drug was either in ongoing

clinical trials or no clinical trials were conducted in relation to the relevant indication. The red cells indicate a lack of safety and/or efficacy in the relevant indication.

Drug	**Brand name**	**Class**	**FDA Approval date**	
			CD	**UC**
Mesalamine	Lialda®	5-ASA	ˣ	2007
Infliximab	Remicade®	Cytokine inhibitor (TNF-α)	1998	2005
Adalimumab	Humira®		2007	2012
Certolizumab pegol	Cimzia®		2008	-
Golimumab	Simponi®		Phase II*	2013
Natalizumabmesal	Tysabri®	Integrin inhibitor	2008	ˣ
Vedolizumab	Entyvio®		2014	2014
Ustekinumab	Stelara®	Cytokine inhibitor (IL-12/IL-23)	2016	Phase III
Tofacitinib	Xeljanz®	JAK inhibitor	ˣ	2018

* in combination with guselkumab

76. The medications approved by the FDA at the Relevant Date included a 5-ASA, as well as pro-inflammatory cytokine inhibitors, an integrin inhibitor and a JAK inhibitor.

77. When treating CD or UC at the Relevant Date, there was no singular approach and no specific guidelines were available to select a particular medication. In selecting a medication, I (and to my knowledge other gastroenterologists working in the Field) would take into account the disease activity and severity, and whether there were any extra-intestinal manifestations or other comorbid inflammatory diseases that required treatment.

78. If lasting remission is unable to be achieved and disease activity and severity cannot be reduced to an acceptable level using medication, it may become necessary to surgically remove the diseased tissue. Such surgery may involve patients having all or part of their colon and rectum removed. While this can offer permanent relief from inflammation-driven symptoms for patients with UC, the surgery can lead to other complications. In CD patients, symptoms may recur in other portions of the GI tract following surgery. Therefore, treatment of CD and UC typically involves managing the patient's inflammation and the associated symptoms using medication prior to considering surgical intervention. However,

there are circumstances where surgery may be performed at an earlier stage, as discussed further below.

D.7.2 Treatment of CD

79. Prior to the introduction of medications that target particular inflammatory mediators associated with CD, such as TNF-α inhibitors in the late 1990s, the available medications for treatment of CD were essentially corticosteroids (such as those mentioned above) and immunomodulators, such as 6-mercaptopurine, azathioprine, methotrexate or cyclosporine.

80. Before the first TNF-α inhibitor, infliximab (Remicade®), was approved as a treatment for CD in 1998, if corticosteroids or immunomodulators were unsuccessful (i.e., the patent was refractory to these medications), patients with moderate-severe CD were typically recommended for surgery. However, by the Relevant Date, there were more options available, in particular medications that specifically target inflammatory mediators of CD as shown in the table above. These therapies could be used as a second line of treatment for CD patients with mild disease activity who were refractory to the broader acting medications mentioned above, or as a first line of treatment for CD patients with moderate-severe disease activity.

81. When starting a patient with moderate-severe CD on a medication, I would commonly start them on a TNF-α inhibitor. TNF-α is a pro-inflammatory cytokine produced by various immune cells in the gut (and elsewhere throughout the body), including macrophages, dendritic cells and T cells, including Th1 and Th2. At the Relevant Date, there were three anti-TNF-α antibodies approved by the FDA for treating CD: infliximab, adalimumab (Humira®) and certolizumab pegol (Cimzia®). The most commonly used were infliximab and adalimumab.

82. In my experience, adalimumab tended to work better in CD than UC (i.e., the magnitude of improvement and number of patients exhibiting improvement tended to be greater in CD). While adalimumab wasn't typically as efficacious as infliximab, adalimumab was advantageous in that it could be administered via subcutaneous (**SC**) injection. In contrast, infliximab is administered by intravenous (**IV**) infusion, which is more difficult and time-consuming to administer, and is associated with more adverse side effects than SC injection). Therefore, I commonly started patients with moderate-severe CD on adalimumab. In more severe cases of CD, or if adalimumab became ineffective over time, I would commonly switch the patient

to infliximab. This approach may also vary depending on any extra-intestinal manifestations or immunogenicity.

83. Immunogenicity is a physiological response some patients may develop to biologic drugs, in which the body forms antibodies to the drug, rendering it less effective or ineffective over time (antibody-mediated drug resistance). Therefore, if a patient became refractory to TNF-α inhibitor (or another biologic) over time, I might try increasing the dose of the drug in the first instance. If the patient was (or became) unresponsive to the increased dose, I would then consider switching the patient to a different drug, such as an anti-integrin antibody.

84. The third TNF-α inhibitor to come to market for CD was certolizumab pegol (Cimzia®). An advantage of certolizumab pegol is that it doesn't cross the placental barrier, so it was commonly prescribed for women who were (or could be) pregnant. However, being the last TNF-α inhibitor to market for CD at the Relevant Date, its use was less widespread than infliximab or adalimumab at that time.

85. The first anti-integrin antibody to be approved by the FDA for treating CD was the anti-α4-integrin antibody natalizumab (Tysabri®) in 2008. However, natalizumab was found to be associated with a neurological side effect called progressive multifocal leukoencephalopathy (PML), so it was not typically used to treat CD, except perhaps in very rare instances. The anti-α4β7-integrin antibody vedolizumab (Entyvio®) was approved by the FDA for treating CD (and UC) in 2014. Since then, if a CD patient was unresponsive to TNF-α inhibitors, or became refractory to TNF-α inhibitors over time, I would typically switch patients to vedolizumab. In some cases, I might have started a patient on vedolizumab instead of a TNF-α inhibitor. However, I would have weighed this against the slower onset of action of vedolizumab compared to TNF-α inhibitors and the needs of the individual patient before deciding how to proceed rather than applying a formulaic approach to treatment.

86. If the patient was (or became) refractory to both TNF-α inhibitors and vedolizumab, the remaining FDA approved option for the treatment of CD patients was the anti-IL-12/IL-23 antibody ustekinumab (Stelara®), which targets the common p40 subunit of the pro-inflammatory cytokines IL-12 and IL-23 (IL-12/IL-23p40). Accordingly, if treatment with TNF-α inhibitors and vedolizumab was unsuccessful for a patient with CD, I would typically switch them to ustekinumab. Additionally, I might consider prescribing a topical corticosteroid, such as budesonide or prednisolone, for a short period of time to help induce remission.

87. I was also aware at the Relevant Date that clinicians were using biologics in combination therapy to treat CD, such as infliximab and azathioprine, after studies reported superior effects over monotherapy with either medication. However, other than combining a biologic (or other medication) with a corticosteroid for a limited time, combination therapy was not a widely accepted approach among clinicians, who would more commonly prescribe a single approved drug at a time.

88. If a CD patient was refractory to all approved medications, I would usually recommend surgical intervention. Surgery to remove the diseased tissue may also be considered, for example, in circumstances where a patient with CD has developed cancerous or precancerous lesions or has developed complications due to perforations of the bowel.

89. The type and extent of surgical intervention will depend on the location of the diseased tissue and the disease progression. For example, surgery may involve a partial colectomy to remove a diseased portion of the colon, or a total colectomy to remove the entire colon, which is commonly performed with ileostomy (i.e., an ileocoloctomy). As CD can affect any part of the GI tract, and is associated with a range of complications (e.g., strictures, fistulas, abscesses, etc.), the surgical options are varied. In addition to colectomy, surgical procedures that may be performed on patients with CD include strictureplasty, fistula removal, abscess drainage, and small bowel resection. While surgery cannot "cure" CD, it can help to improve a patient's quality of life and provide long term drug free remission for a subset of patients.

D.7.3 Treatment of UC

90. Prior to the introduction of medications that target particular inflammatory mediators of UC in the GI tract, the available medications for treatment of UC were corticosteroids, immunomodulators and 5-aminosalicylates (**5-ASAs**). As with CD, corticosteroids, such as prednisone/prednisolone and budesonide, can help to bring disease flares under control in UC patients, but are not suitable for long-term use. Further, like CD, corticosteroids may be administered together with an immunomodulator in treating UC patients. However, of the immunomodulators mentioned above as being suitable for CD, methotrexate is not effective in UC.

91. 5-ASAs, such as mesalamine, sulfasalazine, olsalazine and balsalazide, were also commonly used for the treatment of UC at the Relevant Date. In contrast, 5-ASAs are typically ineffective in treating CD, with the possible exception of sulfasalazine, which has been shown to be effective in treating left-sided colonic CD (although it

has not been approved for this indication). 5-ASAs may be used alone or in combination with a corticosteroid. At the Relevant Date, 5-ASAs were typically used for treating mild-moderate cases of UC, while moderate-severe UC was typically treated in the first instance with more targeted therapies.

92. Infliximab was also the first drug with a targeted mechanism of action approved for treating UC in 2005. Before this, patients with moderate-severe UC were typically recommended for surgery if treatment with corticosteroids, immunomodulators or 5-ASAs was unsuccessful. However, by the Relevant Date, there were several medications available that specifically target inflammatory mediators of UC in the gut as shown in the table above. These therapies could be used as a second line of treatment for patients with mild disease activity who did not respond (i.e., were refractory) to the initial medications mentioned above, or as a first line of treatment for patients with moderate-severe disease activity.

93. When starting a patient with moderate-severe UC on a medication at the Relevant Date, I would typically start them out on either a TNF-α inhibitor or the α4β7-integrin inhibitor vedolizumab. As I mentioned above, the TNF-α inhibitor adalimumab tended to work better in CD than UC. Therefore, when starting a patient with moderate-severe UC on a TNF-α inhibitor, I regularly started them on infliximab instead of adalimumab. The other TNF-α inhibitor available at the Relevant Date for treating UC was golimumab (Simponi®). However, as the third TNF-α inhibitor to market for UC, golimumab was less commonly used than infliximab and adalimumab.

94. Since its approval for UC in 2014, I also commonly started patients with moderate-severe UC on vedolizumab. However, as above, I would have weighed this against the slower onset of action of vedolizumab compared to TNF-α inhibitors and the needs of the individual patient (including any extra-intestinal manifestations) before deciding how to proceed rather than applying a formulaic approach to treatment.

95. If the patient was (or became) refractory to both TNF-α inhibitors and vedolizumab, the remaining FDA approved option for UC patients was the pan-JAK inhibitor tofacitinib (Xeljanz®). Accordingly, at the Relevant Date, I would have considered switching a patient who was refractory to other medications to tofacitanib. Tofacitinib offered a significant advantage over other approved targeted therapies in that it could be administered orally and avoided immunogenicity issues, although it had only recently been approved for UC at the Relevant Date so I did not have much experience using it at the time. Tofacitinib is also a pan-JAK inhibitor,

meaning it inhibits all JAK isoforms (although it predominantly inhibits JAK1 and JAK3) and therefore blocks the signalling pathways triggered by multiple pro-inflammatory cytokines at once. This was thought to increase the likelihood of a treatment effect in circumstances where multiple cytokines are driving disease activity, but also increased the likelihood of adverse and off-target effects. At the Relevant Date, I was aware that a second generation of JAK inhibitors, upadacitinib and filgotinib, were also in clinical development that sought to address this problem by predominantly targeting a single JAK isoform (i.e., JAK1).

96. If a UC patient was (or became) refractory to all approved medications, I would usually recommend surgical intervention. Surgery in UC patients may involve removing part or all of the colon. As with CD patients, surgery may be indicated in UC patients who have developed cancerous or precancerous lesions, or have developed other bowel complications. In contrast to CD, however, once the colon is removed patients no longer experience symptoms of UC and are therefore sometimes referred to as being "cured".

97. The type and extent of surgical intervention in UC patients will also depend on the location of the diseased tissue and its progression. For example, surgery may involve a partial colectomy to remove only the diseased portion of the colon, or a total colectomy to remove the entire colon. If the rectum is also damaged, a proctocolectomy may be performed to remove both the colon and the rectum. Proctocolectomy is typically performed with ileal pouch-anal anastomosis ("J-pouch" surgery), which involves forming a J-shaped pouch with the ileum that connects to the top of the anal canal. However, while J-pouch surgery avoids the need for an ileostomy bag, around 50% of patients who undergo J-pouch surgery experience inflammation of the pouch, a complication termed "pouchitis". Some patients elect to undergo ileostomy instead, which involves connecting the ileum to the abdominal wall to form a stoma, where waste exits the body and is collected in an ileostomy bag.

98. The decision to perform surgery in UC (and CD) patients is typically informed by both patient-related and physician-related factors. Some patients welcome the prospect of surgery, particularly where their quality of life has been severely impacted by the disease. For example, the 6-year old daughter of a patient of mine whose severe UC was refractory to medication was hospitalized for two months before undergoing colectomy with ileostomy and, as a result, her quality of life dramatically improved. Others wish to avoid surgery at all costs, or may not be suitable candidates for surgery.

D.8 Off-label use of medication in CD and UC

99. After I had considered the matters set out above, DCCL asked me to elaborate on the circumstances under which I might consider administering a medication off-label for a patient with CD or UC, and whether or not I would expect such off-label use to be successful.

100. The use of a medication "off-label" in relation to CD means the use of a currently available medication that has regulatory approval (e.g., from the FDA) in an indication that is not CD. Likewise for UC. The term can also apply to the use of a medication in a patient population (e.g., pediatric), dosage, or dosage form that does not have regulatory approval. For example, administration of a medication approved for psoriasis (but not CD) to a patient suffering from CD is an off-label administration of that medication.

101. Depending on the amount of information available in relation to the medication, off-label use can pose significant risks to a patient's health. The less that is known in relation to a medication for the use in CD, the higher the risks posed by off-label use of that medication in CD. Likewise for UC. Off-label use in relation to CD and UC may be divided into three scenarios as follows:

(a) **Scenario 1.** Off-label use of medications that have been administered to a very large number of patients with CD or UC (e.g., in the tens of thousands) over a period of many years. While it is true that these medications have never been approved for CD or UC, as at the Relevant Date gastroenterologists had detailed understanding of their safety and efficacy profiles based on the large volume of real world data gathered over many years. An example of such medication is the corticosteroid prednisone, which has been used in CD and UC for over least 50 years.

(b) **Scenario 2.** Off-label use of medications that do not fall into Scenario 1, however, Phase III clinical data is available confirming the safety and efficacy of that medication in the disease of interest (but regulatory approval has not yet been granted).

(c) **Scenario 3.** Off-label use of medications that do not fall into Scenario 1 and with respect to which Phase III clinical data confirming the safety and efficacy of that medication in CD or UC is *not available*.

102. The risks in relation to the off-label use in Scenario 3 are high, as without Phase III clinical data there is no way of predicting whether or not the medication is safe

and/or effective in relation to the indication of interest. Because of this, there is no way of knowing if such off-label use is even capable of treating the patient. Such off-label use may simply have no effect, or could actually harm the patient. As I consider below, even if the off-label use has no effect, the patients' health may deteriorate further during the time taken to determine this. Accordingly, any decision in relation to such off-label use must be approached with caution.

D.8.1 Consideration of off-label use in Scenario 3

103. I, and to my knowledge other gastroenterologists working in the Field, are cautious in relation to administering drugs off-label, as using drugs in this way may pose a significant risk to the patient's health. In my opinion, a compelling reason is required before Scenario 3 off-label drug use should even be considered. As considered below, When I have used drugs off-label in these circumstances, it has usually been a "Hail Mary" attempt to save the patient from undergoing surgery (or because they are unable to undergo surgery).

104. Even where there is a compelling reason to consider off-label use, this must be balanced against the risks. In my experience, at the stage of disease progression where Scenario 3 off-label use of medication may be considered, the patient is usually refractory or intolerant to all approved medications and, accordingly, often very unwell. In this scenario, it is unlikely that any medication will materially improve the patient's condition. Delaying surgery may cause the patient's condition to worsen, further complicating any subsequent surgery that may be necessary if the off-label use does not work. This deterioration in health may necessitate more extensive surgery (e.g., to remove more damaged tissue or repair fissures that may have formed) or for surgery to performed in additional stages to reduce the risk of surgical complication or infection. Accordingly, for patients who can undergo surgery, progressing with that surgery may well be a better option than delaying it in favor of off-label medication use.

105. Prior to the Relevant Date, having taken into account the matters set out in this part of my declaration, I had administered certain drugs off-label (Scenario 3) to a small number of CD and UC patients. For example, I had administered certain immunomodulators that were not approved in CD or UC patients (e.g., tacrolimus and hydroxychloroquine (Plaquenil®)). A further example is that I administered the anti-TNF-α antibody adalimumab in UC patients after its approval for CD (and other inflammatory diseases) but before its approval for UC. Without Phase III clinical data there is no way of predicting whether or not the off-label use of the medication is safe and/or effective in relation to CD or UC, however I was more

comfortable administering adalimumab at that time because another anti-TNF-α biologic (infliximab) had already been approved for both CD and UC. As indicated earlier in my evidence, these off-label administrations were "Hail Mary" attempts to save the patient from undergoing surgery (or because the patient was unable to undergo surgery).

106. Prior to the Relevant Date, attempts were being made to determine if certain drugs approved in treating other inflammatory diseases might be effective in treating CD or UC. Similarly, such attempts were being made to determine if drugs approved in CD were effective in treating UC (and vice versa). In my opinion, and to my knowledge that of other gastroenterologists working in the Field at that time, there was insufficient understanding about the pathogenesis of CD or UC (which I refer to **Part D.4** above) to predict whether or not a drug that was effective in treating one inflammatory condition would be effective in treating any of the others.

107. From the sources of information I refer to in **Part C** above, I was aware at the Relevant Date that there were numerous drugs in development at the time, many of which targeted various pro-inflammatory cytokines and other inflammatory mediators implicated in CD, UC or both. At that time, I was also aware that in many cases the efforts to block these inflammatory mediators specifically (or in specific combinations) did not lead to the desired safety or efficacy in clinical trials. By way of example:

(a) Efforts to develop drugs that inhibit various pro-inflammatory cytokines, including IFN-γ, IL-6, IL-13 and IL-17 did not result in any successful drug candidates due to lack of efficacy and/or safety. For example, the pro-inflammatory cytokine IL-17A was considered an attractive therapeutic target before the Relevant Date. However, the anti-IL-17A antibodies secukinumab (Cosentyx®; which was approved by the FDA for treating psoriasis, ankylosing spondylitis, plaque psoriasis and psoriatic arthritis) and brodalumab (Siliq®; which was approved by the FDA for treating plaque psoriasis) were found to exacerbate CD in Phase II trials.

(b) Several TNF-α inhibitors were approved for CD and/or UC at the Relevant Date, as discussed above. However, another type of TNF-α inhibitor etanercept (Enbrel®; which was approved by the FDA for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis), was not sufficiently effective in CD or UC.

(c) Abatacept (Orencia®; which was approved by the FDA for treating rheumatoid arthritis and psoriatic arthritis) failed in clinical trials for both CD and UC. Abatacept blocks the interaction between antigen-presenting cells (dendritic cells) and T cells by inhibiting CTLA4. It showed benefits in mouse models for CD and UC, and was taken straight to Phase III trials for CD and UC but failed due to lack of efficacy.

(d) JAKs are involved in the signalling of multiple different cytokines implicated in CD and UC. However, the JAK inhibitor tofacitinib (Xeljanz®; which was approved by the FDA for treating rheumatoid arthritis and psoriatic arthritis), was found to be effective in (and was approved for) treating UC but did not demonstrate adequate efficacy against CD at safe doses in Phase II clinical trials. Similarly, the 5-ASA mesalamine was effective in treating UC but not CD, while the immunomodulator methotrexate was effective in treating CD but not UC.

None of these results surprised me. As at the Relevant Date, the inflammatory pathways involved in CD were incompletely understood and it was not possible to predict how inhibiting a particular pathway would affect the overall immune response within the context of human disease. Because of this lack of understanding, it was not possible to predict whether a drug candidate would be safe or effective in treating CD in the absence of Phase III clinical trial results. This was true even where the drug candidate had been demonstrated to be safe or effective in relation to a different inflammatory condition (including UC). The same applied in relation to UC. Because of this, it was not (and is not) possible to extrapolate safety or efficacy from one inflammatory condition to another, including from CD to UC (and vice versa).

108. While there is some cross-over in terms of the biological mechanisms associated with different inflammatory diseases (such as the involvement of TNF-α or JAKs), the examples I provided above of etanercept and tofacitinib, respectively, indicate that even targeting these common inflammatory mediators does not necessarily lead to the desired treatment effect. Similarly, drugs that have been approved for CD or UC are not necessarily effective in other inflammatory diseases. By way of example, ustekinumab was approved for CD but did not show efficacy in Phase II trials for rheumatoid arthritis, Phase III trials for axial spondyloarthritis, or Phase III trials for systemic lupus erythematosus. Gut-specific medications like vedolizumab would also not be expected to work in other inflammatory diseases that occur outside the gut.

D.9 Clinical trials

109. After I had considered the matters set out above, DCCL asked me to describe my experience with the clinical trial process prior to the Relevant Date. DCCL also asked me to indicate what I (and in my experience other gastroenterologists working in the Field) might infer, if anything, merely from the fact that a drug candidate had progressed to a Phase III clinical trial.

110. As mentioned in **Part B** above, I was involved in several Phase II and Phase III clinical trials for IBD therapies before the Relevant Date, including as an Institutional Principal investigator in Phase II and Phase III trials for UC and/or CD involving the following active agents: andecaliximab/GS-5745 (anti-MMP9 antibody, Gilead); vedolizumab (anti-α4β7 integrin antibody, Takeda Millennium), briakinumab/ABT-874 (anti-IL-12/IL-23 antibody, Abbott Laboratories); MDX-1100 (anti-CXCL10 antibody, Medarex); certolizumab pegol (anti-TNF-α antibody, UCB); and izencitinib/TD-1473 (JAK inhibitor, Theravance Biopharmaceuticals).

111. The clinical trials process involves four phases:

(i) **Phase I** tests the safety and looks for side effects of a drug in a small group of typically healthy volunteers (e.g., 15 to 50 volunteers). A suitable dose of the drug candidate may be identified in this phase.

(ii) **Phase II** tests the drug candidate in a larger group of patients (e.g., 20 to 100 patients) to test its efficacy and further investigate its safety. The size of Phase II trials is typically not sufficient to draw any conclusions about the broader patient population, but indicates whether it is worthwhile trying the drug candidate in a larger, more representative patient group.

(iii) **Phase III** is also focused on safety and efficacy, but on a much larger sample size (e.g., several hundreds to thousands of patients). If a drug candidate is found to be effective in this phase, it may be approved for use in the general patient population.

(iv) **Phase IV** occurs after the drug has been approved and its long term effects, safety and optimal use are monitored.

112. The "gold standard" for clinical trials is a double-blind, randomized, placebo-controlled study, which is designed to demonstrate causality between the intervention (administration of a drug candidate) and any effect observed. This is achieved, for example, by ensuring the sample size is sufficiently large to minimize the probability that any effect observed is due to chance (based on statistical

analysis), controlling for confounding variables and minimizing biases. Double-blinding helps to minimize biases in patient evaluation by ensuring that neither the patients nor the investigators know whether the patient is receiving the intervention or the placebo. Randomization helps to minimize selection biases by randomly assigning patients to the intervention or control groups. The use of a placebo control, while keeping everything else in the trial the same, is an important factor in determining whether any effect observed is attributable to the intervention (and not the well-known placebo effect).

113. The study sample should also reflect the characteristics of the broader patient population, with the selection criteria pre-specified to minimize selection biases. Studies involving multiple sites (i.e., multicenter studies) can also help to ensure the sample of patients being investigated is representative of the broader population.

114. The measure of success in a clinical trial should be specified before the trial begins to avoid the possibility of changing the endpoint to suit the data. This is typically done by specifying one or more endpoints, measured according to one or more predetermined criteria (e.g., primary outcome measures). In the case of clinical trials for CD or UC, the endpoints are typically clinical remission and/or clinical response, measured in terms of one or more DAIs such as those I discuss above in **Part D.6**. Other (secondary) endpoints are also commonly included in clinical trials for CD or UC, such as endoscopic improvement, histologic improvement, biomarker levels, etc. However, for the drug candidate to be deemed efficacious, the clinical trial need only meet its primary endpoints.

115. In my opinion, the prospects of a CD or UC drug candidate succeeding (i.e., being demonstrated to be safe and effective) cannot be inferred merely from the fact that it had progressed to a Phase III clinical trial. As at the Relevant Date, around half of all drug candidates failed in Phase II clinical trials. For those drug candidates that succeed in Phase II clinical trials, the sample size is typically not sufficiently large to generalize the results to the relevant patient population (as I mention in paragraph 111(ii) above). Of the drug candidates that made it to Phase III trials, around a further half again failed at that stage. The majority of drug candidates that fail in Phase III trials do so because of lack of safety and/or efficacy. For these reasons, it is simply not possible to predict the outcome of a clinical trial. Because of this, I am always interested in the results obtained from Phase III clinical trials of potential CD or UC drug candidates. Clinicians typically only become aware of

Phase III clinical trial results when they are published to the world (this is true even if the clinician is involved in the trial as an investigator if the trial is double-blinded).

E HYPOTHETICAL TASK

116. After I had considered the matters set out in **Part D** above, DCCL asked me to assume that as at the Relevant Date I was a member of a pharmaceutical research team (**Team**) seeking to develop a pharmaceutical product (being either an entirely new drug candidate or an existing drug or drug candidate) for the treatment of UC, which would be an improvement on, or useful alternative to, the products that were approved at that time for use for the treatment of UC, based on information that I knew and accepted and regarded to be widely known and generally accepted by other gastroenterologists working in the Field (**Hypothetical Task**).

117. DCCL then asked me to explain what, if anything, I would consider and recommend to the Team and to explain my reasoning and rationale.

118. For the reasons stated earlier in my declaration, absent Phase III clinical trial data, it wasn't possible to predict whether or not a drug candidate would be effective in relation to UC (see paragraphs 106-108 above). Because of this, I would have recommended that the Team develop a product with the greatest potential to address the unmet needs in UC treatment at the Relevant Date.

119. The drugs that were approved for UC at the Relevant Date were the 5-ASA mesalamine; the TNF-α inhibitors infliximab, adalimumab and golimumab; the integrin inhibitor vedolizumab; and the pan-JAK inhibitor tofacitinib (see paragraph 75 above).

120. By reference to the properties of the approved products, I consider that the unmet needs in UC as at the Relevant Date were the efficacy ceiling, speed of onset of action, immunogenicity, oral administration and gut specificity (as would be relevant to improving efficacy and limiting off-target effects). I consider each of these unmet needs in the following paragraphs.

121. First, it was well-recognized that there is an efficacy ceiling with respect to the approved drugs. This manifested in the following ways. For each of the approved drugs there was a substantial portion of the UC patient population in whom that drug was simply ineffective, or in whom remission could not be achieved despite using any of these drugs. In the case of biologics, for the patients who did respond to a particular drug, there was also a proportion of patients who experience secondary loss of response (i.e., the drug becomes ineffective over time due to

anti-drug antibodies or other reasons). Further, each time a patient failed a biologic, the patient was less likely to respond to a second or further biologic. Therefore, the unmet need in relation to the efficacy ceiling included a need to identify drugs that have the same efficacy despite history of prior therapy (e.g., TNF-α failure).

122. Second, the time taken for many of the approved drugs to work was in the order of many weeks or even months, rather than days. For the drugs with a long onset of action, a patient's condition may materially worsen while waiting to see if the drug is effective. I would consider anything with an onset of action under two weeks to be relatively fast.

123. Third, biologics can elicit an immunogenic anti-drug antibody response (i.e., immunogenicity) that rapidly clears the drug from the body and eliminates its effectiveness (see paragraph 83 above).

124. Fourth, biologics require parenteral (e.g., IV and/or SC) administration because, as proteins, they degrade rapidly in the intestinal environment. However, in my experience (and I believe the experience of other gastroenterologists in the Field), there was a strong preference among UC patients to take a tablet instead of receiving an injection. This is in part because of patient perception that an ongoing tablet regimen is far less serious than an ongoing injection regimen.

125. Finally, many of the approved drugs do not have gut-specific effects (i.e., their activity is not confined to the gut). By acting on targets outside the gut, non-gut specific drugs may have an increased risk of off-target effects.

126. The primary classes of therapeutic targets that I was aware were being investigated by others at the Relevant Date were:

(i) cytokine signalling molecules (e.g., JAKs);

(ii) mediators of leukocyte trafficking (e.g., integrins and their corresponding endothelial cell adhesion molecule receptors, and S1P modulators); and

(iii) pro-inflammatory cytokines.

127. For completeness, I note that other therapies were also being investigated at the Relevant Date, such as therapies targeting enhanced T_{reg} cell function and altering the composition of the microbiome. However, I considered these therapies to be less advanced (and more speculative), and I would not have recommended them to the Team.

128. At the Relevant Date, it was known that JAKs are involved in downstream signalling of many pro-inflammatory cytokines. Because of this, JAK inhibitors had the potential to block the signalling pathways triggered by multiple pro-inflammatory cytokines at the same time.

129. The ability of JAK inhibitors to block multiple cytokine signalling pathways at the same time carried with it the potential of having greater efficacy in the treatment of UC than those approved drugs that targeted only individual cytokines or other inflammatory mediators. This is because of the complexity of the UC inflammatory processes, which involve (among many other factors) multiple cytokine pathways. Because of this, as at the Relevant Date, I would have considered JAK inhibitors (as a class) to have the potential surpass the therapeutic efficacy ceiling of the approved UC drugs.

130. I was also aware that tofacitinib had recently been approved for UC (but had failed in Phase II trials for CD due to lack of efficacy). Tofacitinib is a pan-JAK inhibitor, meaning it inhibits all JAK isoforms (although it predominantly targets JAK1 and JAK3). While tofacitinib had FDA approval for UC at the Relevant Date, there was concern that the mechanism of action of pan-JAK inhibitors might be overly broad and could give rise to off-target effects. Additionally, I was aware that drugs were being developed that were more specific to individual JAK isoforms (i.e., JAK1, JAK2, JAK3 or TYK2) at the Relevant Date. This approach was thought to have the potential to balance the benefits of blocking multiple cytokines against the possibility of off-target effects. At the Relevant Date, I was aware that upadacitinib and filgotinib (which predominantly target JAK1 at therapeutic doses) were in Phase III clinical trials for UC. Further benefits of JAK inhibitors are that they are non-immunogenic, can be delivered orally, have the potential to be gut specific and have a relatively fast onset of action.

131. Integrin inhibitors that were being investigated for the treatment of UC prior to the Relevant Date included α4-, α4β7- and β7-integrin inhibitors. α4-Integrin inhibitors such as natalizumab were not attractive because of safety concerns (see paragraph 85 above). I also did not consider there to be a further need for α4β7-integrin inhibitors that mimicked vedolizumab. However, drug candidates were being investigated that bind to the α4β7-integrin receptor, MAdCAM-1, which is expressed on the surface of blood vessels in the intestinal tract. This approach was thought to have the potential to address the efficacy ceiling and also be gut selective.

132. β7-integrin inhibitors were being investigated at the Relevant Date with respect to the potential to block both α4β7- and αEβ7-integrins, which was thought to inhibit

leukocyte trafficking to the gut via two different pathways. Because of this, there was a possibility that β7-integrin inhibitors may be more effective than vedolizumab. Another benefit of β7-integrin inhibitors is their gut-specificity. I understand the anti-β7 integrin antibody etrolizumab was in Phase III clinical trials for UC at the time. However, β7-integrin inhibitors are biologics and were therefore not orally deliverable and could still have the limitation of immunogenicity.

133. S1P receptor modulators were also being investigated at the Relevant Date and I understand the S1P modulators ozanimod (Zeposia®) was in Phase III clinical trials for UC at the time. S1P receptor modulators bind to and inactive S1P receptors on the surface of leukocytes, thereby inhibiting their migration to the site of inflammation in the intestinal mucosa. Benefits of S1P modulators include that they are orally deliverable and non-immunogenic. However, they have a slow onset of action and, in my view, do not have the same potential to increase the efficacy ceiling as JAK inhibitors.

134. The pro-inflammatory cytokine inhibitors that were being (or had been) investigated for the treatment of UC prior to the Relevant Date included (but were not limited to) inhibitors of IFN-γ, TNF-α, IL-12, IL-13, IL-17 and IL-23. The majority of pro-inflammatory cytokine inhibitors investigated at that time were biologics, and therefore could not have addressed the unmet needs of oral delivery or lack of immunogenicity. Further, pro-inflammatory cytokines are not isolated to the gut, so drugs that target these cytokines may have off-target effects. In relation to efficacy, targeting individual pro-inflammatory cytokines (with the exception of TNF-α) did not carry with it the same efficacy possibilities as targeting multiple cytokines (as with JAKs). The reason TNF-α was the exception, and arguably the most successful therapeutic target for UC at the Relevant Date, was because of its prevalence and level of expression in relation to inflammation. At the Relevant Date, however, there were already three TNF-α inhibitors available on the market, and adding yet another TNF-α inhibitor would not have materially addressed the unmet needs in UC that I discuss above.

135. In light of the above, at the Relevant Date I would have considered JAK inhibitors, particularly JAK inhibitors that predominantly target individual JAK isoforms, to have the potential to address each of the unmet needs in the treatment of UC. Specifically, JAK inhibitors have the potential to address the efficacy ceiling, have a fast onset of action, are non-immunogenic, are orally deliverable and have the potential to be gut specific. Because of this, my recommendation would have been for the Team to investigate the development of JAK inhibitors that predominantly

target (i.e., have greater specificity for) an individual JAK isoform. Examples of such products that were in Phase III clinical trials at the Relevant Date were upadacitinib and filgotinib.

F PRIOR ART

136. After I had considered the matters set out in **Part E** above, DCCL asked me to review the following documents and asked me to consider what these documents would have disclosed to me at the Relevant Date and whether, if I had been provided with or obtained them in the course of undertaking the Hypothetical Task, it would have assisted me and, if so, how.

(i) Clinical trial record of the clinical trial titled "A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UNIFI)" and identifiable by ClinicalTrials.gov identifier NCT02407236, as published on the ClinicalTrials.gov website on 13 August 2018 (**CTR 236**), a copy of which is provided as **Annexure MAC-3**;

(ii) Ochsenkühn et al (2018) "P759 Ustekinumab as rescue treatment in therapy-refractory or –intolerant ulcerative colitis" 12(S1) *Journal of Crohn's and Colitis* S495 published on 16 January 2018 (**Abstract P759**), a copy of which is provided as **Annexure MAC-4**;

(iii) Ochsenkühn et al (2018) "Tu1713 Clinical outcomes with ustekinumab as recue [sic] treatment in therapy-refractory or -intolerant ulcerative colitis: real worl [sic] experience in a large single center cohort" 154(6;S1) *Gastroenterology* S-997 published in May 2018 (**Abstract Tu1713**), a copy of which is provided as **Annexure MAC-5**; and

(iv) Poster titled "Tu1713: Clinical outcomes with ustekinumab as rescue treatment in therapy-refractory or -intolerant ulcerative colitis: real world experience in a large single center cohort", allegedly presented at the AGA's annual conference, DDW, on 5 June 2018 (**DDW Poster**), a copy of which is provided as **Annexure MAC-6**.

F.1 CTR 236

137. CTR 236 is a Clinicaltrials.gov record of a Phase III clinical trial to evaluate the safety and efficacy of ustekinumab in participants with moderate to severely active UC, sponsored by Janssen Research & Development, LLC. The version of this record

shown in CTR 236 is the version published on 13 August 2018, which I understand is the latest version available at the Relevant Date.

138. The official title of the study described in CTR 236 is "*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*". The "Detailed Description" provides a further description of the study design, including that it consists of two studies: an 8 week Induction study and a 44 week Maintenance study (the latter involving only those participants who demonstrated a clinical response in the Induction study). There are various different "Arms and Interventions" described in CTR 236, with participants randomly assigned to one of these arms. The "Study Design" section further specifies there are 971 participants enrolled in the study. The study design described in CTR 236 accords with the "gold standard" for clinical trial design I described in paragraph 112 above.

139. The primary and secondary outcome measures (and the relevant endpoints) for the trial are set out in the "Outcome Measures" section. The primary outcome measure for the Induction study is the number of participants with clinical remission, and for the Maintenance study is the number of participants with clinical response in the Induction study. In both cases, clinical remission is defined as "*the global definition of Clinical remission is defined as Mayo score less than or equal to (<=) 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*".

140. The use of the Mayo scoring system in the primary outcome measure is typical of clinical trials for UC. As I mentioned in paragraph 64 above, the Mayo scoring system for UC disease activity is preferred because it incorporates endoscopic assessment of disease activity. I understand that the definition of clinical remission for US participants also includes certain Mayo subscore limitations to align with more stringent FDA recommendations for characterizing clinical remission introduced a few years prior to commencement of the clinical trial.

141. There are several secondary outcome measures defined for the Induction study, including clinical response and endoscopic healing (both defined with reference to the Mayo scoring system), as well as a mean change from baseline in the IBDQ, which I briefly described in paragraph 60 above. There are also several secondary outcome measures defined for the Maintenance study, including clinical response

and endoscopic healing among participants with clinical response to the Induction treatment, and clinical remission (including corticosteroid-free remission) among participants in clinical remission at maintenance study baseline.

142. The remainder of CTR 236 describes the eligibility criteria for the study (including inclusion and exclusion criteria) and the locations where the trial took place. The inclusion criteria include, among other things, failure of biologic therapies such as TNF antagonists (i.e., TNF-α inhibitors) or vedolizumab. In this case, vedolizumab must have been discontinued for at least 4 months and anti-TNFs for at least 8 weeks. This "wash out" period is important because certain active agents can interact (e.g., synergize with or counteract one another, or increase infection risk) if not properly cleared from the system.

143. Notably, CTR 236 does not include any results from the Phase III trial. As stated in CTR 236, the purpose of the trial was to evaluate the safety and efficacy of ustekinumab in participants with moderately to severely active UC. For the reasons I discuss in paragraph 115 above, it was not possible to predict the outcome of a clinical trial for UC. This was true even in circumstances where the drug candidate had already been approved for CD, as was the case with ustekinumab (see paragraphs 106-108 above). CTR 236 does not include any indication or rationale that ustekinumab will be safe or efficacious in UC patients. Therefore, there is nothing in the CTR 236 document that would have led me to believe the trial would succeed in achieving any of the primary or secondary endpoints, or that it would be safe in UC patients.

144. Nothing in CTR 236 alters my view that it is not possible to predict the outcome of a clinical trial (see paragraphs 106-108 and 115 above). Therefore, reading CTR 236 would not have changed the way I approach the Hypothetical Task at the Relevant Date.

F.2 Abstract P759

145. Abstract P759 is an abstract published in the *Journal of Crohn's and Colitis* (the journal of the ECCO) describing a small-scale observational study using ustekinumab in UC patients.

146. According to the Methods section, the study involved 17 UC patients selected from a single referral center. All patients were said to be intolerant or refractory to purine analogues, TNF antibody therapy and vedolizumab, and had been offered ustekinumab as a rescue treatment after colectomy had been offered as the only other option. The off-label use of ustekinumab "*as approved for Crohn's disease*"

in Abstract P759 corresponds to Scenario 3 as set out in paragraph 101(c) above. As I mention in paragraph 105 above, without Phase III clinical data there is no way of predicting whether or not the off-label use of the medication is safe or efficacious in relation to CD or UC.

147. The Results section also indicates that all patients were either corticosteroid refractory or steroid dependent at the start of the study, and that six patients were already in remission at the start of the study (having stopped TNF or integrin blocking treatment due to intolerable side effects). The primary outcome measure was achievement of clinical remission at 3 and 6 months, defined as a score of ≤5 points in the modified Truelove and Witts colitis activity index (**CAI**). I understand this DAI does not involve any endoscopic assessment of disease activity in the patients and I understand it is not widely used.

148. The Results section reports median CAI values at 0 months, 4 weeks, 3 months and 6 months, together with CAI ranges. It also reports that two patients stopped ustekinumab at 6 and 24 months due to refractory disease, and one patient stopped due to drowsiness. All three of these patients underwent colectomy. Including these three patients, clinical remission is reported in 11/17 patients at 1, 3 and 6 months, compared to 6/17 patients in remission at the start of the study.

149. The Conclusions section states: "*Ustekinumab was effective as rescue medication in therapy refractory or intolerant UC in a large IBD referral center*". However, there are a number of limitations to the study that, in my view, render this conclusion unsubstantiated by what is actually described in Abstract P759. I discuss these limitations in the following paragraphs.

150. The study involves retrospective data analysis, which relies on clinical records that were not recorded with the study in mind, as is desirable for clinical studies. Therefore, relevant data may be missing, or it may be necessary to rely on the memory of the doctor (and patient), which may be less accurate after a period of time such as 6 (or more) months have elapsed. The details available in the doctor's clinical records may also have factored into the choice of DAI used (i.e., the modified Truelove and Witts CAI). I understand that the modified Truelove and Witts CAI corresponds to the Lichtiger CAI (published by Lichtiger et al., *N Engl J Med.* 1994 Jun 30;330(26):1841-5), which I refer to in paragraph 67 above. As this CAI doesn't involve endoscopic assessment, it is possible patients could meet the criteria for remission but not meet the criteria for remission according to a more objective and widely used DAI like the Mayo scoring system (e.g., based on the criteria I mention in paragraph 65 above).

151. The sample of 17 patients is also very small, especially when six of these patients were already in remission at the start of the study (it is unclear to me how ustekinumab could be characterized as a "rescue treatment" in these patients). While there is no set number of participants required for a clinical study, the sample size should be large enough to represent the broader population of UC patients (as I mentioned in paragraph 113 above). This typically requires hundreds of participants in each arm of the study. A sample selected from a single referral center is also unlikely to represent the broader population of UC patients, which is why clinical trials preferentially involve multiple referral centers (as I also mentioned in paragraph 113 above).

152. The sparsity of detail provided in Abstract P759 coupled with the retrospective study design makes it difficult to determine whether any effects that are reported are actually due to administration of ustekinumab. For example, Abstract P759 doesn't report each patient's condition before and at the end of the study, doesn't contain a placebo control group, does not specify when or if the steroid-dependent patients stopped steroid therapy (meaning any remission reported could be due to steroid use), and doesn't specify how long after stopping other medications the ustekinumab was administered (i.e., the wash out period, if any, as I mentioned in paragraph 142 above).

153. I, and in my experience other gastroenterologists working in the Field, generally do not base our decision making on small clinical studies such as the one described in Abstract P579. While it is not always necessary for clinical studies to meet the gold standard I described in paragraph 112 above in order to be compelling, I do not find the results of this study to compelling in view of the numerous limitations I described above. The 30% increase in the number of patients reported to be in remission is similar to the placebo effect rates observed in IBD clinical trials (e.g., about 20-30%). Therefore, in the absence of a placebo control, it is not possible to conclude that "*Ustekinumab was effective as rescue medication in therapy refractory or intolerant UC in a large IBD referral center*". In my view, based on the information provided, it is not possible to determine whether any effect observed is attributable to the administration of ustekinumab.

154. Nothing in Abstract P579 alters my view that without Phase III clinical data there is no way of predicting whether or not the off-label use of a medication is safe and/or efficacious (see paragraph 105 above). Reading Abstract P759 at the Relevant Date would not have affected my approach to the Hypothetical Task.

F.3 Abstract Tu1713

155. Abstract Tu1713 is an abstract published in *Gastroenterology* (the journal of the AGA). Abstract Tu1713 is essentially the same as Abstract P579. Therefore, my comments in **Part F.2** above apply equally to Abstract Tu1713.

156. The only real difference between Tu1713 and Abstract P579 is in the title. I am surprised that the title of Tu1713 refers to a "*large single center cohort*" given the study cohort consists of only 17 patients.

F.4 DDW Poster

157. I understand the DDW Poster was purportedly presented at the AGA's DDW conference in 2018. While I attended that conference, I do not recall seeing the DDW Poster.

158. Given the title of the DDW Poster includes a reference to "Tu1713" and has the same title as Abstract Tu1713, I assume they describe the same study. However, there are a number of differences between the DDW Poster and Tu1713 (and Abstract P759). For example, two additional patients are reported in the DDW Poster, bringing the total sample size to 19 patients. Of the two additional patients, one was in remission and one had moderately to severely active UC at the start of the study. Also, the study reported in the DDW Poster had a 9 month duration, as opposed to 6 months in the Tu1713 Abstract.

159. The Characteristics of Patients section of the DDW Poster includes additional information about the patients compared to the Tu1713 Abstract, including their sex, age and extent of inflammation. However, other baseline characteristics of the patients, such as which patients were taking which medications prior to the study and when they ceased those medications, are not presented. This section also specifies that 9 of 19 patients were taking steroids at the start of the study.

160. The DDW Poster clarifies that the modified Truelove and Witts CAI is the same as the Lichtiger CAI. The criteria for the modified Truelove and Witts CAI are also defined in the DDW Poster, and include scores for the following domains: diarrhea (number of bowel movements per day), nocturnal diarrhea, bloody stools, fecal incontinence / soiling, abdominal pain/cramping, general well-being, antdiarrheals / narcotics, and abdominal tenderness. In my experience, some of these domains may be difficult to score retrospectively (e.g., general well-being) and all of these domains rely on patient self-reports, as opposed to more objective measures like endoscopy.

161. It can be seen from the DDW Poster that the modified Truelove and Witts CAI involves an overall score from 0-21. The DDW Poster reports that 12/19 patients had moderately or severely active disease and a median CAI of 8.5 (range 1-12) at the start of the study. I understand that a CAI of > 10 is classified as severe UC. However, from reviewing the domains of the modified Truelove and Witts CAI it seems possible that patients could be characterized as being in remission (CAI ≤ 5) while still having moderate to severe disease activity according to the Mayo scoring system, for example, if they have high scores for bloody stools with every bowel movement and/or diarrhea, which are indicative of active disease.

162. I understand there are differing reports in the literature about what qualifies as "clinical remission" according to the Lichtiger CAI (modified Truelove and Witts CAI). For example, other studies I have identified that use the Lichtiger CAI use thresholds of 4, 3 or 2 for clinical remission. This lack of consistency about what qualifies as clinical remission is another drawback of using this scoring system.

163. The graph in the DDW Poster also appears to show 6 patients in remission at the start of the study, whereas other sections of the poster (Methods, Characteristics of Patients, and Results) report that there were 7 patients in remission at the start of the study. The graph is difficult to read and there is a lot of overlap in the lines and the points at 3, 6 and 9 months, so it is not entirely clear in some instances which patients had which CAI values at each time point.

164. The Results section starts by describing the patients who stopped ustekinumab part way through the study period, as well as other adverse events. However, the data reported in this section is not reconcilable with the data reported in the Abstract Tu1713 (and Abstract P579). For example, all three patients who stopped ustekinumab in the abstracts are reported as undergoing colectomy, whereas of the five patients who stopped ustekinumab in the DDW Poster only two underwent colectomy, although it is not clear which ones. The abstracts also refer to a patient who stopped ustekinumab at 24 months, but the study had only been running for 6 months at that point so it is unclear when this patient stopped ustekinumab.

165. Next, like the abstracts, the Results section of the DDW Poster reports median CAI values at 3, 6 and 9 months, together with ranges. However, unlike the abstracts, the DDW Poster also reports median values and ranges for the inflammatory biomarkers CRP and (fecal) calprotectin. There is no mention of these biomarkers anywhere else in the DDW Poster, and the individual patient data is not reported (i.e., which patients had improvements in biomarker levels). In any case, as I

mentioned in paragraphs 56 and 59 above, neither of these biomarkers can form the basis for a definitive diagnosis (or indication of disease progression).

166. The final two parts of the Results section report the total number of patients in remission generally at 3, 6 and 9 months, and the proportion of patients in remission at 1, 3, 6 and 9 months who had active disease at the start of the study. However, like the data reported in the abstracts, I do not find this data compelling. This is because the study described in the DDW Poster still has the same issues with the study design as the posters, such as being retrospective, uncontrolled, involving only a small sample size, and various characteristics of the patients not being reported.

167. Nothing in DDW Poster alters my view that without Phase III clinical data there is no way of predicting whether or not the off-label use of a medication is safe and/or efficacious (see paragraph 105 above). As such, reading the DDW Poster at the Relevant Date would not have affected my approach to the Hypothetical Task.

F.5 Stelara 2017 PI and CTR 236 as a single source of information

168. After I had considered the matters set out in **Parts F.1-F.4** above, DCCL provided me with the Product Information for Stelara® (ustekinumab) dated 27 February 2017 (**Stelara 2017 PI**), a copy of which is provided as **Annexure MAC-7**. DCCL asked me to explain whether or not I consider the relationship between the Stelara 2017 PI and CTR 236 to be such that I would regard them as a single source of information at the Relevant Date.

169. There is nothing in either the Stelara 2017 PI or CTR 236 that would indicate to me they should be considered as a single source of information because neither document refers either directly or indirectly to the other and there is nothing from the Stelara 2017 PI that I require in order to understand CTR 236.

170. The only indications mentioned in the Stelara 2017 PI are plaque psoriasis, psoriatic arthritis and CD; there is no mention of UC. For the reasons I provide in paragraphs 106-108 above, it was not possible to extrapolate safety or efficacy from one inflammatory condition to another. This included predicting safety and efficacy in UC based on data for CD. In any case, I note that ustekinumab was approved for treating CD by the FDA in 2016 and by the TGA in 2017. Therefore, I understand CD would not have been added as an indication to the 2017 Stelara PI until 2017, whereas the clinical trial described in CTR 236 commenced on 10 July 2015.

G CONSIDERATION OF THE PAVLI DECLARATION

G.1 Consideration of Section D of the Pavli Declaration

176. After I had considered the matters set out in **Part F** above, DCCL provided me with Section D of the declaration of Professor Paul Pavli dated 12 October 2023 (**Pavli Declaration**).

177. DCCL asked me to review each paragraph of Section D carefully and where I consider it appropriate, to respond to the matters expressed by Prof. Pavli.

178. DCCL further instructed me that in undertaking the above task, I am to provide my answer based upon knowledge that I consider was widely known and generally accepted in the Field as at the Relevant Date.

179. I set out my views in relation to Section D of the Pavli Declaration in the following paragraphs. Where I do not comment in relation an aspect of Prof. Pavli's evidence, it does not mean that agree with that aspect of the evidence.

180. As a general comment in relation to Section D, I note that in paragraph 80, Prof. Pavli states that that *"for convenience"* he uses the term "IBD" in Section D to refer to CD and UC collectively. As I discuss in **Part D** of this declaration, CD and UC are not the same disease. In my opinion, certain aspects of Prof. Pavli's evidence in Section D has limits to its accuracy because they appear to gloss over the differences between CD and UC. By way of example, at paragraph 93 Prof Pavli states: "*The treatment of patients with Crohn's disease and patients with UC is not vastly different. Most medications which are indicated for the treatment of one disease are also indicated for the treatment of the other*". In my view, this statement fails to acknowledge the differences in the treatment options for CD and UC at the Relevant Date and is therefore incorrect (see **Part D.7** above). For example, methotrexate worked in CD but not UC and adalimumab tended to work better in CD than UC (see paragraph 82 above). By comparison, tofacitinib worked in UC but CD, and 5-ASAs (such a mesalamine) worked in UC but were typically ineffective in treating CD (see paragraph 91 above). Of the FDA approved drugs at the Relevant Date, certolizumab pegol, natalizumab and ustekinumab were approved for CD but not UC, and golimumab and tofacitinib were approved for UC but not CD (see paragraph 75 above). Finally, the surgical interventions differ between CD and UC (see paragraphs 89 and 97 above).

181. At paragraphs 75 and 76, Prof. Pavli states that "*The cardinal features of inflammation of tissues are: redness, heat, swelling, tenderness and loss of*

function", and that "*inflammation has common features regardless of which organ system is affected*". This is true when speaking in broad general terms about inflammation. However, as I state above in **Parts D.3** and **D.4** (and elsewhere throughout my declaration), when looking at the specific presentation and pathogenesis of CD and UC there are a number of distinct features that clearly differentiate these two diseases from each other (and from other inflammatory diseases).

182. At paragraph 77, Prof. Pavli states that "*… a number of the underlying mechanisms of the inflammation are well understood (e.g. certain cells produce certain proteins which result in inflammation)*" and that IBDs are "*thought to arise from interactions between genetic (including immune) and environmental factors*". For the reasons that I explain in **Part D.4** above, I agree that some (but not all) of the underlying mechanisms of CD and UC were well understood at the Relevant Date. As I mention in paragraph 44 above, there was a substantial amount that was not yet understood about the underlying mechanisms of CD and UC, and why an immune response leads to CD in some patients and UC in others (and remains incompletely understood to this day).

183. Prof. Pavli discusses the CRP biomarker in paragraph 97 and states that CRP "*generally correlates well with disease activity in Crohn's disease and with UC*". In my opinion, CRP does not sufficiently correspond with disease activity to form the basis for a definitive diagnosis (see paragraph 56 above). Normal CRP levels do not necessarily correlate with endoscopic remission. There is also a subset of the population (about 20-30%) who do not have a profound CRP response to inflammation. Finally, CRP tends to be more elevated in CD patients than UC patients.

184. I note that in Section D.3 (paragraphs 99-126), Prof. Pavli refers only to medications approved in Australia, and omits reference to medications approved elsewhere. For example, at the Relevant Date, the FDA had approved certolizumab pegol for CD and tofacitinib for UC.

185. At paragraph 100(a) Prof. Pavli states that "*it is preferable to avoid surgery for Crohn's disease patients*". In my opinion, there are a numerous factors relevant to the appropriateness of surgery (refer paragraph 98 above), and early surgical intervention may be preferable in some cases. Prof. Pavli also states that "*when surgery is required, [it is preferable] to remove as little of the bowel as possible*". In my view, when surgery is required it is preferable to remove as much of the

diseased portion of the bowel as possible, while removing as little of the bowel as possible to achieve this.

186. At paragraph 103(c) Prof. Pavli states that immunosuppressive agents (i.e., immunomodulators) "*act by inhibiting the proliferation of immune cells*". I note for completeness that this is not true of all immunomodulators, which generally change the overall activity of immune cells, with some (but not all) acting to reduce immune cell proliferation.

187. In relation to paragraphs 108-113, I note that the regulatory approval dates of various biologics by the TGA (which I have been informed by DCCL is the regulatory authority in Australia equivalent to the FDA) tends to be later than the FDA approval dates. For example, Prof. Pavli mentions at paragraph 108 that infliximab was approved by the TGA in 2003 for CD and in 2007 for UC, whereas the FDA approved infliximab for these indications in 1998 and 2005, respectively (see paragraph 75 above). Similarly, in paragraph 109, Prof. Pavli states that adalimumab was approved by the TGA in 2007 for CD and in 2013 for UC, whereas the FDA approved infliximab for these indications in 2007 and 2012, respectively. Prof. Pavli also mentions that golimumab was approved by the TGA for UC and ustekinumab was approved by the TGA for CD in the year following their respective FDA approvals for these indications (see paragraphs 109 and 113 of the Pavli Declaration, respectively). Vedolizumab, on the other hand, was approved for CD and UC by both the TGA and the FDA in 2014 (see paragraph 111 of the Pavli Declaration).

188. At paragraphs 114-123, Prof. Pavli discusses the "step-up" approach. The step-up approach to treatment was commonly used in both CD and UC in the 1990s and 2000s when biologics such as infliximab were first introduced. However, in my view, the treatments for CD and UC still differed at this time (e.g., methotrexate was used for CD but not UC, and 5-ASAs were used for UC and not CD). At the Relevant Date, I (and in my experience other gastroenterologists working in the Field) were moving away from the step-up approach to a more tailored approach that focuses on the needs of the individual patient (e.g., disease activity and extent, potential for complications, etc.) in deciding when to use particular therapies, as I describe in **Part D.7** of this declaration.

189. With reference to Prof. Pavli's comments at paragraphs 117 and 123 that the first choice of biologic medicine for CD and UC was an anti-TNF-α agent, in my experience this was not necessarily the case at the Relevant Date. In particular, by the Relevant Date, disease activity and severity were more of a factor in treatment approaches, and the use of immunomodulators was starting to decrease at that

time. For example, in patients with moderate to severe UC, I (and other gastroenterologists in the Field) would commonly administer vedolizumab as a first line therapy at the Relevant Date (as I discussed in paragraphs 85 and 94 above).

190. At paragraph 125, Prof. Pavli indicates that if the therapeutic approaches he describes in paragraphs 114-124 were unsuccessful, he "*would always consider alternative therapies that were available, even if they were not approved for Crohn's disease or UC (as relevant) at the time. This included medications the subject of clinical trials and medications approved for the treatment of diseases other than Crohn's disease or UC (as relevant) available for "off-label" use*". In my opinion, alternative therapies were not always the best option for the patient. I, and to my knowledge other gastroenterologists working in the Field, remained cautious in relation to administering drugs off-label, as using drugs in this way may pose a significant risk to the patient's health. In my opinion, a compelling reason is required before off-label drug use should even be considered (see paragraphs 102-104 above).

191. At paragraph 129 Prof. Pavli states "*Phase III IBD clinical trials were only embarked upon when the pharmaceutical company sponsoring the trial had a high expectation that the trial would be successful in view of the expense involved*". I am not sure how Prof. Pavli knows this to be the case. In the clinical trials I have been involved with, at no time has the pharmaceutical company running the trial informed me of its level of expectation of success. For the reasons I mention in paragraph 115 above, a CD or UC drug candidate's prospects of success cannot be inferred merely from the fact that it had progressed to a Phase III clinical trial. For these reasons, I do not agree that Phase III IBD clinical trials were only embarked upon when the pharmaceutical company sponsoring the trial had a "*high expectation*" that the trial would be successful.

192. At Paragraph 131, Prof. Pavli states that "*If a drug works for one [] idiopathic inflammatory disease[], then there is generally a rational basis for an expectation that it would work (at least to some extent) on another [] idiopathic inflammatory disease[]. This is more so where there is a greater overlap between the relevant basic inflammation mechanisms, such as the involvement of TNF-α in inflammation in the joints and gut (i.e. infliximab) and the involvement of IL-23 in inflammation in the skin and gut (i.e. ustekinumab)*". I (and in my experience other gastroenterologists working in the Field) do not agree with this statement. In my opinion (and in my experience others in the Field) in the absence of Phase III clinical trial data, it was not possible to extrapolate safety or efficacy from one

inflammatory condition to another, including from CD to UC (and vice versa) (see paragraphs 106-108 above).

193. At paragraph 135 of the Pavli Declaration, Prof. Pavli mentions numerous drug candidates that were undergoing clinical trials for CD and/or UC but were not yet approved by the TGA at the Relevant Date. I refer to a number of these drugs in my response to the Hypothetical Task in **Part E** above.

194. The first drug candidate Prof. Pavli mentions at paragraph 135(a) is tofacitinib. Prof. Pavli states that he "*had some reservations about the use of JAK inhibitors before [the Relevant Date] because the JAK signalling pathway is present in many different cells in the body*" and that he "*was concerned that it might result in unintended consequences when used long-term*". As I mentioned in paragraph 187 above, there may be a lag between FDA approval and TGA approval. This was the case for tofacitinib, which was approved by the FDA for treating UC before the Relevant Date but was not yet approved by the TGA at that time. Despite not yet being approved by the TGA, the results of the Phase III clinical trials indicating the safety and efficacy of tofacitinib in UC patients would have been publicly available at the Relevant Date. These results showed that tofacitinib was similarly effective to medications like adalimumab. It also offered the advantage of being orally deliverable, having a fast onset of action and being non-immunogenic (see **Part E.1.2** above).

195. Prof. Pavli refers to upadacitinib and filgotinib at paragraph 135(b), and states that he "*held similar reservations about these as [he] did for tofacitinib*". However, as I also mentioned in paragraphs 95 and 130 above, upadacitinib and filgotinib predominantly target a single JAK isoform (i.e., JAK1) at therapeutic doses, as opposed to being a pan-JAK inhibitor like tofacitinib. For the reasons I provide in paragraph 130, I would have considered upadacitinib and filgotinib to potentially be more promising drug candidates than tofacitinib at the Relevant Date. Prof. Pavli's comment does not change this view.

196. Prof. Pavli refers to the S1P inhibitor ozanimod at paragraph 135(c) and states that he "*considered ozanimod to be less promising than the JAK inhibitors due to its mechanism of* action". As I mention above in paragraph 132 above, S1P inhibitors such as ozanimod provide several advantages, including that they are orally deliverable and non-immunogenic. Prof. Pavli's comment does not change this view.

197. Prof. Pavli refers to etrolizumab – a modified version of vedolizumab – at paragraph 135(d), which had the potential for increased efficacy over vedolizumab for the reasons I mention above in paragraph 131. I am aware that etrolizumab was taken straight to Phase III clinical trials for CD and UC in view of the success of vedolizumab (although it ultimately was not approved for either condition).

198. Prof. Pavli refers to the IL-23p19 inhibitor risankizumab at paragraph 135(e), followed by the IL-12/IL-23p40 inhibitor ustekinumab at paragraph 135(f), both of which were in Phase III clinical trials for UC at the Relevant Date.

199. In the absence of Phase III results, it would not have been possible to predict whether any of the above drug candidates would be effective in treating CD or UC (see paragraphs 106-108 above). Moreover, their safety at doses used in the studies would not be known until results were made publicly available. The only drug Prof. Pavli mentions in paragraph 135 that had Phase III results confirming its safety and efficacy available at the relevant time was tofacitinib.

200. Prof. Pavli states at paragraph 136(a) that, as a general rule, he "*typically considered biologic medicines to be more promising than small molecules because they specifically bind to a single target, rather than potentially being involved in interactions at unintended sites in the body*". I disagree with this statement, in part because biologics are also capable of exerting off-target effects. As I have outlined in **Part E** above, I also consider that small molecule drugs such as single JAK inhibitors provide certain advantages over biologics, including that they are non-immunogenic an can be delivered orally. In any case, at the Relevant Date, it was not possible to predict how blocking a particular inflammatory pathway would affect the overall immune response (see paragraphs 106-108 above). This is true regardless of whether the inhibitor is a small molecule or a biologic (see **Part D.4** above).

201. At paragraph 136(b), Prof. Pavli states that he was "*typically more interested in drugs which had been approved by the TGA for any indication than drugs which had not* been *approved by the TGA*" because "*a TGA-approved drug must have demonstrated sufficient safety in humans (and efficacy for the approved indication(s))*". I understand the same safety and efficacy data is used to support applications for regulatory approval at various regulatory authorities around the world, including the TGA, the FDA and the European Medicines Evaluation Agency (**EMEA**). For that reason, in addition to locally (FDA) approved drugs, I was also interested in drugs that had been approved by other regulatory authorities.

202. At the conclusion of paragraph 136(b), Prof. Pavli notes that only two of the seven drugs he mentions in paragraph 135 were approved for other inflammatory indications. This appears to be inconsistent with his remark at paragraph 130 that "*clinical trials for IBD patients (both Crohn's disease and UC) often involved medications which had already been approved for the treatment of other diseases*". In paragraph 130, Prof. Pavli also includes a further example (vedolizumab) of a drug that had not been approved for any other indications prior to CD and UC.

203. Paragraphs 137-153 of the Pavli Declaration are directed to Prof. Pavli's off-label use of medications in patients with CD or UC. Nothing in these paragraphs causes me to alter my evidence provided in **Part D.8** above.

204. At paragraphs 143-162, Prof. Pavli details various medications that he used off-label in CD and UC patients in the circumstances corresponding to Scenario 3 as set out in paragraph 101(c) above (and which I discuss in more detail in **Part D.8.1** above). Examples include the immunomodulators tacrolimus and sirolimus (paragraphs 143-145). The decision to use these medications off-label appears to have been driven by small-scale reports (just two patients for sirolimus) and had limited success (success in two or three out of eight to ten patients is similar to placebo effect rates).

205. For the reasons I consider at paragraphs 102-104 of my declaration, the decision to prescribe a drug off-label in the circumstances of Scenario 3 rather than proceed with surgery potentially carries health risks for the patient (e.g., perforation, infection, etc.), and is therefore a decision that requires careful consideration and shared decision making with the patient. I would not prescribe a drug off-label based on reports of success in only a few patients (see paragraph 153 above). In my opinion (based on my experience and interactions with my colleagues as described in **Part C** of my declaration), the great majority of gastroenterologists would similarly not prescribe a drug off-label based on such reports. Accordingly, in my opinion, the use of a drug off-label in these circumstances is outside the normal scope of practice and is not generalizable to other gastroenterologists.

206. At paragraphs 149-151, Prof. Pavli mentions that he used infliximab off-label in patients with CD starting in the year 2000. However, he also notes at paragraph 149 that infliximab was already approved by the FDA for CD at that time, so the Phase III results confirming the safety and efficacy of infliximab in CD patients would have been publicly available at the time. These circumstances correspond to Scenario 2 set out in paragraph 101(b) above. The availability of

Phase III clinical results confirming the safety and efficacy of infliximab in CD significantly reduced the risk of using this drug off-label.

207. At paragraph 152, Prof. Pavli also indicates that he administered infliximab to a UC patient in 2001. Prof Pavli states: "*… given the similarity in the treatment of the two diseases (as I discuss in paragraph 99 above) I expected that infliximab may well improve the patient's condition*". I do not agree with this statement. In my opinion, as at the Relevant Date, it was not possible to extrapolate safety or efficacy from one inflammatory condition to another, including from CD to UC (see paragraphs 106-108 above).

208. Prof. Pavli notes at paragraph 155 that he was a Principal Investigator in a Phase II clinical trial for ustekinumab in CD (CERTIFI) and that a participant (who was also a patient of his) went into remission during the course of the trial. As Prof. Pavli notes, this trial was blinded so there was no way of knowing whether the improvement in the patient's condition was due to ustekinumab or fell within the placebo effect. This information also would not have been known to me or other gastroenterologists in the Field. Prof. Pavli goes on to describe in paragraph 156 that he was also the Principal Investigator in three Phase III clinical trials involving ustekinumab in CD patients (UNITI-1, UNITI-2 and IM-UNITI). Prof. Pavli notes that these trials involved different dosages and routes of administration to those approved for ustekinumab in plaque psoriasis, so his off-label use in CD was confined to the approved dose and route of administration for use in plaque psoriasis. Not necessarily having access to the appropriate dosages or dosage forms (or even knowing what these should be for an off-label indication) is a common problem with off-label use. This problem is further highlighted in paragraph 159 of the Pavli Declaration.

209. At paragraph 158, Prof. Pavli describes off-label use of ustekinumab for a patient with UC. The circumstances of this use correspond to Scenario 3 as set out in paragraph 101(c) above. Like the other examples of off-label use described in the Pavli Declaration, it is difficult to comment on or characterize this off-label use because I did not examine the patient and do have access to Prof. Pavli's notes. The relevant details in relation to this particular patient are not available to me, including the extent of disease activity before receiving the off-label drug, whether they went into remission, whether they were taking steroids at the time, and the wash out period of other drugs (e.g., infliximab). I note, however, that the patient ultimately underwent J-pouch surgery to remove the colon and rectum. This result is not surprising to me for the reasons outlined in **Part D.8.1**, above.

G.2 Consideration of Sections E.2.1, E.2.2, E.2.4 and E.2.5 of the Pavli Declaration

210. After I had considered the matters set out in **Part G.1** above, DCCL provided me with Sections E.2.1, E.2.2, E.2.4 and E.2.5 of the Pavli Declaration and asked me to:

(a) consider all paragraphs except paragraphs 191, 204 (last sentence), 205, 228 (last sentence) and 229; and

(b) comment on the conclusions drawn by Prof. Pavli in each of the sections I consider.

G.2.1 CTR 236 (Section E.2.1 of the Pavli Declaration)

211. In Section E.2.1 (paragraphs 175-191), Prof. Pavli discusses CTR 236. In the great majority of these paragraphs, Prof. Pavli summarizes aspects of the study and provides numerous extracts from CTR 236. Because of this, the only paragraph I respond to here is paragraph 178 (noting that I have been asked not to consider paragraph 191).

212. As Prof. Pavli notes at paragraph 178, and consistent with my observations in **Part F.1** above, CTR 236 "*record[s] information regarding the UNIFI Phase III clinical trial examining the use of ustekinumab in UC patients [in which he was involved as a Principal Investigator]*". The purpose of the trial was to evaluate the safety and efficacy of ustekinumab in participants with moderately to severely active UC. CTR 236 does not contain any results, or any indication or rationale, that ustekinumab would be safe or efficacious in UC patients (see also paragraph 143 above). Therefore, it was not possible to know from CTR 236 whether ustekinumab is safe or efficacious in participants with moderately to severely active UC. Prof. Pavli's opinions on CTR 236 do not change my view.

G.2.2 Abstract P759 (Section E.2.2 of the Pavli Declaration)

213. In Section E.2.2 (paragraphs 192-205), Prof. Pavli discusses Abstract P759. In a number of these paragraphs, Prof. Pavli summarizes aspects of the study and provides several extracts from Abstract P759.

214. At paragraph 195, Prof. Pavli notes that "*Before 24 September 2018, I was aware that Dr Truelove and Dr Witts had published a classification of disease severity for UC but I had typically used one or more of the various Mayo Scores I have discussed in paragraphs 91 to 95 above to assess the severity of a patient's disease*". As I

mentioned in paragraph 160 above, I understand the modified Truelove and Witts CAI corresponds to the Lichtiger CAI (published by Lichtiger et al., 1994), as opposed to the original Truelove and Witts CAI published in 1955. In my experience, it is unusual for the modified Truelove and Witts CAI to be used, either by clinicians or in clinical trials. Moreover, the modified Truelove and Witts CAI, as described by Lichtiger et al., was used in patients who were hospitalized to receive therapy. In my opinion, the Mayo scoring system is far more widely used and is a more reliable measure of disease activity because it includes an endoscopic assessment of the patient.

215. Prof. Pavli notes at paragraphs 196-197 that 5/17 patients in the study described in Abstract P759 had failed IV cyclosporine, and that he "*did not use cyclosporine in the treatment of UC once [he] had off-label access to infliximab*". In my experience, IV cyclosporine (also known as "ciclosporine") is typically only used when a corticosteroid-resistant patient has been hospitalized with severe UC (as was the case in Lichtiger et al., 1994). Once a patient has failed IV cyclosporine they are usually extremely ill and require urgent surgery. I note from the plot that only two patients have a CAI > 10 at the start of the study (see paragraph 161 above), which is inconsistent with at least five of those patients having severe UC requiring IV cyclosporine.

216. At paragraph 200, Prof. Pavli notes that TNF or integrin blocking had been stopped before ustekinumab was administered to the patients, "*but it is not clear to me how long before treatment with ustekinumab this occurred*". This is consistent with my observation at paragraph 152 above and leaves open the possibility that there was still a TNF-α inhibitor or vedolizumab in the patient's system at the start of the study.

217. I disagree with Prof. Pavli's conclusions at paragraphs 202 and 204 that the results presented in Abstract P759 are "*very good*" and "*provide[] examples of the successful use of ustekinumab therapy in UC patients who had failed a number of prior therapies, including at least one immunosuppressant, anti-TNF-α antibody and anti-integrin antibody*", respectively, for the reasons I have provided in **Part F.2** above. Further, Prof. Pavli states at paragraph 202 that it was "*[his] understanding before 24 September 2018 that [UC] patients can achieve clinical response or clinical remission after one or two doses of ustekinumab*". This understanding appears to be based on inferences made during his time as a Principal Investigator on the double-blinded UNIFI trial and limited off-label use carried out in the course of his clinical practice, the details of which are not available to me (or the public in

general). Prof. Pavli's opinions on Abstract P759 do not change my views in relation to off-label medication use in patients with moderately to severely active UC as expressed in **Part D.8.1**, above (see paragraphs 103-105).

G.2.3 DDW Poster (Section E.2.4 of the Pavli Declaration)

218. In Section E.2.4 (paragraphs 217-229), Prof. Pavli recites extracts of the DDW Poster and largely repeats his observations in Section E.2.2 (made in relation to Abstract P759). Accordingly, I reiterate my comments in **Part G.2.2** above to the extent they apply to the DDW Poster. Specifically, I disagree with Prof. Pavli's conclusions at paragraphs 225, 226 and 228 that the results presented in the DDW Poster are "*very good*", "*excellent*" and "*provided examples of the successful use of ustekinumab therapy in UC patients who had failed a number of prior therapies, including at least one immunosuppressant, anti-TNF-α antibody and anti-integrin antibody*", respectively, for the reasons I have provided in **Part F.4** above.

G.2.4 Abstract Tu1713 (Section E.2.5 of the Pavli Declaration)

219. In Section E.2.5 (paragraphs 230-232), Prof. Pavli discusses Abstract Tu1713. At paragraph 231, Prof. Pavli states "*I observe that Abstract Tu1713 is virtually identical to Abstract P759*", which is consistent with my observation in **Part F.3** above. Therefore, I refer to and reiterate my comments in **Part G.2.2** above in relation to Abstract P759.

G.3 Consideration of Section F of the Pavli Declaration

220. After I had considered the matters set out in **Part G.2** above, DCCL provided me with Section F of the Pavli Declaration. and asked me to:

(a) consider all paragraphs except paragraphs 284, 285, 303, 305, 317 and 319; and

(b) where I consider it appropriate, to respond to the matters expressed by Prof. Pavli.

221. DCCL also provided me with the Opposed Application, to which Section F of the Pavli Declaration relates. A copy of the Opposed Application is provided as **Annexure MAC-8**.

222. I confirm that I have read and understand the Opposed Application, to which Prof. Pavli refers in Section F of his declaration, and that I have considered this document in providing my comments on Section F of the Pavli Declaration in this **Part G.3** of my declaration.

223. As a general matter, I note that a large proportion of Section F of the Pavli Declaration appears to restate the information provided in the Opposed Application. Where a paragraph (or part thereof) substantially restates the information provided in the Opposed Application, or where I agree (or do not materially disagree) I have not made any specific comments in relation to that paragraph (or part thereof).

224. I also note there are several instances of inaccuracies in the reproduction of passages from the Opposed Application in the Pavli Declaration. However, the majority of these inaccuracies appear to be of a minor typographical nature. Therefore, I have only noted these inaccuracies where I believe they make a material difference to the meaning of the relevant passage.

G.3.1 Specification (Section F.1 of the Pavli Declaration)

225. In Section F.1 (paragraphs 238-278) of his declaration, Prof. Pavli discusses the specification of the Opposed Application. In many of these paragraphs, Prof. Pavli summarizes aspects of the description and provides numerous extracts. Therefore, I have not specifically commented on a number of these paragraphs.

226. At paragraph 238, Prof. Pavli notes that the Opposed Application defines the "Field of the Invention" as follows (page 1, second paragraph):

> *The invention relates to methods of providing a clinically proven safe and clinically proven effective treatment of ulcerative colitis, particularly moderately to severely active ulcerative colitis in patients who have had an inadequate response to or are intolerant of a conventional or existing therapy by intravenous and/or subcutaneous administration of an anti-IL-12/IL-23p40 antibody.*

227. At paragraph 241, Prof. Pavli refers to page 3, paragraph 2 of the Opposed Application, including the following:

> *When tested, biologic therapies that are currently approved for the treatment of UC have also demonstrated efficacy in Crohn's disease ... Multiple lines of evidence suggest that inflammatory bowel disease (UC and Crohn's disease) is mediated by Th-1 or Th-17 cells with strong contribution from the proinflammatory cytokines, IL-12, and IL-23. 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-12Rf31 receptor protein ... Through this mechanism of action,*

ustekinumab effectively neutralizes IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses. …

As I discuss in **Part D.4** above, while certain cytokine profiles and the cell types that secrete them were known in the Field to be associated with either CD or UC, or both, it was not well understood why the immune response leads to CD in some patients and UC in others. Further, for the reasons I discuss in paragraphs 106-108 above, it was not possible to extrapolate safety or efficacy from one inflammatory condition to another. This was true even for CD and UC. As such, it was not possible at the Relevant Date (and is still not possible today) to predict whether a drug that treats CD will also be effective in treating UC (and vice versa). In this regard, I refer to paragraph 107 above, where I outline various examples in which blocking a particular inflammatory pathway did not lead to the desired inhibition of disease activity.

228. At paragraphs 244-245, Prof. Pavli expresses his disagreement with page 4, paragraph 1 of the Opposed Application (which is shown below):

> *Prior to the present invention, no studies had been conducted with ustekinumab for UC. [T]here is a need in the art for improved methods of treating UC, particularly moderately to severely active UC, in subjects who had previously failed or were intolerant of a biologic therapy or other conventional therapy, or subjects who had demonstrated corticosteroid dependence.*

229. Prof. Pavli states: "*Insofar as this passage is suggesting that ustekinumab had not been used in the treatment of UC patients before 24 September 2018, I disagree*". I disagree with Prof. Pavli, who goes on to refer to the UNIFI Phase III clinical trial, as well as his own off-label use and that described in Abstract P759 as examples of "treating" UC using ustekinumab. In my opinion, none of these is an example of "treatment" of UC patients with ustekinumab for the reasons I discuss below.

230. In my opinion (and in my experience the opinion of other gastroenterologists working in the Field), to "treat" a condition with a drug requires administering a drug that is known at that time to be capable of treating that condition in the relevant patient population. A drug is only known to be capable of treating a condition if both its safety and efficacy have been established by Phase III clinical trial results (subject to the exception I mention in paragraph 101(a) above at **Part D.8** where there is real world data collected from a large number of patients over a prolonged period of time that establishes safety and efficacy of that drug).

This is consistent with the definition of the term "clinically proven" in the Opposed Application as follows (page 15, first paragraph):

> *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.*

231. The term "clinically proven safe" is defined in the Opposed Application at page 14, last paragraph, an extract from which is as follows:

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

232. The term "clinically proven effective" is also defined in the Opposed Application at page 13, first paragraph as follows:

> *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. For example, an anti-IL12/23p40 of the present invention (e.g., ustekinumab) is administered 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. Various indicators that reflect the extent of the subject's illness, disease or condition can be assessed for determining whether the amount and time of the treatment is sufficient. Such*

indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. ...

233. Taken together, I understand the above passages to mean that in the context of the Opposed Application, "treating" moderately to severely active UC involves administering a drug that is known at that time to be safe and effective in a patient with moderately to severely active UC based on Phase III clinical trial results. The way in which "treatment" is used in the Opposed Application is consistent with what I considered to be "treatment" in the course of my clinical practice at the Relevant Date (see **Part D.7** above).

234. Contrary to Prof. Pavli's comments at paragraph 245 of his declaration, CTR 236 does not include any results (or any suggestion, rationale or other information) that demonstrate ustekinumab was safe and effective in patients with moderately to severely active UC. This is self-evident from CTR 236; the stated purpose of the trial is to evaluate whether or not ustekinumab is safe and efficacious in participants with moderately to severely active UC. For the reasons I explain at paragraph 143 above, there is no way of knowing from reading CTR 236 whether or not ustekinumab will be safe or achieve any of the primary and secondary outcome measures defined in CTR 236.

235. In my view, none of Abstract P759, the DDW Poster and Prof. Pavli's off-label use of ustekinumab disclose or amount to the use of ustekinumab in "treating" UC patients. This is because the safety and efficacy of ustekinumab in UC patients had not been established in Phase III clinical trials (or by extensive real world data as I mention in paragraph 101(a)) prior to the administration of ustekinumab to the UC patients in any of Abstract P759, the DDW Poster or Prof. Pavli's off-label use. I would characterize this sort of off-label use as a "Hail Mary" (see paragraphs 103-105, above). I would not categorise it as a "treatment", because it was not known at that time to be safe and effective.

236. In my view (and in my experience the view of other gastroenterologists in the Field), the results of the Phase III clinical trial of ustekinumab in UC patients with moderately to severely active UC (UNIFI clinical trial) demonstrated for the first time that administering ustekinumab is safe and effective in that patient population (and therefore capable of treating moderately to severely active UC).

237. At paragraphs 259-275 of his declaration, Prof. Pavli discusses the Examples of the Opposed Application. I understand Examples 1 and 2 describe the Induction study and the Maintenance study, respectively, which were the subject of the UNIFI

clinical trial. The Examples show that ustekinumab was "clinically proven safe" in participants with moderately to severely active UC (see, e.g., page 86, line 4 to page 87, line 21). The Examples also show that ustekinumab was "clinically proven effective" in participants with moderate to severe UC (see, e.g., page 80, line 4 to page 84, line 28).

238. In Example 1 (the Induction study), the "Experimental Design" section (page 64, lines 13-29) explains:

> *The Phase 3 development program for ustekinumab comprised 2 separate studies, an induction study and a maintenance study. In the induction study, subjects were randomized at Week 0 into one of three treatment groups: placebo, low-dose ustekinumab, and high-dose ustekinumab. At Week 8, all subjects were evaluated for the primary endpoint of clinical remission and clinical response. Subjects who achieved a clinical response at Week 8 were eligible to enter the maintenance study. Subjects who did not achieve clinical response at Week 8 received a second dose of ustekinumab at Week 8 of treatment.*
>
> *At Week 16, subjects who did not achieve clinical response at Week 8 were re-evaluated for clinical response. Subjects who achieved clinical response at Week 16 were eligible to enter the maintenance study. …*

239. The subjects who did not achieve clinical response at Week 8 received a second dose of ustekinumab at Week 8 as follows (see page 65, lines 9-14):

(i) Subjects who were randomized to placebo at Week 0 received 1 dose of ustekinumab ~6 mg/kg IV + placebo SC (to maintain the blind) at Week 8.

(ii) Subjects who were randomized to ustekinumab at Week 0 received 1 dose of ustekinumab 90 mg SC + placebo IV (to maintain the blind) at Week 8.

240. The "Efficacy Evaluation" section bridging pages 66-67 states:

> *Efficacy evaluations were collected throughout the study. Mayo score and partial Mayo score, [Ulcerative] Colitis Endoscopic Index of Severity (UCEIS), Bristol Stool Form Scale 20 (BSFS), C-reactive protein (CRP), fecal lactoferrin, fecal calprotectin, Inflammatory Bowel Disease Questionnaire (IBDQ), 36-item Short Form Health Survey (SF-36), and EuroQoL-5D Health Questionnaire were all evaluated to determine efficacy.*

241. As Prof. Pavli mentions as paragraph 266 of his declaration, the efficacy criteria included, among other things:

- Clinical remission (global submissions): Mayo score ≤2 points, with no individual subscore > 1 (**Global Definition**).
- Clinical remission (US submissions): absolute stool number ≤3, rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (**US Definition**).
- Clinical response: a decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
- Endoscopic healing (i.e., improvement in the endoscopic appearance of the mucosa): Mayo endoscopy subscore of 0 or 1.
- Histologic healing: based on the Geboes score and is defined as 0 to <5% neutrophils in epithelium and no crypt destruction, erosions, ulcerations, or granulations.
- Mucosal healing: both endoscopic healing and histologic healing.

242. I note that while Prof. Pavli has correctly reproduced the Global Definition and US Definition of clinical remission from page 66 of the Opposed Application in paragraph 266 of his declaration, the same definitions appearing on page 77 of the Opposed Application have been incorrectly reproduced at paragraph 267 of his declaration. I have assumed that the errors at paragraph 267 of the Pavli Declaration are typographical errors only and are not intended to change the meaning of the definitions.

243. In the Induction study, efficacy was demonstrated by a statistically significant improvement in the following outcome measures, among others (see page 69, line 19 to page 75, line 7):

- clinical remission (Global Definition);
- clinical remission (US Definition);
- endoscopic healing;
- clinical response;
- total IBDQ score;

- histologic healing;
- Mayo score;
- Partial Mayo score; and
- UCEIS score.

244. In Example 2 (the Maintenance study), the "Methodology" section describes two study populations:

(i) Primary (randomized) population: subjects who achieved a clinical response at Week 8 in the Induction study and subjects who achieved a clinical response at Week 16 in the Induction study after receiving a second dose of IV ustekinumab. These subjects were randomized in a 1:1:1 ratio at maintenance Week 0 to receive ustekinumab 90 mg SC every 8 weeks (q8w), ustekinumab 90 mg SC every 12 weeks (q12w), or placebo SC.

(ii) Nonrandomized population: subjects who achieved a clinical response at Week 16 in the Induction study after receiving a second dose of SC ustekinumab and subjects with a clinical response to placebo IV induction. These subjects received placebo SC.

245. The "Criteria for Evaluation" in the Maintenance study are set out at page 77, line 6 to page 78, line 29 of the Opposed Application. The primary endpoint is said to be "*clinical remission at Week 44*". Given some subjects are entering the Maintenance study after Week 8 of the Induction study, and some are entering the Maintenance study after Week 16 of the Induction study, I understand Week 44 to mean 44 weeks after entering the Maintenance study (i.e., after having been identified as achieving a clinical response in the Induction study and receiving the first maintenance dose). This is consistent with Figure 1 of the Opposed Application, which is a diagrammatic representation of the study design showing "*Subjects in clinical response at W8 and W16 of induction*" entering Week 0 of the 44 week Maintenance study. Example 2 also refers in various places to "*maintenance Week 0*" (e.g., page 75, line 22; page 76, lines 3 and 13; page 79, line 7) which further indicates that the reference to Week 44 is 44 weeks from the start of the Maintenance study.

246. The major secondary endpoints of the Maintenance study are listed as:

- Maintenance of clinical response through Week 44.
- Endoscopic healing at Week 44.

- Clinical remission and not receiving concomitant corticosteroids (corticosteroid-free clinical remission) at Week 44.
- Maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline.

Again, I understand the reference to Week 44 in each of these secondary endpoints to mean 44 weeks after entering the Maintenance study.

247. In the Maintenance study, efficacy was demonstrated at Week 44 for both q8w and q12w subjects compared to the placebo group by a statistically significant improvement in each of the following outcome measures, among others (see page 80, line 4 to page 84, line 28):

- clinical remission (Global Definition);
- clinical remission (US Definition);
- maintenance of clinical response;
- endoscopic healing;
- corticosteroid-free clinical remission;
- histologic healing;
- mucosal healing; and
- total IBDQ score.

248. As noted by Prof. Pavli at paragraph 275, the "Conclusion" of Example 2 states (at page 88):

> *The ustekinumab maintenance study provided consistent and definitive evidence that the ustekinumab 90 mg SC q12w and q8w dose regimens were both effective in adult subjects with moderately to severely active UC who had responded to a single IV ustekinumab induction dose.*

249. Based on my review of the data from the clinical trial provided in Examples 1 and 2, I agree with the above conclusion and consider that ustekinumab has been clinically proven to be safe and effective in inducing a treatment response (i.e., a statistically significant improvement over placebo in each of the outcome measures mentioned in paragraph 247 above) in patients with moderately to severely active UC. My view is supported by the fact ustekinumab was approved by the European

Commission for the treatment of UC on 4 September 2019 (see Annex I of the Opposed Application). I understand this to be around the same time Stelara® was approved by the FDA for UC.

G.3.2 Claims (Section F.2 of the Pavli Declaration)

250. In Section F.2 (paragraphs 279-325) of his declaration, Prof. Pavli discusses the claims of the Opposed Application. In many of these paragraphs, Prof. Pavli summarizes aspects of the claims and provides numerous extracts. Therefore, I have not specifically commented on a number of these paragraphs.

251. Claim 1 of the Opposed Application is in the following terms:

> *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 an effective amount of an anti-IL-12/IL-23p40 antibody, … 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 ≥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.*

252. In claim 1 (and in claims 19 and 33), the anti-IL-12/IL-23p40 antibody is defined in terms of its CDRs, specifically three CDRs of the VH chain (SEQ ID NOs:1-3) and three CDRs of the VL chain (SEQ ID NOs:4-5). I note from the Opposed Application, including at page 31, lines 16-18, and the Sequence Listing, that SEQ ID NOs:1-6 are the CDR sequences of the VH and VL chains of ustekinumab. As I mentioned in paragraph 74 above, these CDRs inform the binding specificity and affinity of the antibody molecule. Therefore, other antibodies with the same six CDRs would be expected to have the same binding specificity and affinity as ustekinumab. This appears to be consistent with Prof. Pavli's comments at paragraph 282.

253. I note that each of the measures of response to treatment in items (i)-(vii) of claim 1 corresponds to one of the outcome measures I mentioned in paragraph 247 above, which were demonstrated in Example 2 to have a statistically significant improvement over placebo in the Maintenance study.

254. At paragraph 283 of the Pavli Declaration, it appears Prof. Pavli has interpreted the reference to the "Mayo score" in claim 1 to mean the full, partial or modified Mayo Score in some instances (but not others). I disagree with this interpretation, since the term "Mayo score" is used throughout the description to refer to the full Mayo score and is clearly delineated from the terms "partial Mayo score" and "modified Mayo score" where they appear in the description (e.g., at page 13, lines 19-28). In particular, in Examples 1 and 2, the (full) Mayo score and partial Mayo scores are discussed separately (see, e.g., page 72, line 20 to page 72, line 4). Therefore, I understand the reference to "Mayo score" (absent the word "partial" or "modified" preceding it) in the claims to be a reference to the full Mayo score.

255. Claims 10-18 use the term "*at least 44 weeks after week 0*". For the reasons I state at paragraph 245 above, I disagree with Prof. Pavli's interpretation of these claims at paragraph 308 of his declaration, in which he says the term "*at least 44 weeks after week 0*" is a reference to "*44 weeks after the first dose of ustekinumab (i.e. the IV induction dose referred to in claim 6)*". Each of claims 10-18 refer to claim 9 (with the exception of claim 12, which appears to me to have been intended to refer to claim 9 rather than claim 8), which defines that "*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*". As Prof. Pavli notes, in the UNIFI Phase III trial, as reflected in Examples 1 and 2 of the Opposed Application, "*patients were assessed at 44 weeks after the first maintenance dose of ustekinumab*". This is also consistent with Annex I, including Label Table 6, which refers to key efficacy measures at "*week 44; 52 weeks from initiation of the induction dose*". I also note that elsewhere the claims state "*week 0 of the treatment*" when referring to the first induction dose (see claims 6, 19, 33 and 34). Therefore, it is apparent to me that the reference to "*at least 44 weeks after week 0*" (absent the qualifier "of the treatment" following "week 0") in claims 10-18 is a reference to at least 44 weeks after the first maintenance dose.

256. At paragraphs 309-325, Prof. Pavli addresses claims 19-34. In those paragraphs, Prof. Pavli states that he repeats his comments in various permutations of paragraphs 280-287, 289, 291, 293, 295 and 297-299. In response to paragraphs

309-325, I repeat my comments in response to paragraphs 280-287, 289, 291, 293, 295 and 297-299 as applicable.

G.4 Consideration of Section E.1 of the Pavli Declaration

257. After I had considered the matters set out in **Part G.3** above, DCCL provided me with Section E.1 (paragraphs 163-174) of the Pavli Declaration and asked me to comment on the conclusions drawn by Prof. Pavli, and whether those conclusions change how I would approach the Hypothetical Task in **Part E** of my declaration.

258. I note that Prof. Pavli has been asked to "*propose a medication for the treatment or management of UC which would be a useful alternative to, or better than, the medications that were approved for use for the treatment and/or management of UC … (the **Task**)*".

259. My understanding of Prof. Pavli's evidence is that his primary criteria in answering the Task is to choose an existing (commercially available) medication that was already approved in Australia for CD. Prof. Pavli then refines his choice by adding the further criteria of being in Phase III clinical trials for UC. I agree that if these criteria are used, the only available medication to be proposed is ustekinumab. For the reasons set out below and in **Part E** of my declaration, I do not believe these criteria are appropriate.

260. I believe that the Task Prof. Pavli was asked to carry out, which is to "*propose a medication*", has driven his choice of criteria. I note that, in carrying out the Hypothetical Task put to me in **Part E** above, I did not limit myself to existing commercially available medications that had already received regulatory approval for other inflammatory indications.

261. I also note that Prof. Pavli's choice of ustekinumab takes into account information he has gleaned from his involvement in the UNIFI clinical trial and his off-label use (see paragraph 169 of the Pavli Declaration), which was not available to me and would not have been available to other gastroenterologists in the Field at the Relevant Date.

262. I expand on my above comments and provide a more detailed analysis of Prof. Pavli's evidence in the following paragraphs.

263. At paragraphs 167 and 168, Prof. Pavli states, "*The response to the Task which immediately would have sprung to mind is the use of ustekinumab*" and ustekinumab was "*the standout choice*", respectively. Prof Pavli sets out three reasons for this choice, which I summarize as follows:

(a) ustekinumab was approved by the TGA for CD in February 2017;

(b) most medications indicated for treating CD were also indicated for UC; and

(c) ustekinumab was in ongoing clinical trials for UC.

264. I disagree with Prof. Pavli's rationale for recommending ustekinumab. In relation to reason (b), I note that of the three medications approved for both CD and UC at the Relevant Date, two were TNF-α inhibitors and one was an integrin inhibitor (see paragraphs 75 and 76 above). In my opinion, it is also not possible to extrapolate from one class of drugs (e.g., TNF-α inhibitors or integrin inhibitors) to another class of drugs (e.g., IL-12/IL-23p40 inhibitors), as they are directed to different therapeutic targets. In relation to reason (c) above, as I have indicated in **Part D.8** above, it is not possible to extrapolate efficacy of a drug approved for the treatment of CD to the use of the same drug for the treatment of UC (see paragraphs 106-108 above).

265. Prof. Pavli further states at paragraph 169 that "*[his] involvement in the UNIFI trial, and [his] off-label experience with ustekinumab, before 24 September 2018 would have further cemented ustekinumab in [his] mind as the clear first choice in response to the Task*". As I mention in paragraph 208 above, the UNIFI trial was blinded so there is no way of knowing whether the improvement in the patient's condition was due to ustekinumab or the placebo effect. In any case, the information Prof. Pavli has inferred from his involvement in the UNIFI trial would not have been available to other gastroenterologists in the Field. Further, as I discuss in paragraph 230 above, in my opinion the off-label use of ustekinumab Prof. Pavli describes in his declaration (e.g., at paragraph 158) did not establish that ustekinumab is capable of treating UC patients. In any event, any knowledge gained by Prof. Pavli in respect of his off-label use of ustekinumab was not available to me or other gastroenterologists in the Field.

266. At paragraph 172, Prof. Pavli states that he would have also considered using tofacitinib because "*it had been TGA-approved for use in the treatment of rheumatoid arthritis and was the subject of Phase III clinical trials for use in the treatment of UC before [the Relevant Date]*". However, he goes on to state that "*tofacitinib would have been a very distant second choice compared to ustekinumab*" because it had not been approved for CD and he "*had some reservations about the use of JAK inhibitors before [the Relevant Date]*" (as set out in paragraph 135(a) of his declaration).

267. Prof. Pavli also fails to distinguish how pan-JAK inhibitors, such as tofacitinib, may differ in efficacy or safety from JAK inhibitors with greater specificity for a single

JAK isoform (i.e., JAK1), including upadacitinib and filgotinib, which were in Phase III clinical trials at the time. Specifically, Prof. Pavli states at 135(b) that "*Upadacitinib and filgotinib were other JAK inhibitors which are more specific than tofacitinib. […] As JAK inhibitors, I held similar reservations about these as I did for tofacitinib".* For the below reasons, I do not agree with Prof. Pavli's characterization of both tofacitinib and (by inference from paragraph 135(a) of his declaration) JAK inhibitors with greater specificity for a single JAK isoform, as a "*very distant second choice compared to ustekinumab*".

268. As an initial comment, I note that tofacitinib had already been approved for treating UC by the FDA at the Relevant Date. The results of the Phase III clinical trial demonstrating the safety and efficacy of tofacitinib in UC would therefore have been available to the public at that time. Dr Pavli omits this fact from his analysis.

269. In my opinion Prof. Pavli's analysis fails to take into account the features of JAK inhibitors (and particularly JAK inhibitors with greater specificity for a single JAK isoform) that had the potential to address multiple aspects of the unmet need in relation to UC treatment at the Relevant Date (see paragraphs 128-130 and 135 above). In particular, as at the Relevant Date, JAK inhibitors were known to be non-immunogenic, orally deliverable and to have a relatively fast onset of action. They also had the potential for gut specificity and to address the efficacy ceiling by inhibiting numerous pro-inflammatory cytokines at the same time (as opposed to ustekinumab which targets only IL-12/IL-23 and is therefore more limited).

270. Prof. Pavli states he has "*reservations about the use of JAK inhibitors before [the Relevant Date] because the JAK signalling pathway is present in many different cells in the body*" (see paragraph 135(a)). However, he does not explain why he believes this "*might result in unintended consequences when used long-term*", particularly in view of the FDA regulatory approval of tofacitinib for treating UC. Further, in paragraph 135 (b) of his declaration, Prof. Pavli states that he had the same concern in relation to upadacitinib and filgotinib, despite also acknowledging that they were more specific than tofacitinib. While the long term differences in safety between pan-JAK and single JAK inhibitors were not yet known at the Relevant Date, single JAK inhibitors had the potential to minimize any off-target effects observed with pan-JAK inhibitors (see paragraph 130 above).

271. I note that Prof. Pavli states at paragraph 170(c) that the onset of action of ustekinumab is "*relatively quick*" compared to vedolizumab. However, in my view it had not yet been established that ustekinumab was effective in UC patients at the Relevant Date (as the Phase III results were not yet available), let alone that its onset of action was as stated by Prof. Pavli.

272. After I had considered the matters set out above, DCCL asked me to consider paragraphs 191, 204 (last sentence), 205, 228 (last sentence) and 229 of the Pavli Declaration, which refer to paragraphs 165-173 of that declaration, and comment on whether or not the views expressed by Prof. Pavli in those paragraphs would change how I would approach the Hypothetical Task in **Part E** of my declaration.

273. At paragraph 191, I understand Prof. Pavli to be indicating that in responding to the Task he would recommend using ustekinumab in accordance with the dosing that was approved for CD patients (as set out in paragraphs 167, 170 and 171 of his declaration), and that the evaluation of dosages in CTR 236 that were not ultimately approved for CD would not change this view. Further, at paragraphs 205 and 229, Prof. Pavli appears to indicate that Abstract P759 and the DDW also support this view. As stated earlier in my evidence at paragraph 107, it is not possible to predict whether the dosing of a medication for CD will be appropriate for UC (and vice versa). This evidence does not change how I would approach the Hypothetical Task in **Part E** of my declaration.

274. In the first sentence of each of paragraphs 204 and 228 of the Pavli Declaration, Prof. Pavli expresses the view that Abstract P759 and the DDW Poster "*provide[] examples of the successful use of ustekinumab in UC patients who had failed a number of prior therapies, including at least one immunosuppressant, anti-TNF-a antibody and anti-integrin antibody*". In the last sentence of each of paragraphs 204 and 228, Prof. Pavli goes on to stated that "*This would have even further supported the matters I have discussed in paragraphs 165 to 173 above*". I disagree with the first sentence of paragraphs 204 and 228 for the reasons I provide at paragraphs 217 and 218 above, respectively. As I do not consider that either Abstract P759 or the DDW Poster demonstrates the safety and effectiveness of ustekinumab in the broader UC patient population, Prof. Pavli's comments at paragraphs 204 (last sentence) and 228 (last sentence) would not have changed how I would approach the Hypothetical Task in **Part E** of my declaration.

H DECLARATION

275. I make this declaration conscientiously believing the statements contained in this declaration to be true and correct.

Matthew A. Ciorba, MD

Signed:	Professor Matthew Aaron Ciorba
Date:	14 January 2024
Place where declaration is made:	Arizona, USA