

## **Single Technology Appraisal**

# **Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

## **Committee Papers**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Ustekinumab for treating moderately to severely active ulcerative colitis  
[ID1511]**

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*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

**Single Technology Appraisal**

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**Type of stakeholder:**

**Consultees** – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

**Commentators** – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public** – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Patient group	Crohn's & Colitis UK	<p><b>We are very concerned by the Committee's initial recommendation to not make this drug available as a treatment option for this indication on the NHS.</b></p> <p>We note that the Committee agrees with patient and clinical experts that there is significant unmet need and that new medical treatments are needed.</p> <p>In this vein, ustekinumab has shown itself to be clinically effective within its indication for groups of patients. It offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making). This is particularly relevant given how individual a person's condition can be and consequently how personalised treatments are required to be.</p> <p>It also very importantly has the potential to significantly improve the lives of patients with uncontrolled and unresponsive refractory disease, who are likely to be experiencing an extremely low quality of life.</p> <p>We believe that for this small and defined group of patients —estimated to be <b>&lt;5% of any cohort of patients with ulcerative colitis</b><sup>1</sup> - making this drug available on the NHS would be a good use of finite NHS resources in the circumstances and is in the best interests of these patients. Untreated and unresponsive disease has risks associated with mortality and life-threatening complications. It gives this cohort the ability to avoid costly and traumatic interventions like surgery which have lifelong consequences and ongoing cost both to the NHS and to the individual.</p> <p>As such, our position remains that ustekinumab should be recommended and we urge the Committee to reconsider its initial recommendation.</p> <p><i>"Before I started Stelara, my calprotectin levels were in excess of 2000, and now 5 months on, they have hugely improved and are just 66. I have noticed over this time my pouch function has improved; my output is reduced to an average of 5-6 BMs a day on a good day. I have little or no pressure feeling and no urgency. I can eat better and am only up once at night. This is all on the good days which are about 50% of the time."</i></p>	<p>Thank you for your comment. The committee discussed your comment, as well as perspectives from other commentators and a patient expert. The recommendation has changed and an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the final appraisal document [FAD]).</p>

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			<p><i>“When I am unwell, I struggle with extreme tiredness and extended periods in the bathroom which makes my working life very difficult. I work in construction so spend a lot of time away from toilets. Vedolizumab, when I first started it, was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.”</i></p> <p><i>“We, as clinicians, are very excited to see the latest data demonstrating the effectiveness of ustekinumab for the induction and maintenance of remission in UC. This will be a very important addition to the therapeutic toolkit for people with UC, particularly given the evidence of remission and mucosal healing in both bio-naïve patients and in those previously failing anti-TNF therapy.”</i></p>	
2	Patient group	Crohn's & Colitis UK	<p><b>We have concerns that the Appraisal Consultation Document (ACD) conflates the experience of those who experience mild to moderate Ulcerative Colitis with those with moderate to severe / refractory disease.</b></p> <p>The ACD advises that the patient expert was suggesting “effects of the disease and side effects of medication can be moderated, to an extent, by individual circumstances including a patient’s support network and responsibilities.”<sup>3</sup></p> <p>Our understanding was that the patient expert was pointing out the role that self-management and support can play in managing their symptoms, but not in controlling or moderating their disease itself which is quite different. While self-management and support can play an important role in helping to manage symptoms and the emotional impact of the condition, it would be inaccurate to suggest an individual can induce remission or control disease severity through self-management or self-care alone.</p> <p><i>“Uncontrolled or poorly managed acute severe colitis is still a medical emergency requiring effective therapy or life-saving surgery regardless of whether these other factors are in place. It is NOT possible for the natural course of the disease or side effects of medication to be altered in any way by support networks or patients taking responsibility for their overall wellbeing or self-care”.</i><sup>4</sup></p> <p>Given that disease severity is wide-ranging, and while each person has their own individual experience, we would like to take this opportunity to reiterate the impact and experience of the specific cohort of patients this guidance is targeting. It is important to recognise that differences occur</p>	<p>Thank you for your comment. The committee discussed your comment, as well as perspectives from other commentators and a patient expert. The recommendation has changed and an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>

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			<p>not just between those with mild to moderate and moderate to severe disease, but also apply within the group who experience moderate to severe disease.</p> <p>This sub-group is likely to comprise <b>&lt;5% of patients with Ulcerative Colitis</b> who experience <b>more severe</b> flares, weight loss, fever and constitutional symptoms and whose disease has not responded to other treatment options, are unable to tolerate these, and/or can benefit from this treatment in particular</p> <p><b>Truelove and Witts</b> define severe Ulcerative Colitis as six or more stools a day plus at least one of the features of systemic upset (marked with an *): visible blood; pyrexia*; pulse rate greater than 90 BPM*; erythrocyte sedimentation rate (mm/hour)* and anaemia.<sup>5</sup></p> <p>The <b>Mayo Score</b> defines severe Colitis as more than five stools a day, blood passed without stool, obvious blood with stools in most cases and severe disease (spontaneous bleeding, ulceration).<sup>6</sup></p> <p>For this sub-group (&lt;5%) of patients with moderate to severe Ulcerative Colitis, <b>the condition is more than challenging, but frequently overwhelming and detrimentally life altering, as described below:</b></p> <p><i>“it stopped me from being a full-time carer to my son”</i></p> <p><i>“I had my relationship break down”</i></p> <p><i>“I have become isolated and really hid myself away from society”</i></p> <p><i>“Your life is on hold and all normality is replaced by a ‘new normal’ of pain, distress and sickness”</i></p> <p><i>“The isolation I have felt has been overwhelming. I can’t take my children to the park, for a walk or play date, or any of the other simple things that I used to take for granted”<sup>7</sup></i></p>	
3	Patient group	Crohn’s & Colitis UK	<p><b>We are concerned that this recommendation may imply that for those who cycle through available treatment options without success, steroids are an alternative treatment.</b></p> <p>However, <i>“corticosteroids have no proven efficacy in maintaining remission in IBD and should not be used for this purpose.”<sup>8</sup></i> The BSG guidelines set out clear stipulations on the best practice of prescribing of steroid therapies given their diminishing returns, harsh side effects and risk of dependency.<sup>9</sup></p>	<p>Thank you for your comment. The committee heard from clinical experts who explained that for people with inadequate response to current therapies, and in people in whom these therapies stop working, the only option other than surgery is long-term corticosteroid use. The clinical experts explained that this is associated with extreme side effects. The committee concluded that new medical treatments would be welcome (see the final appraisal document [FAD], section 3.3). The clinical experts also explained that conventional therapy (including corticosteroids) should not really be considered as a comparator for ustekinumab (see section 3.2 of the FAD). The committee agreed that conventional therapy is an inappropriate comparator to ustekinumab; based on</p>

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				<p>this and other considerations, the committee agreed to change the draft recommendation in the appraisal consultation document based on amended cost-effectiveness analyses (see section 3.14). In the final appraisal document (FAD) an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>
4	Patient group	Crohn's & Colitis UK	<p><b>We would strongly urge the Committee to reconsider their position that surgery is an alternative to ustekinumab.</b></p> <p>If ustekinumab was not made available on the NHS, next steps for this small group of refractory patients would be surgery. Yet, for many patients, surgery is unacceptable, but with no other option becomes a very desperate last resort.</p> <p><b>We would draw the Committee's attention to previous discussions on this issue during NICE's consideration of</b> infliximab, adalimumab and golimumab for treating moderately to severely active Ulcerative Colitis after the failure of conventional therapy [TA329]. To quote our submission:</p> <p><i>"We welcome the Committee's agreement that surgery is not a relevant comparator for most patients with moderately to severely active disease. While it can offer the individual concerned the feeling they have 'got their life back', for many it is not an option that they want to consider except as a last resort when all available options have been exhausted, and can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult".</i><sup>10</sup></p> <p><b>Surgery has both associated risks and an impact on quality of life.</b></p> <p><i>"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life."</i></p> <p><i>"Surgery was on the cards, but my mum, dad and I begged the surgeon not to do it."</i></p> <p><i>"Personally, I'm not prepared for the drastic surgery of having my colon removed."</i><sup>11</sup></p> <p>The most common surgeries are:</p>	<p>Thank you for your comment. The committee discussed your comment and the views of other consultees and commentators and heard from clinical experts that surgery is avoided until this is the last available treatment option (see the final appraisal document [FAD], section 3.3). Based on this, the committee agreed that additional treatment options which improve the likelihood of avoiding surgery would be welcomed. Based on the clinical and cost-effectiveness evidence, the committee agreed to an optimised recommendation for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>

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			<p><b>Colectomy with ileostomy (subtotal):</b> The colon is removed, leaving the rectum, with the end of the small intestine brought out through an opening in the wall of the abdomen.</p> <p><b>Restorative proctocolectomy with ileo-anal pouch:</b> This generally requires two or three operations, but in rare circumstances may be done as a single stage.</p> <p><b>Proctocolectomy with ileostomy:</b> The entire colon is removed, together with the rectum and the anal canal. The surgeon then brings out the end of the small intestine through a permanent ileostomy in the wall of the abdomen.</p> <p><b>Colectomy with ileo-rectal anastomosis:</b> The colon is removed and the surgeon joins the end of the small intestine directly to the rectum.<sup>12</sup> Surgery has significant associated long- and short-term risks which include:</p> <ul style="list-style-type: none"> <li>- general anaesthetic complications</li> <li>- infections.</li> <li>- anastomosis</li> <li>- adhesions</li> <li>- pouchitis,</li> <li>- pouch leakage,</li> <li>- pelvic abscesses</li> <li>- pouch fistulae</li> <li>- small bowel obstruction,</li> <li>- post-operative bleeding</li> <li>- sexual dysfunction</li> <li>- delayed wound healing</li> <li>- nerve damage<sup>13,14</sup></li> </ul> <p>A 2011 research study found severe postoperative complications were experienced for 27% of surgeries.<sup>15</sup> Additionally, a meta-analysis has shown ‘an approximate threefold increase (from 15% to 48%) in the risk of infertility in women with Ulcerative Colitis as a result of ileal pouch anal anastomosis (IPAA) (Waljee et al. 2006). Johnson et al. reported the infertility rate in females who had pelvic pouch surgery was significantly higher compared to females who were managed medically (38.1 % compared with 13.3 %; p &lt; 0.001).’<sup>16</sup></p> <p>We would also urge the Committee to consider the ‘persistent quality of life issues that impact multiple domains, including psychological and</p>	

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			<p>sexual functioning'.<sup>17</sup> A 2015 study found 81% experienced problems in at least one of the following areas: depression, work productivity, restrictions in diet, body image, and sexual function. In the same study, amongst moderate to severe Ulcerative Colitis patients, post-colectomy, 27% of men and 28% of women reported that their sexual life was worse now than before surgery.<sup>18</sup></p> <p>Surgery should not be considered as curative or a one-off. Patients may require multiple surgeries, increasing the risk of complications.</p> <p>Pouch failure rates in high volume centres have been estimated at 5.7%.<sup>19</sup></p> <p>The BSG Guidelines cite research that 'up to 50% of patients will develop pouchitis at some time after IPAA (as many as 40% in the first year). Typical symptoms of pouchitis include increased bowel frequency, urgency, nocturnal seepage or incontinence, pelvic discomfort and abdominal cramps.'<sup>20</sup></p> <p>The Ileoanal Pouch Report 2017 (ACGBI) found that 'complications occur in about 1 in 5 patients and 1 in 17 patients will need an early second operation to sort out a complication.'<sup>21</sup></p> <p>'The literature suggests that pouch failure over the long term is between 10 and 15%.<sup>22</sup></p>	
5	Patient group	Crohn's & Colitis UK	<p><b>We would urge the Committee to review its initial recommendation taking into consideration the fuller NHS costs associated with surgery.</b></p> <p>We would ask the Committee to consider: the costs of surgery itself; post-operative costs; complications, inpatient stays, emergency admissions, nursing/stoma support and appliances.</p> <p><i>'Perhaps the most unexpected finding from SWORD is the 27.4% 30-day readmission rate after pouch surgery'.<sup>24</sup></i></p> <p>These include:</p> <ul style="list-style-type: none"> <li>- <b>Potential second or third operations</b> (e.g. restorative proctocolectomy with ileoanal pouch is usually undertaken as two operations; colectomy with ileostomy may be followed by pouch surgery at a later date or permanent ileostomy)</li> <li>- <b>Ongoing stoma care and appliances</b> (estimated at £5,000 per year by Clinical Commissioning Groups for up to 50 years for younger patients)</li> <li>- <b>Potential fertility treatment</b> for young women after surgery</li> <li>- <b>Hospital costs</b> for the treatment of infections and other complications</li> </ul>	<p>Thank you for your comment. The model included the probability of 1<sup>st</sup> surgery, post-surgery chronic complications and the probability of 2<sup>nd</sup> surgery, with incidence data taken from a large UK-based study. The committee agreed that this was an appropriate model for decision making.</p>

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			- <b>Psychological support</b> – IBD-related surgery or hospitalisation is associated with a significant risk for depression and anxiety. <sup>25</sup>	
6	Patient group	Crohn's & Colitis UK	<p>We would ask the Committee to <b>consider growing evidence that psychological factors have on the impact of surgical outcomes.</b> This is very relevant given that many patients state that they wish to avoid surgery.</p> <p>There are many reasons for this including the impact on their bodies; self-esteem; wishing to complete studies; start or keep up with their young family and those for whom surgery would be considered unacceptable due to cultural or religious factors.</p> <p>Increasingly, evidence suggests <i>'that psychological factors have an impact on surgical outcomes in both the short and long term. Pre-operative anxiety, depression and low self-efficacy are consistently associated with worse physiological surgical outcomes and postoperative quality of life'</i>.<sup>26</sup></p>	<p>Thank you for your comment. The committee heard from clinical experts that surgery is avoided until this is the last available treatment option and considered the complications of surgery, including psychological impact (see the final appraisal document [FAD], section 3.3). Based on this, the committee agreed that additional treatment options which improve the likelihood of avoiding surgery would be welcomed.</p> <p>Based on the clinical and cost-effectiveness evidence, an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>
7	Patient group	Crohn's & Colitis UK	<p>We would ask the Committee <b>to consider evidence around the risks and mortality associated with untreated and uncontrolled disease</b> if this treatment option is not made available on the NHS.</p> <p>NICE Guideline on Ulcerative Colitis 130 states: 'Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled.'<sup>27</sup></p> <p>This is echoed by BSG Guidelines that state that 'acute severe colitis is a potentially life-threatening condition.'<sup>28</sup></p> <p>Acute severe colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).<sup>29</sup> Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare up at some stage. Often this will be the first presentation of their disease.<sup>30</sup></p> <p>When a flare occurs in acute severe colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications.</p> <p>The very real risks associated with acute severe colitis include:</p> <ul style="list-style-type: none"> <li>• Life-threatening haemorrhage</li> <li>• Toxic megacolon - can occur in up to 1 in 40 people with Colitis<sup>31</sup></li> <li>• Perforation of the bowel<sup>32</sup></li> </ul>	<p>Thank you for your comment. The committee heard from clinical experts, a patient expert and other comments from consultees and commentators that moderate to severely active ulcerative colitis is a life-long disease that is associated with significant physical and emotional burden. The committee considered the risks associated with active ulcerative colitis within the health economic modelling (see sections 3.1 and 3.12 of the FAD).</p>

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8	Patient group	Crohn's & Colitis UK	<p>We would ask that the Committee further <b>consider the complications of chronic, uncontrolled, active disease.</b></p> <ul style="list-style-type: none"> <li>- Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity<sup>33</sup></li> <li>- Anaemia is a common complication of IBD. Iron deficiency and anaemia of chronic disease are the commonest causes of anaemia in IBD<sup>34</sup></li> <li>- Increased risk of cancer<sup>35</sup></li> </ul>	<p>Thank you for your comment. The committee considered the risk of complications and steroid use associated with active ulcerative colitis (see section 3.9 of the final appraisal document).</p>
9	Patient group	Crohn's & Colitis UK	<p>We would invite the Committee to <b>consider that the regular review of patients and stopping rules (where clinically appropriate) mitigate against inappropriate use of biologics</b> and should allay concerns around inappropriate costs.</p>	<p>Thank you for your comment. The committee heard from clinical experts who explained that it is usual clinical practice to review treatment every 12 months and that if a person is in sustained remission, it may be appropriate to stop treatment. However, the ERG explained that it is difficult to model stopping rules to reflect clinical practice in economic analysis and therefore these were not further considered (see section 3.13 of the final appraisal document).</p>
10	Patient group	Crohn's & Colitis UK	<p>We would ask the Committee to further <b>consider the impact on social functioning.</b></p> <p>Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. Research shows that young people aged 16-25 with IBD who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. There is a clear associated "productivity loss" by health state, whereby the lowest score for health state (Visual Analogue Score 0-2.5) corresponds with a 71% productivity loss.<sup>36</sup> More recent research supports this.</p> <p>Emotional function is affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness, and fears of needing surgery or developing cancer.<sup>37</sup></p>	<p>Thank you for your comment. The committee heard from clinical experts, a patient expert and other comments from consultees and commentators that active ulcerative colitis can significantly impact social functioning (see section 3.1 of the final appraisal document [FAD]). Based on the clinical and cost-effectiveness evidence, an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>
11	Patient group	Crohn's & Colitis UK	<p>A number of equalities issues were raised in evidence and discussed by the Committee such as:</p> <ul style="list-style-type: none"> <li>- sexual relationships</li> <li>- pregnancy</li> <li>- fecundity</li> </ul>	<p>Thank you for your comment. The committee discussed the equalities issues raised in your comment (see public committee slides – ACM2). The committee also discussed the views of other consultees and commentators and heard from clinical experts that surgery is usually avoided until this is the</p>

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			<p>There are significant equality/diversity issues in terms of effectively compelling patients in this group to having surgery:</p> <ul style="list-style-type: none"> <li>particularly for young people who have not begun a family and whose fertility may be affected,</li> <li>and for religious groups such as Muslims, for whom this may impact on religious practices and cause distress.</li> </ul> <p>We would ask the Committee to outline to what degree these issues have been taken into consideration when making their final decision.</p>	<p>last available treatment option (see the final appraisal document [FAD], section 3.3). The committee agreed that additional treatment options which improve the likelihood of avoiding surgery would be welcomed in all people with moderate to severely active ulcerative colitis, including young people and people from certain religious groups. Based on the clinical and cost-effectiveness evidence, an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>
12	Patient group	Crohn's & Colitis UK	<p>Patients have asked us to share the following experiences on their behalf:</p> <p><i>"I was diagnosed with Ulcerative Colitis in 2016. During the first year of treatment, I was given numerous types of drugs, some of which worked for a short amount of time, others for longer, but often my body would begin to react against them. During that first year, I was hospitalised four times due to the severity of the flare ups. Steroids helped to calm the symptoms, but as soon as the dosage was tapered, the flare ups returned. In hospital, the steroid injections were sometimes painful, sometimes distressing. I was given biological drugs for over a year. This entailed 6-weekly trips to hospital and the best part of day hooked up for an infusion. It left me feeling more fatigued than usual, but it seemed to work. Then blood tests revealed my body was reacting against the drug, so they were changed again. A constant has been immune suppressants, which seem to work well, but of course bring their own set of issues.</i></p> <p><i>I have developed side effects that have been worrying and caused even more stress, such as hair loss, joint pains, fatigue, onset of rashes and eczema. My body and face shape changed and I felt generally unwell. Living with UC is unpredictable and soul-destroying. It impacts on your daily life, especially during a flare up. It is messy, painful and depressing. Your life is on hold and all normality is replaced by a "new normal" of pain, distress and sickness. This is borne by sufferers as well as by relatives and friends.</i></p> <p><i>Hope of using a new drug can be a lifeline; something that gives an opportunity to start living life to the full again."</i></p> <p><i>"I was diagnosed with acute severe Ulcerative Colitis at the start of 2018. My condition arrived very suddenly and within three weeks of starting to notice symptoms I was hooked up to a steroid drip in hospital for a week. As I was currently pregnant, I was limited to taking 5ASAs and steroids.</i></p>	<p>Thank you for your comment. The committee considered the experiences of people with ulcerative colitis. Based on the clinical and cost-effectiveness evidence, an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>

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			<p><i>Despite taking high dose prednisolone for almost the entirety of my pregnancy, this did little to control my symptoms. I was severely anaemic and struggling to do day to day tasks because of the fatigue. I was visiting the toilet up to 20 times a day. Taking high dose steroids for this length of time was also very difficult - I experienced severe mood swings which were difficult to deal with for me and those around me.</i></p> <p><i>Following the birth of my son I was given the opportunity to start with adalimumab. Unfortunately, this was not successful in controlling my symptoms either and I had to remain on steroids. Following an arthritis diagnosis in 2019, I also started on methotrexate which finally started to control things. However, I have since experienced a further flare up and my consultant is reviewing my options, including possible surgery.</i></p> <p><i>It cannot be underestimated how important it is for patients to have a choice of drug treatments, especially where other initial drug choices have failed. Patients want to be able to continue their lives symptom free for as long as possible, so refusing to back a drug that has already been shown to be effective in some patients is really disappointing. I have one more drug choice left now and otherwise it will be surgery. For many reasons, patients should be able to put off surgery for as long as they can - the general risks associated with surgical procedures and anaesthetics are often forgotten, never mind the procedure specific issues that can occur with bowel surgery. The cost to the NHS of surgeries, hospital stays, and follow up treatments must be more than the possible cost of this drug being available to treat patients who have tried other drugs and whose only other option is surgery.</i></p> <p><i>I hope that, on the basis of the comments received from patients, NICE will reconsider its decision.”</i></p> <p><i>“Since 2018, I have had a huge flare up, I have taken long term prednisolone and mesalazine.</i></p> <p><i>I am a young mum to 4 young children, one of whom is severely disabled. My flare up stopped me from being a full-time carer to my son. My 8-year-old daughter made a comment to me that I was no longer a "proper" mummy anymore because I spent all my time in hospital or in bed or the toilet.</i></p> <p><i>In October 2019, I had an emergency operation which resulted in an ileostomy being fitted because no meds were working even after long stints in hospital of IV hydrocortisone and infliximab. The steroids caused me to gain weight which have caused other medical complications and pains in my joints. As well as loss of appetite, I also have severe anxiety</i></p>	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			<p><i>due to my looks now due to a massive weight gain. I have become isolated and really hidden myself away from society.”</i></p> <p><i>“My daughter has colitis and this was a drug I was reading about only because my niece is on it for Crohn’s and is in remission , I have read some literature that supports this treatment and feel strongly that NICE review this decision.”</i></p> <p><i>“I have suffered from ulcerative colitis for 4 years. After the failure of a number of conventional treatments (prednisone/azathioprine/mesalazine) I have been taking regular infusions of infliximab. Whilst this has shown some improvement in the condition, I still experience flare ups and struggle to control the condition on a regular basis. Oral steroid use causes many side effects and no longer brings about any substantial benefit for the condition. My consultant has suggested the next step may be surgery.”</i></p> <p><i>“As a father with a young family, with two children under 4, and who works full time, the strain on my mental and physical health has been significant. Should the condition continue to worsen, and surgery be necessary, it is unlikely I would be able to carry on working and support my family adequately. The stress and worry of all of this has a huge impact on myself and my family every day.</i></p> <p><i>Any possibility of alternative treatments would be welcome, and I would encourage the NICE panel to support those suffering with this condition by approving any new treatments.”</i></p>	
13	Patient expert	NA	<p>The summary of the committee discussion notes that:</p> <p>“The patient expert explained that the experience of living with moderately to severely active ulcerative colitis varies on an individual level, but in their experience it is extremely challenging.”</p> <p>Whilst I agree that I did indicate that I found living with the condition extremely challenging, I would say that in its severe form, with the type of symptoms I described, ulcerative colitis can also be life-altering, i.e. ‘normal’ functioning ( socially, emotionally and economically) is on hold indefinitely. This is all encompassing and creates significant disability.</p> <p>With severe UC, a person’s entire life revolves around going to the toilet, pain and loss of function and the emotional impact is severe, frequently triggering anxiety and depression. With severe symptoms they will also be systemically unwell.</p>	<p>Thank you for your comment. The committee considered your comments alongside other responses to the appraisal consultation document. The final appraisal document (FAD) has been amended to describe the quality of life for people with moderately to severely active ulcerative colitis (see section 3.1 of the FAD).</p>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			<p>I may have described going to work and leaving the house with severe symptoms, but I would counter that by explaining that I was doing so while in constant pain and distress, suffering fatigue, nausea, heart palpitations, shortness of breath walking from the station to my office and anxiety about the location of toilets.</p> <p>I continued to work whilst having over 20 bowel movements per day simply because I was worried about taking time off, I was committed to my job and because I saw no point in taking one or two days off when my condition had remained like this for months and would continue to do so without effective treatment ( I was on high doses of steroids and these were having no effect). I saw no end in sight and taking time off would not have helped me to get better in the same way it might help someone recover from a gastric bug.</p> <p>I would therefore disagree that the word “challenging” accurately describes the experience of living with moderate to severe ulcerative colitis. Perhaps alternatives might be something like “life-altering”, “disabling” or even “devastating”?</p>	
14	Patient expert	NA	<p>The summary also notes that:</p> <p>“They (the patient expert) commented that the effects of the disease and side effects of medication can be moderated, to an extent, by individual circumstances including a patient’s support network and responsibilities.”</p> <p>I would like to point out that there may have been some misinterpretation of my comments in relation to the work I had been involved in, listening to the experiences of many people living with the condition around self-management and how they benefit from support networks to help manage their condition.</p> <p>Whilst a person living with quite severe disease can ‘self-manage’ with the right support in place, i.e. they can develop resilience and coping methods to help them tolerate certain symptoms or employ strategies such as avoiding social activities, taking adequate rest, relaxation techniques, working from home, mapping local toilets etc, the severity of their symptoms and their disease activity itself cannot be moderated without effective treatment.</p>	<p>Thank you for your comment. The committee considered your comment alongside other responses to the appraisal consultation document. The final appraisal document (FAD) has been amended to describe that although the effects of the disease and side effects of medication can be moderated to an extent through management strategies, this still contributes an extreme burden and does not significantly reduce the impact of the symptoms (see section 3.1 of the FAD).</p>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			<p>For a more in-depth understanding of the concept of self-management in Inflammatory Bowel Disease please see <a href="https://www.crohnsandcolitis.org.uk/improving-care-services/self-management/self-management-position-statement">https://www.crohnsandcolitis.org.uk/improving-care-services/self-management/self-management-position-statement</a></p> <p>Medical management of UC is only one component (but an essential one) of self-management, along with:</p> <ul style="list-style-type: none"> <li>-A responsive Inflammatory Bowel Disease service that is easy to access when needed</li> <li>-IBD services with resources to support self-management</li> <li>-IBD Health Care Professionals who are confident and knowledgeable about self-management</li> <li>-Good relationships between people with Crohn's and Colitis and Health Care Professionals</li> <li>-Good quality information and support for people with IBD to feel empowered and in control</li> <li>-Access to emotional and psychological support</li> <li>-Access to e-health and technology resources.</li> </ul> <p>Uncontrolled or poorly managed acute severe colitis is still a medical emergency requiring effective therapy or life-saving surgery regardless of whether these other factors are in place. It is NOT possible for the natural course of the disease or side effects of medication to be altered in any way by support networks or patients taking responsibility for their overall wellbeing or self-care.</p>	
15	Company	Janssen	<p><b>The company's response to the appraisal consultation document has been summarised in this table. For the full response to consultation, please see item 2 of this document.</b></p> <p><u>Ustekinumab is a cost-effective use of NHS resources when decision rules consistent with previous Appraisal Committee decision making are applied.</u></p> <ul style="list-style-type: none"> <li>• TA329 and TA342 (previous appraisals in this indication) and other immunology appraisals have been guided by pair-wise ICERs vs CT, whereas fully incremental analysis are guiding decision making here.</li> </ul>	<p>Thank you for your comments. The committee agreed that it was appropriate to use cost-utility analysis for decision-making. This is because the cost-comparison analysis presented by the company did not account for the uncertainty in the clinical efficacy of ustekinumab (see section 3.14 of the final appraisal document [FAD]).</p> <p>The committee also agreed that conventional therapy, TNF-alpha inhibitors and tofacitinib are inappropriate comparators for ustekinumab and that ustekinumab's place in the clinical pathway is likely to be where vedolizumab is currently being used (see section 3.2</p>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			<ul style="list-style-type: none"> <li>• A cost-comparison analysis between ustekinumab and vedolizumab should be considered – this demonstrates that savings are available to the NHS with ustekinumab.</li> <li>• An updated base-case is presented with relative effectiveness in maintenance from the company NMA, 0% rate for remission and response and utility values from Woehl et al. 2008 – compared with CT, ustekinumab is cost-effective in this model.</li> <li>• The updated base-case is conservative against the use of ustekinumab</li> <li>• Stopping rules should be considered (as in previous UC appraisals), which improve the cost-effectiveness of ustekinumab</li> </ul>	<p>of the FAD). Therefore, when considering cost-utility analysis, the committee directly compared ustekinumab with vedolizumab (see section 3.15 of the FAD).</p> <p>The committee discussed the company’s updated base-case and the ERG’s critique of these analyses and agreed it was suitable for decision-making (see section 3.9 of the FAD).</p> <p>The committee heard from clinical experts who explained that it is usual clinical practice to review treatment every 12 months and that if a person is in sustained remission, it may be appropriate to stop treatment. However, the ERG explained that it is difficult to model stopping rules to reflect clinical practice in economic analysis and therefore these were not further considered (see section 3.13 of the final appraisal document).</p>
16	Company	Janssen	<p><b>The company’s response to the appraisal consultation document has been summarised in this table. For the full response to consultation, please see item 2 of this document.</b></p> <p><u>Additional evidence provides greater certainty on the long-term effectiveness of ustekinumab</u></p> <ul style="list-style-type: none"> <li>• The ERG’s preferred NMA is the Company maintenance only NMA</li> <li>• The ERG’s maintenance only NMA has methodological and application issues: it violates the similarity assumption required to conduct NMAs; the data inputs for the ERG NMA and its application in the model are inaccurate; the ERG NMA has not been incorporated appropriately into the economic model</li> <li>• The committee should reconsider the company base-case 1-year NMA</li> <li>• Long-term extension data from UNIFI, and from real-world evidence in psoriasis and Crohn’s disease shows that the effects of ustekinumab are maintained long-term; this shows that the ERG’s NMA underestimates the effects of ustekinumab at 1 and 2 years</li> </ul>	<p>Thank you for your comments. The committee discussed the updated company-base case which was submitted in response to the appraisal consultation document (ACD). It agreed that both the ERG maintenance-only NMA and the company’s 1-year NMA conditional on response have limitations, but that the company’s NMA was most appropriate to inform the cost-effectiveness model (see the final appraisal document [FAD] section 3.7).</p>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
17	Company	Janssen	<p><b>The company's response to the appraisal consultation document has been summarised in this table. For the full response to consultation, please see item 2 of this document.</b></p> <p><u>The committee's conclusions about health-related quality of life are inconsistent with previous decision making and do not reflect the impact UC has on patients.</u></p> <ul style="list-style-type: none"> <li>• Committees in previous NICE appraisals for UC have had a preference for using utility values from published sources rather than from clinical trials</li> <li>• Utility values from UNIFI for the active UC health state do not align with the published utility values or the patient expert's experience of the disease</li> <li>• The 'active' UC definition from the UNIFI trial does not represent the same population at the active UC health state in the model</li> <li>• There are several limitations to the methodology of the UNIFI utility data collection</li> </ul>	<p>Thank you for your comments. The committee discussed which utility values were most appropriate for decision-making in this appraisal. It agreed that there are different utility values available and that it is not possible to determine which is the most robust based on the information available. Therefore, the committee considered both Woehl et al. 2008 and the UNIFI data in its decision making (see final appraisal document section 3.12).</p>

### Summary of comments received from members of the public

Theme	Response
<p><b>Ulcerative colitis has a significant negative impact on quality of life</b></p>	<p>The committee considered the comments received in response to the appraisal consultation document (ACD) which highlighted the significant impact the symptoms of ulcerative colitis have on quality of life. The committee also heard from clinical experts and a patient expert who shared similar views to those from consultees and commentators (see section 3.1 in the final appraisal document). An optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>

Theme	Response
<p><b>There is unmet need for new treatments; multiple treatment options are highly beneficial in people with ulcerative colitis</b></p> <ul style="list-style-type: none"> <li>• Treatments options are needed at 2<sup>nd</sup>/3<sup>rd</sup>/4<sup>th</sup> line and for people who cannot take TNF-alpha inhibitors (e.g. they cannot be given immunomodulators due to co-morbidities or old age, which are co-prescribed with TNF-alpha inhibitors)</li> <li>• Avoiding surgery is highly desirable</li> <li>• Risk of bowel cancer is higher in people with ulcerative colitis, so treatment options to control symptoms of inflammation is desirable to reduce this risk</li> <li>• Many patients loose response to biologics and (to an extent) vedolizumab over time</li> <li>• Treatments with different mechanisms of action are needed</li> </ul>	<p>The committee discussed the comments received in response to the appraisal consultation document (ACD) which highlighted that there are certain populations who would benefit from additional treatment options for ulcerative colitis. The committee understood that this is especially so because the avoidance of surgery is highly valued. Clinical experts explained that for some people (for example, people who are at high risk from immunosuppression), currently available treatment options are not appropriate, and in other people, the currently available treatment options are not effective (see the final appraisal document sections 3.2 and 3.3)</p> <p>An optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>
<p><b>Administration of ustekinumab</b></p> <ul style="list-style-type: none"> <li>• Ustekinumab has advantages (in cost savings and quality of life) of being able to be administered at home by patients</li> </ul>	<p>The committee discussed the benefits of self-administration and agreed that this was an advantage of ustekinumab over other currently available treatment options. Based on other clinical and cost-effectiveness evidence, an optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD).</p>

Theme	Response
<p><b>Queries on cost-effectiveness modelling</b></p> <ul style="list-style-type: none"> <li>• Queries on whether dose escalation has been considered within cost-effectiveness analysis</li> <li>• The wider benefits of ustekinumab have not be considered (e.g. reduced time off work)</li> <li>• Post-surgery health states and post-surgical costs have not been fully considered</li> <li>• Response and remission rates are close to 0%</li> <li>• There are limitations with Woehl utility values, but to use clinical trial utility values is inconsistent with previous appraisals</li> </ul>	<p>The committee accepted the assumption that 30% of patients would have escalated doses of maintenance treatment (see section 3.10 of the final appraisal document [FAD]). It concluded that although there was uncertainty around this, it was not a major driver of cost effectiveness.</p> <p>The perspective of the NHS was used in the cost-effectiveness model, therefore benefits such as reduced time off work have not been formally considered.</p> <p>The model included the probability of 1<sup>st</sup> surgery, post-surgery chronic complications and the probability of 2<sup>nd</sup> surgery, with incidence data taken from a large UK-based study, and the relevant costs and QALYs associated with these possibilities. The committee agreed that this was an appropriate model for decision making.</p> <p>The committee agreed that the response and remission rates are likely to be near to 0% (see section 3.11 of the FAD) and the company's updated base-case reflected this.</p> <p>The committee agreed that there are different utility values available and that it is not possible to determine which is the most robust based on the information available. Therefore, the committee considered both Woehl et al. 2008 and the UNIFI data in its decision making (see final appraisal document section 3.12).</p>
<p><b>Addition of stopping rules would aid understanding of use in practice</b></p> <ul style="list-style-type: none"> <li>• Recommendations should be clear on starting and stopping criteria, including where it sits in the treatment pathway with respect to tofacitinib and vedolizumab</li> <li>• Prolonged and deep remission should be seen before stopping unconventional therapies (e.g. TNF-alpha inhibitors, tofacitinib)</li> <li>• Chance of developing antibodies to ustekinumab is low, therefore ustekinumab could be stopped once remission is induced</li> </ul>	<p>The committee discussed the use of 'stopping rules' for this appraisal. It heard from clinical experts who explained that it is usual clinical practice to review treatment every 12 months and that if a person is in sustained remission, it may be appropriate to stop treatment. However, the ERG explained that it is difficult to model stopping rules to reflect clinical practice in economic analysis and therefore these were not further considered (see section 3.13 of the final appraisal document).</p> <p>An optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD). This recommendation clearly states where ustekinumab is expected to be used in the treatment pathway.</p>

Theme	Response
<p><b>Further evidence should be considered</b></p> <ul style="list-style-type: none"> <li>This ACD proposal does not align with recently research submitted in conference abstracts</li> <li>Singh et al. 2020 NMA shows ustekinumab is superior to vedolizumab and adalimumab</li> </ul>	<p>The committee noted the evidence highlighted in these comments. Although there are limitations, the committee agreed that the company 1-year NMA was the most appropriate estimate of clinical effectiveness to inform the economic model. It was also aware that the ERG had provided critique on this analysis, which they had not provided for the published NMA. Therefore, the committee was unable to formally consider this evidence.</p>
<p><b>Ustekinumab has shown effectiveness in Crohn's disease</b></p> <ul style="list-style-type: none"> <li>Ustekinumab has demonstrated long-term effectiveness in Crohn's</li> <li>Rapid onset of action, durability and good safety profiles have been seen in Crohn's trials</li> </ul>	<p>In response to the real-world data provided in people with Crohn's disease and psoriasis, the committee agreed that these are different conditions and the validity of using this as a proxy for ulcerative colitis is unclear (see the ERG critique of company response to ACD, section 2.1.3).</p>
<p><b>Paediatrics has not been accounted for</b></p>	<p>NICE cannot make recommendations outside of the marketing authorisation of a technology. The marketing authorisation for ustekinumab is for adults with moderate to severely active ulcerative colitis. Therefore, recommendations for children cannot be considered in this appraisal.</p>
<p><b>Wording of the ACD recommendation did not align with the indication wording</b></p> <ul style="list-style-type: none"> <li>Need to account for treatment in people who have medical contraindications to conventional therapy or biologics as in the indication wording</li> </ul>	<p>An optimised recommendation has been made for the use of ustekinumab in ulcerative colitis (see section 1 of the FAD). This recommendation is aligned with the wording in the marketing authorisation.</p>

# **Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

## **Janssen response to the NICE Appraisal Consultation Document (ACD)**

**11<sup>th</sup> of February 2020**

### **Executive Summary**

Janssen welcomes the opportunity to comment on the NICE appraisal consultation document (ACD) for the review of ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]. Despite the disappointing draft decision, we remain committed to making ustekinumab available to appropriate patients in England and Wales.

Ustekinumab has been recommended by NICE in four separate indications, the first of which was in 2009. NICE has concluded that ustekinumab is a clinically and cost-effective use of NHS resources in multiple other disease areas and we believe that ulcerative colitis (UC) is no exception. We welcome the Committee's conclusions in 3.2 of the ACD that "There is an unmet need for new treatments that reduce the need for corticosteroids or surgery". Ustekinumab is the only treatment option that has shown efficacy for patients for whom both an anti-TNF and vedolizumab has failed to work, as well as efficacy in patients who have not failed on biologics. Ustekinumab could therefore fulfil this unmet need.

The three main points of our response to the ACD are as follows:

#### **1) The committee's decision making is inconsistent with previous NICE appraisals in UC**

We have concerns that the Committee's decision making in this appraisal has not been consistent with previous appraisals in UC, and immunology appraisals more generally. The Committee appear to have relied on the results of fully incremental cost-effectiveness analyses, despite pair-wise comparisons being commonplace for appraisals in UC. Under all reasonable scenarios, the pair-wise cost-effectiveness results of ustekinumab versus Conventional Therapy (CT) are within the range usually considered a cost-effective use of NHS resources.

#### **2) Fully incremental analyses are uncertain; a cost-comparison to vedolizumab is appropriate for the Committee to consider**

The Committee's reliance on fully incremental analyses to reach its draft conclusions mean that Janssen cannot know what our fully incremental ICERs are due to the confidential Patient Access Schemes (PASs) associated with the comparator treatments. Fully incremental analyses have not been utilised for decision making in previous UC NICE appraisals (TA329 and TA342). It would seem that if fully incremental analyses from this appraisal were to be applied under the strictest NICE decision rules, some currently NICE-recommended treatments would not have been recommended, which would have limited patient options.

In order to pragmatically address the uncertainty in cost-effectiveness analyses noted in the ACD, Janssen propose that a simple cost-comparison to vedolizumab should be further considered by the Committee. This analysis demonstrates the savings available should NICE decide to recommend ustekinumab, and reduces the uncertainty noted in the ACD regarding the cost-effectiveness analyses.

### **3) The updated base-case demonstrates that ustekinumab is cost-effective and that cost-effectiveness estimates remain conservative for ustekinumab**

In response to the ACD we have updated our base-case economic model to reflect the Committee's preference for modelling long-term outcomes via a Network Meta-Analysis (NMA). The updated base-case model includes the following reasonable assumptions:

- modelled relative effectiveness in maintenance from the Company NMA
- 0% rate for spontaneous remission and response
- utility values from Woehl et al.

The updated base-case demonstrates that ustekinumab is a cost-effective use of NHS resources when all reasonable assumptions and scenarios are considered. Furthermore, the cost-effectiveness of ustekinumab is likely to be underestimated in the updated base-case given that the model uses conservative assumptions.

Janssen had provided stopping rules in response to Technical Engagement, but this had not been considered by the Committee. When stopping rules are considered, the cost-effectiveness of ustekinumab is further improved.

In addition, we provide further evidence on the long-term effectiveness of ustekinumab and further rationale on the limitations of UNIFI utility values, which provides greater certainty on the cost-effectiveness estimates.

Lastly, ustekinumab as a new treatment option would allow clinicians and patients greater choice and would allow clinicians to optimise the patient treatment pathway based upon patient needs. This could save the NHS valuable resources that would otherwise be spent on cycling patients through biologics with similar mechanisms of action that may not be the best treatment option for all patients.

*The following sections provide further details on these key points for consideration.*

## **Section 1. Ustekinumab is a cost-effective use of NHS resources when decision rules consistent with previous NICE Appraisal Committee decision making are applied**

### Overview

We have concerns that the NICE Appraisal Committee have not been consistent in its application of resource decision rules for this appraisal. In previous appraisals for Ulcerative Colitis (UC), pair-wise ICERs versus conventional therapy have been used for decision making. The pair-wise ICERs for ustekinumab versus CT are below £30,000 per QALY gained under all reasonable scenarios. On this basis, we believe that ustekinumab represents a cost-effective use of NHS resources in this appraisal.

We also note that in previous NICE appraisals in UC and in immunology more broadly, fully incremental analyses were deemed problematic, and as such, were not used as the basis for decision making in TA329 and TA342. In this appraisal, we note that the fully incremental analyses are also problematic due to the uncertainty noted by the Appraisal Committee regarding the long-term relative effectiveness of treatments. To pragmatically address these uncertainties, Janssen propose that a simple cost-comparison to vedolizumab is appropriate for the Committee to consider. This cost-comparison demonstrates that the introduction of ustekinumab to the NHS will result in acquisition and administration cost savings versus vedolizumab.

The updated economic base-case demonstrates that ustekinumab is a cost-effective use of NHS resources versus CT and cost saving versus vedolizumab. The updated base-case is conservative and when stopping rules are applied the cost-effectiveness is improved.

### **1.1 The committee's decision making is inconsistent with previous NICE appraisals in UC – ustekinumab is cost-effective vs CT**

We have concerns regarding how the Appraisal Committee have applied resource allocation decision rules in this appraisal and how this is inconsistent with previous decision making in UC, and immunology appraisals more generally. Pair-wise ICERs vs CT have been presented in the previous appraisals TA329 [*infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy*] and TA342 [*vedolizumab for treating moderately to severely active ulcerative colitis*], whereas fully incremental analyses appear to be guiding decision making in this appraisal. Under all reasonable scenarios the ICERs for ustekinumab versus CT are less than £30,000 per QALY gained and it appears that the Committee have not appraised ustekinumab using the same decision criteria it has used in TA329 and TA342.

We note in particular in TA329, the Committee concluded that all three anti-TNFs could be considered cost-effective, despite two of the anti-TNFs being dominated or extendedly dominated, and despite the fact that all three anti-TNFs had pair-wise ICERs versus CT exceeding £50,000 per QALY gained using the Assessment Group's base-case results.

In addition, in previous NICE appraisals for biologics in psoriatic arthritis, juvenile idiopathic arthritis and rheumatoid arthritis, pair-wise analyses of biologics compared to best supportive care or standard of care treatments such as methotrexate have been considered for decision

making purposes. In TA199, TA373, and TA375, NICE have recommended biologics consistently if they have demonstrated cost-effectiveness through a pair-wise analysis compared to the standard of care, such as methotrexate. Most recently, in January 2020, NICE issued a positive draft ACD for a new treatment for rheumatoid arthritis 'Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]'.

In Section 3.18 of the ACD for upadacitinib in rheumatoid arthritis, the NICE Committee concluded that:

*“The clinical and cost-effectiveness estimates for upadacitinib with conventional DMARDs were similar to what was previously seen for rheumatoid arthritis. This was upadacitinib either dominating (that is, it was cheaper and more effective than the comparator) or giving an ICER over £30,000 per QALY gained when confidential comparator discounts were applied. The committee concluded that it could recommend upadacitinib with methotrexate as a cost-effective use of NHS resources...”*

It is therefore clear there are inconsistencies in the way in which NICE currently appraises treatments: giving a positive recommendation for upadacitinib despite it not being cost-effective in fully incremental analyses, at a threshold of £30,000 per QALY gained. We therefore ask that the Committee considers pair-wise ICER comparisons to CT in order to be consistent with previous decision making in UC and across other disease areas where biologics have been recommended.

## **1.2 Fully incremental analyses are uncertain; a cost-comparison to vedolizumab is appropriate for the Committee to consider**

The reliance on pair-wise comparisons to make decisions in previous NICE appraisals of biologics is due to a large degree to the uncertainty produced in fully incremental analyses, which results from relative treatment effects derived in network meta-analyses. We agree, in part, with the Committee's conclusions regarding the limitations of the maintenance NMAs, in Section 3.6 of the ACD:

*“The committee concluded that both maintenance-phase NMAs had limitations and the results are very uncertain, but because no alternative data are available the results provided the best available estimates of relative effectiveness.”*

However, given these limitations, we do not agree with the Committee's preference for basing decision making upon fully incremental analyses. As relative effectiveness estimates between comparators are somewhat uncertain it is more appropriate to consider the pair-wise ICERs for ustekinumab versus CT.

In order to pragmatically address the uncertainty in cost-effectiveness analyses noted in the ACD, Janssen propose that a simple cost-comparison analysis to vedolizumab should be further considered by the Committee. Vedolizumab is the only comparator in the NICE scope to have shown head-to-head superior efficacy versus one of the anti-TNFs (adalimumab) in the VARSITY trial [Sands et al. 2019]. Vedolizumab currently has the largest market share after the anti-TNFs, with approximately 30% of the total market (please see Appendix 1 for full details of the market research data). This demonstration of benefit versus older mechanisms of action (anti-TNFs) makes vedolizumab a particularly relevant comparator, and the treatment that ustekinumab would most likely displace in the NHS. In the NMAs, the

treatments with newer mechanisms of action (vedolizumab, tofacitinib, and ustekinumab) appear to have efficacy improvements versus the anti-TNFs, but tofacitinib has emergent safety concerns, as noted by the EMA, meaning it is not suitable for some patients (please see Appendix 2 for full details of the EMA’s guidance on the safety concerns with tofacitinib). Vedolizumab therefore represents the most relevant comparator within a cost-comparison framework.

Cost-comparison analysis to vedolizumab:

In a simple cost-comparison analysis, the efficacy of ustekinumab and vedolizumab has been assumed equivalent. The analysis forecasts the total acquisition and administration costs of each treatment over a 5-year period, assuming all patients remain on treatment (equal efficacy, no discontinuation). Costs in years 2 to 5 are discounted at 3.5% per annum. All costs are taken from the economic model. The Commercial Medicines Unit (CMU) price of ustekinumab is compared to the list price of vedolizumab. The user can modify the price of vedolizumab according to the confidential Patient Access Scheme, which Janssen does not have access to.

Two analyses are provided, one comparing the standard doses of ustekinumab (q12w) and vedolizumab (q8w) in maintenance and one comparing the escalated doses of ustekinumab (q8w) and vedolizumab (q4w) in maintenance. Both results demonstrate that the introduction of ustekinumab to the NHS could result in substantial cost savings, in terms of acquisition costs and administration costs.

**Table 1: Standard dose comparison and cost savings of ustekinumab versus vedolizumab**

Standard dose comparison – cost saving associated with ustekinumab treatment						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Net budget saving impact	██████	██████	██████	██████	██████	██████

**Table 2: Escalated dose comparison and cost savings of ustekinumab versus vedolizumab**

Escalated dose comparison – cost saving associated with ustekinumab treatment						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Net budget saving impact	██████	██████	██████	██████	██████	██████

It is important to note that only the NHS reference costs associated with IV administration have been included – the savings associated with reducing capacity constraints in IV administration suites has not been modelled. Whilst the analysis is simple, it clearly

demonstrates the savings available should NICE decide to recommend ustekinumab, and reduces the uncertainty noted in the ACD regarding the cost-effectiveness analyses. We therefore request that the Committee consider this cost-comparison analysis in their final deliberations.

### 1.3 The updated base-case demonstrates that ustekinumab is cost-effective and that cost-effectiveness estimates are conservative for ustekinumab

In response to the ACD we have updated our base-case economic model to reflect the Committee’s preference for modelling long-term outcomes via a NMA. This reduces the uncertainty in decision making and shows that ustekinumab is a cost-effective use of NHS resources. The updated base-case model includes the following reasonable assumptions based upon the Committee’s considerations:

- modelled relative effectiveness in maintenance from the Company NMA
- 0% rate for spontaneous remission and response
- utility values from Woehl et al.

These changes are reflected in the updated base-case results versus CT, presented in Table 3 below:

**Table 3: Updated base-case, ICER results vs CT**

Scenario	ICER; Ustekinumab versus CT	
	Non-biologic failure	Biologic failure
Updated base-case	<b>£24,849</b>	<b>£28,348</b>
Updated base-case (alternative 1% spontaneous remission/response scenario)	£26,359	£29,290

The updated base-case demonstrates that ustekinumab is a cost-effective use of NHS resources when all reasonable assumptions and scenarios are considered. Furthermore, the cost-effectiveness of ustekinumab is likely to be underestimated in the updated base-case given that the model uses conservative assumptions. We agree with the ERG (ERG Report, page 14) in their conclusion that *“The base case uses relatively conservative assumptions and decisions are based on precedent where available, albeit with a few exceptions.”* Some key examples of where the model is conservative that we believe the Committee should further consider include:

- The benefit of corticosteroid-free remission associated with ustekinumab has not been modelled, nor has the long-term consequences of corticosteroid use for other treatments been modelled. As per section 3.1 of the ACD, a reduction in corticosteroid use would be welcomed by patients given the side effects associated with corticosteroids “...explained that using corticosteroids is associated with side effects

and contributes to low mood.” Evidence in the Company Submission (CS) [page 53, Table 16, Document B] demonstrated that both the q12w and the q8w doses of ustekinumab were associated with significantly greater proportions of patients in clinical remission and corticosteroid free at week 44, than maintenance placebo, in the UNIFI maintenance study. If the negative consequences of long-term corticosteroid use were to be modelled the cost-effectiveness of ustekinumab would improve.

- Serious infection rates were modelled equally for ustekinumab, CT, vedolizumab and tofacitinib, despite emergent safety concerns associated with tofacitinib. Due to its safety concerns, not all patients can initiate treatment with tofacitinib, nor can all patients receive the escalated dose in maintenance. Adherence to treatment with tofacitinib in the real-world is likely to differ from clinical trials, given its oral formulation. If this were to be modelled the ICER for ustekinumab versus tofacitinib would improve.
- The Company NMA makes an assumption that the Biologic Failure population in the UNIFI trial is similar to the ‘biologic exposure’ populations in the other trials. This is conservative because in the UNIFI trial the Biologic Failure population included 32.6% of patients who have failed to respond to both an anti-TNF and to vedolizumab (ITT population, 160/491 patients) [CS, Document B, page 61]. This means that the ICERs for ustekinumab versus all comparators in the Biologic Failure population are higher than if ustekinumab had been studied in an anti-TNF-exposed population only.

In summary, the updated base-case demonstrates that ustekinumab is a cost-effective use of NHS resources when reasonable assumptions are modelled compared to CT. The updated base-case model is conservative for ustekinumab given the assumptions made.

### **1.3.1 The committee should consider stopping rules when assessing cost-effectiveness in ulcerative colitis to be consistent with previous NICE decision making**

In the Janssen response to Technical Engagement we submitted evidence on stopping rules, but this has not been considered by the Committee. This is not consistent with previous appraisals given that stopping rules were explicitly considered in the MTA for the anti-TNFs (TA329); ‘Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy’ and the STA for vedolizumab (TA342); ‘Vedolizumab for treating moderately to severely active ulcerative colitis.’ In fact, stopping rules have played a large part in Committee decision making for the anti-TNFs and for vedolizumab, and as a result, they should be considered in this appraisal. If the stopping rules for ustekinumab are applied in the economic model, the cost-effectiveness of the updated base-case is further improved.

#### NICE TA329:

*“Without further evidence on the cost-effectiveness of continuing or stopping TNF-alpha-inhibitor therapy in different clinical circumstances, the Committee concluded that the criteria in NICE’s technology appraisal guidance for TNF-alpha inhibitors for treating Crohn’s disease could also be applied in this appraisal (see section 4.65).”* Technology Appraisal Guidance, 4.71

*“In addition, applying the criteria for continuing and stopping TNF-alpha inhibitors (see section 4.71) would further improve the cost-effectiveness of treatment.”* Technology Appraisal Guidance, 4.80

**NICE TA342:**

*“The Committee concluded that a similar stopping rule to that recommended in NICE’s technology appraisal guidance on infliximab (review) and adalimumab for the treatment of Crohn’s disease was appropriate and was likely to reflect how clinicians would prescribe vedolizumab in clinical practice.”* Technology Appraisal Guidance, 4.13

*“The Committee considered that the utility values reported by Swinburn et al. were as plausible as those by Woehl et al. and that the company’s assumption that people stopped treatment at 1 year was not unreasonable.”* Technology Appraisal Guidance, 4.17

As noted in the Janssen response to Technical Engagement, Page 30, *“The ERG’s spontaneous remission and response scenario has overridden the stopping rule functionality within their model.”* This has now been corrected in the ERG model and an updated model has been uploaded to NICE Docs titled *‘ID1511 UC (mod-sev active) ERG model v0.1 28.08.19 ACIC\_11Feb2020.xlsm.’* Different stopping rules have been incorporated into the model to demonstrate the improved cost-effectiveness of ustekinumab. We appreciate there is some uncertainty when assuming that all patients would stop treatment at the same point in time, and as a result, four different scenarios for stopping rules have been applied for the Committee to consider:

**Table 4: Updated base-case, ICER results vs CT including different stopping rules**

	ICER; Ustekinumab versus CT	
Scenario	Non-biologic failure	Biologic failure
Updated base-case	<b>£24,849</b>	<b>£28,348</b>
Updated base-case and stopping rule at 5 years	£23,020	£27,610
Updated base-case and stopping rule at 3 years	£20,428	£25,844
Updated base-case and stopping rule at 2 years	£17,476	£23,388
Updated base-case and stopping rule at 1 year	£11,148	£17,189

**Table 5: Company NMA, 1% spontaneous remission/response, ICER results vs CT including different stopping rules**

Scenario	ICER; Ustekinumab versus CT	
	Non-biologic failure	Biologic failure
Company NMA, 1%	£26,359	£29,920
Company NMA, 1% and stopping rule at 5 years	£24,445	£29,155
Company NMA, 1% and stopping rule at 3 years	£21,733	£27,319
Company NMA, 1% and stopping rule at 2 years	£18,642	£24,762
Company NMA, 1% and stopping rule at 1 year	£12,004	£18,293

### **Conclusion to Section 1**

In summary, ustekinumab represents a cost-effective use of NHS resources when all reasonable assumptions are made. Ustekinumab has pair-wise ICERs versus CT that are below £30,000 per QALY gained and the comparison to CT is consistent with previous decision making in UC. A simple cost-comparison analysis also demonstrates that ustekinumab could result in acquisition and administration cost savings versus vedolizumab. The cost-effectiveness model remains conservative against the cost-effectiveness of ustekinumab; when stopping rules are considered, the cost-effectiveness of ustekinumab is further improved.

## **Section 2. Additional evidence provides greater certainty on the long-term effectiveness of ustekinumab**

### Overview

We note the Committee has concluded there is uncertainty in the NMA because of the lack of additional evidence to support the treatment effect of ustekinumab. We have submitted additional evidence that provides greater certainty on the long-term effectiveness of ustekinumab, confirming that the Company's NMA is appropriate to use to model long-term outcomes. Further evidence on which utilities to use in the model is also provided below, and we strongly believe it is most appropriate to use the Woehl et al. utilities to ensure consistent decision making, particularly given the limitations of the utilities derived from the UNIFI trial.

### **2.1 The Committee has not considered all of the relevant evidence in reaching its conclusions on comparative effectiveness**

We have concerns that the Committee has not reached an appropriate conclusion on the relative effectiveness of treatments in maintenance. We believe that it is likely because the Committee has not appreciated that both the ERG and the Company prefer the Company NMA for modelling long-term outcomes. The Committee has also not appropriately considered all the evidence available on relative effectiveness in maintenance. We have further concerns that the long-term effectiveness of ustekinumab has not been considered in relation to the plausibility of different modelling approaches.

#### **2.1.1 The Committee should reconsider that both the ERG and the Company prefer the Company NMA to the ERG NMA**

In considering how to model outcomes in maintenance in the economic model, we feel the Committee have not appreciated that the ERG preferred NMA *is* the Company NMA and *not* the ERG NMA in their base-case.

As noted above, in the updated base-case we have adopted the Company NMA to model outcomes in maintenance and this represents the ERG's preferred base-case for economic modelling. We therefore disagree with the conclusions in the ACD that appear to suggest there is disagreement and high uncertainty between which NMA in maintenance to consider for decision making.

#### Limitations with the ERG NMA

As described in the Janssen response to ERG Factual Inaccuracies we have extreme concerns with the ERG's NMA in maintenance 'maintenance only no carry-over'. These concerns stem from both methodological issues and application issues, as described below:

1 *The ERG NMA violates the similarity assumption required to conduct NMAs*

In the CS, [Document B, pages 83-84] the chi-squared test of re-randomised maintenance placebo arms show that these maintenance placebo arms are statistically significantly different. As a result, to assume that they are similar is factually inaccurate. The similarity assumption required to conduct a NMA does not hold in light of the fact that response and remission rates in maintenance placebo arms are statistically significantly different. Therefore, we believe it is not appropriate to conduct such an NMA, as a core assumption is violated. Results should be viewed with caution and we do not believe they provide reliable treatment effects estimates of maintenance outcomes due to the differences in placebo rates.

## *2 The data inputs for the ERG NMA and its application in the model are inaccurate*

The ERG NMA included the ITT population in maintenance for UNIFI and not the restricted population that includes only the licensed dose of ~6 mg/kg in induction. The ERG's NMA includes all data from the UNIFI maintenance study, i.e. the ITT population who entered the maintenance study having achieved a response to ustekinumab IV administration in induction. The ERG NMA therefore includes data from both the ustekinumab doses in induction – the 130 mg dose (unlicensed) and the ~6 mg/kg dose (licensed). This is conservative against the effectiveness of ustekinumab because the ~6 mg/kg dose achieved better remission and response outcomes in both the induction and maintenance study.

## *3 The ERG NMA has not been incorporated appropriately in the economic model*

The ERG NMA includes data from the re-randomised placebos in maintenance for the re-randomised trials and converts the trials with a treat-through design to match a re-randomised design. The odds ratios calculated in the ERG NMA therefore relate to the re-randomised placebos. As noted, these are not 'true' placebo arms and statistical heterogeneity between these placebo arms makes this ERG NMA methodologically challenging.

When the ERG NMA is applied in the model, the odds ratios from each treatment versus the re-randomised placebo are applied in the model to predict long-term outcomes in maintenance. However, the application of these odds ratios in the model is in fact in relation to a common placebo-placebo arm baseline effect, as used in the Company NMA. The placebo-placebo arm baseline effect is substantially lower than the re-randomised placebo arm effects, and so the odds ratios from the ERG NMA are not being applied appropriately in the model. This leads to the underestimation of all treatment effectiveness in maintenance.

Furthermore, because the Induction NMA appropriately uses only the licensed ~6 mg/kg induction dose for ustekinumab, the application of the ERG NMA in the model is at odds with the induction modelling approach applied.

For these reasons, we believe that the Committee should re-consider the limitations associated with the ERG NMA and should consider whether these limitations lead to highly uncertain treatment effect estimates that lack both internal and external validity.

### **2.1.2 – The Committee should reconsider the Company base-case NMA – the 1 year NMA**

We are concerned that the Committee have not considered all of the relevant evidence submitted in reaching its conclusions on comparative effectiveness. The conclusion reached in the ACD that there are no further data available is not a reasonable summary of the evidence submitted.

ACD 3.6 *“The committee concluded that both maintenance-phase NMAs had limitations and the results are very uncertain, but because no alternative data are available the results provided the best available estimates of relative effectiveness.”*

Janssen submitted evidence for its base-case detailing the full year NMA as its preference for comparative effectiveness analyses. This NMA is preferable for assessing the relative effectiveness of treatments covering a full year of treatment as it explicitly includes both initial and delayed induction responders. However, because this 1-year NMA assesses outcomes at the end of one year of treatment it cannot be incorporated into the economic model. This is because the economic model appropriately reflects SmPC indication wording for all comparators that if a response is not achieved after early or delayed induction then treatment should not continue. Nevertheless, the 1-year NMA still provides the most complete and comprehensive evidence base for the Committee to consider the relative effectiveness of treatments over both induction and maintenance and we request that the Committee reconsiders its conclusions based upon the evidence submitted.

As noted in the Company Submission (CS) the results of the 1-year NMA, reported in Table 26 and Table 28 of the CS, demonstrate that ustekinumab has very high Bayesian probabilities of being better than the other comparators over a full year of treatment. Because the 1-year NMA assesses the probability of being in remission or response at the end of one year (i.e. response can occur at any time point over the year) it most accurately provides evidence on maintenance outcomes, irrespective of induction outcomes: it appropriately creates a true ‘treat-through’ design for all treatments.

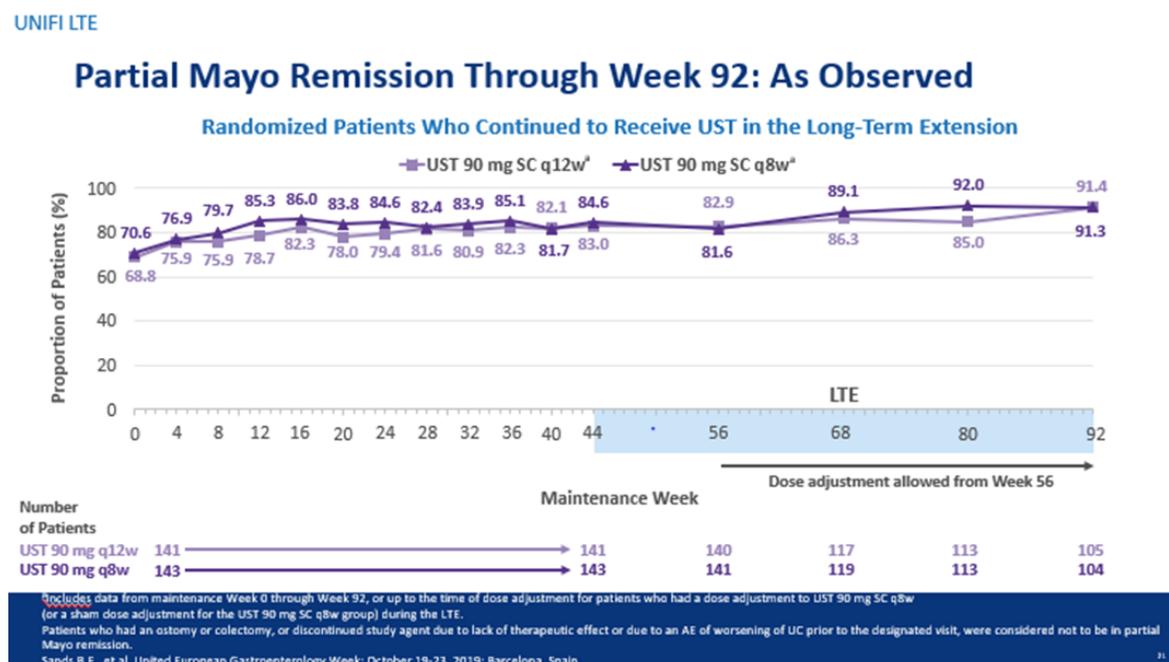
### 2.1.3 Comparison to other evidence on the long-term effectiveness of ustekinumab

In order to provide the Committee with a firmer basis for its decision making regarding the long-term effectiveness of ustekinumab, we propose that the Committee consider further evidence submitted by Janssen during Technical Engagement and in this ACD response. The Long-Term Extension data from UNIFI was submitted in the Janssen response to Technical Engagement but this evidence was not considered by the Committee. We suggest the Committee compares the outcomes predicted from the Company NMA and the ERG NMA with the long-term data observed for ustekinumab. The data submitted for the long-term effectiveness of ustekinumab is consistent in showing the response of ustekinumab is maintained in the long term and is likely to provide additional benefit versus other comparators. This is consistent with the Company NMA and increases the certainty that the effect seen in the Company NMA is likely to be consistent with real world effectiveness of ustekinumab.

#### *2.1.3.1 Ustekinumab Long-Term Extension data from UNIFI*

The Long-Term Extension (LTE) data from UNIFI was submitted in the Janssen response to Technical Engagement but these data were not further considered by the Committee. We suggest that these data should be considered as they provide the most relevant information available about the long-term effectiveness of ustekinumab in UC. Indeed, the partial MAYO remission scores in UNIFI are maintained through a further year of treatment; these data suggest that both the Company NMA and the ERG NMA underestimate the treatment effect of ustekinumab.

**Figure 1: Partial Mayo remission from the LTE UNIFI presentation, as observed**

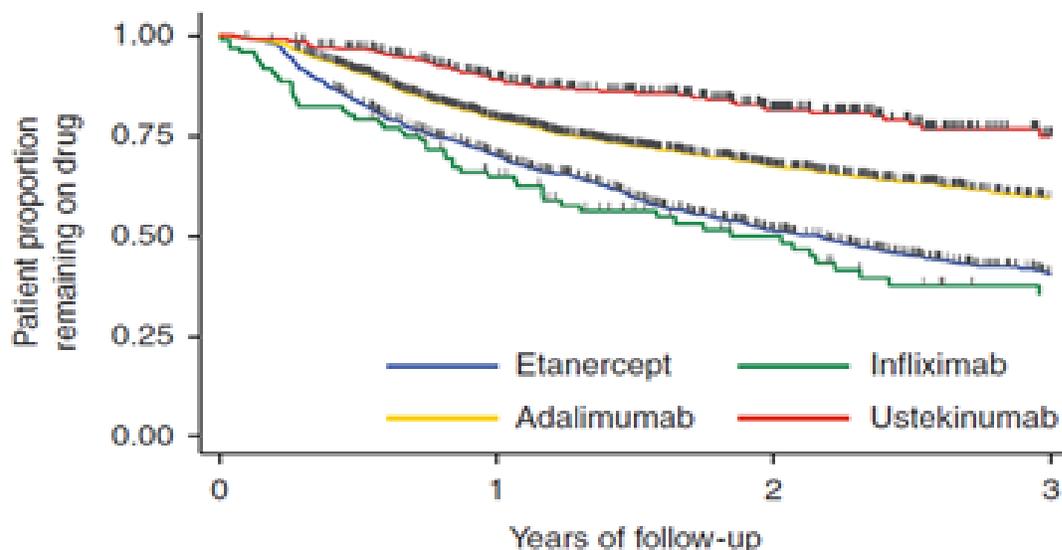


### 2.1.3.2 Ustekinumab real-world data in psoriasis

Ustekinumab has been recommended by NICE as a treatment option for severe plaque psoriasis and has been used in the NHS for over a decade. There is a growing body of evidence and publications in psoriasis that show that the treatment effect of ustekinumab in the real-world is longer-lasting than for the anti-TNF therapies. The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)<sup>1</sup> established in 2007, is a UK and Republic of Ireland prospective, longitudinal pharmacovigilance register that aims to assess the long-term safety and effectiveness of biologic and immunomodulator treatments for psoriasis. The data presented in Figure 2 below clearly demonstrate that there are minimal discontinuations of ustekinumab in the real-world UK setting, with approximately 80% of patients receiving ustekinumab still on treatment at 2 years. Appendix 3 provides additional evidence on the long-term effectiveness of ustekinumab.

<sup>1</sup> This registry was formally known as The British Association of Dermatologists Biologic Intervention Register

**Figure 2: Crude drug survival of the first biologic course showing disaggregated biologic data from the BADBIR data set:**



Number at risk

Etanercept	1,098	718	418	225
Infliximab	96	55	30	15
Adalimumab	1,879	1,175	596	277
Ustekinumab	450	307	120	40

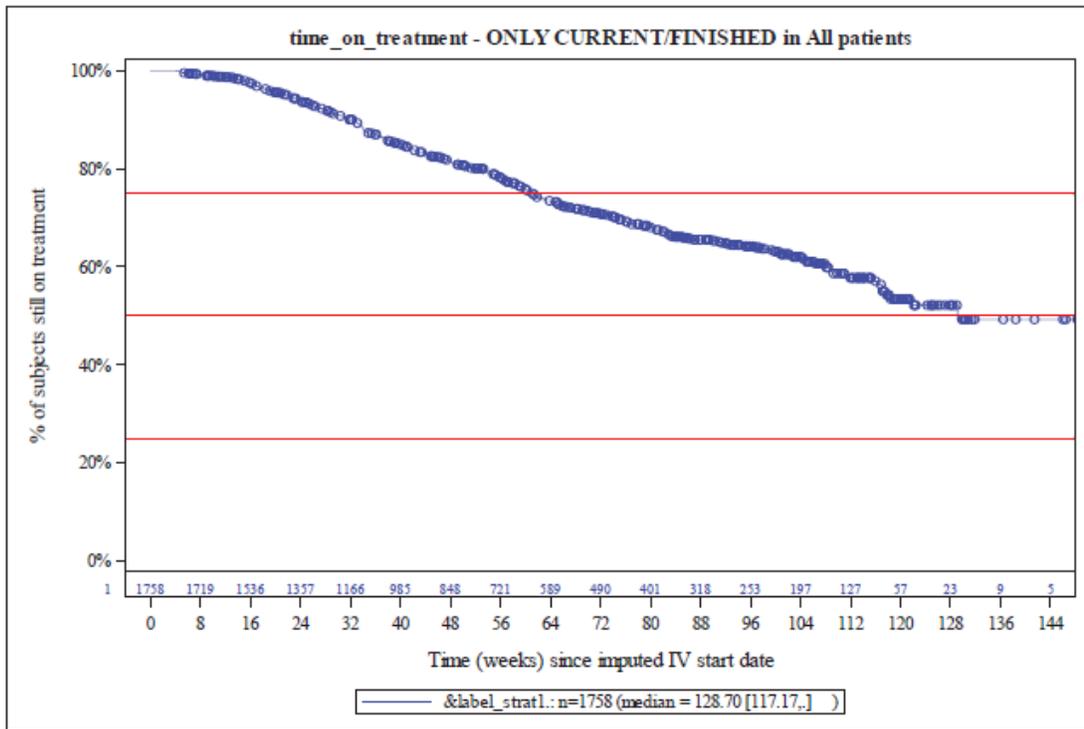
Ref: Warren RB. et al, *Differential drug survival of biologic therapies for the treatment of psoriasis: A prospective observational cohort study from the British Association of Dermatologists Biologics Interventions Register (BADBIR)*, *Journal of Investigative Dermatology*, 2015, 135, pg: 2632-2640

### 6.3.2 Ustekinumab real-world data in Crohn's disease

Sales data provided to Janssen from Homecare for over 1,700 patients treated with Crohn's disease (CD) in the UK demonstrate that the effect of ustekinumab is long-lasting, even with relatively short medium follow-up. Data received from Homecare has been reformatted so that Kaplan-Meier survival analyses can be calculated. Further details of this analysis are provided in Appendix 4.

The analysis demonstrates that the median time on treatment is not reached at 2 years, with a median follow-up of ~11 months. This suggests that the treatment effect observed in clinical trials for ustekinumab in CD (IM-UNITI) is replicable in the UK practice, in terms of time on treatment as a proxy for treatment effect. In IM-UNITI, the clinical response to ustekinumab at week 44 in maintenance was 58.1% (q12w) and 59.4% (q8w).

**Figure 3: Real-world time on treatment analysis for ustekinumab in CD**



#### 6.3.4 Comparison of modelled outcomes versus long-term data

We suggest the Committee consider the extent to which the Company NMA and the ERG NMA are able to predict long-term outcomes, in reference to data observed in UNIFI and the analysis of real-world data in Crohn's disease.

In Table 6 below, we demonstrate that the Company NMA appears to reasonably predict outcomes from UNIFI at 1 year but there appears to be an underestimation of effect at 2 years. The ERG NMA underestimates the effects of ustekinumab at both 1 year and 2 years, which contradicts the body of evidence available.

**Table 6: Model predictions from NMAs versus long-term data**

	Non-biologic failure		Biologic failure	
	End of 1 year	End of 2 years	End of 1 year	End of 2 years
Model predictions:				
Company NMA <sup>a</sup>	75%	53%	64%	38%
ERG 'maintenance only' <sup>a</sup>	58%	30%	44%	17%
Long-term data:				
UNIFI data <sup>a</sup>	81.5% <sup>b</sup>	91.3% (all patients) <sup>d</sup>	71.3% <sup>b</sup>	91.3% (all patients) <sup>d</sup>
Crohn's Disease RW data <sup>c</sup> (all patients) <sup>d</sup>	80%	62%	80%	62%
a: Data refers to induction responders only for consistency with UNIFI presented results b: Data refers to maintenance outcomes for ~ 6 mg/kg induction group; simple non-weighted average c: Data is from the real-world and therefore includes both induction and delayed induction responders d: Data refers to all patients, not split by biologic failure status				

For all of the reasons detailed above, we suggest that the Committee reconsiders whether the ERG NMA represents a plausible estimation of treatment effect from which to inform its decision making. We further suggest that the Committee considers whether the Company NMA could be regarded as a conservative approach to modelling.

**2.2 The committee's conclusions about health-related quality of life are inconsistent with previous decision making and do not reflect the impact UC has on patients**

In all previous NICE appraisals for UC, the Committee has had a preference for using utility values from published sources rather than from clinical trials. Utility values from Woehl et al. (2008) were used in the Company base-case and the ERG base-case, consistent with previous appraisals. However, utility values are available from the UNIFI trial and these were used in both the Company submission and ERG report as a scenario analysis. To ensure consistency with previous decision making and due to the limitations noted in the CS with the UNIFI utilities, we suggest that the Committee rely on the utility values from Woehl et al. We disagree with the Committee's conclusions in 3.11 of the ACD that:

*"The committee concluded that both data sources had some strengths and some limitations, and the choice of data sources had a large effect on the cost-effectiveness estimates."*

The main concerns with using the UNIFI utilities are described in detail below:

**2.2.1 The utility values from UNIFI for the active UC health state do not align with the published utility values or the patient expert’s experience of the disease**

The main difference between the UNIFI trial utility results and those from Woehl et al. regard the active UC health state. In the UNIFI trial the utility score for this health state was ■■■, whereas in Woehl et al. the utility score was 0.41. This is what drives the large differences in cost-effectiveness results observed.

We welcome the Committee’s considerations of the patient expert’s experiences of living with moderately to severely active UC and we suggest that the Committee further consider these experiences in its deliberations over which utility values to use, as we believe these are informative in showing that the Woehl et al. utilities are the most appropriate source of evidence.

ACD 3.1. *“The patient expert explained that the experience of living with moderately to severely active ulcerative colitis varies on an individual level, but in their experience it is extremely challenging.”*

ACD 3.1. *“During periods of active disease, they never had fewer than 4 to 5 bowel movements per day. They experienced constant pain, sleep deprivation (caused by being awake in the night to go to the toilet) and depression.”*

ACD 3.1. *“The committee also took account of comments submitted in writing by patient experts and research undertaken by the company, which highlighted the effects of the disease and current treatments, including surgery, on daily activities, relationships, self-esteem and body image. It concluded that living with moderately to severely active disease is physically and emotionally challenging.”*

Based upon the Committee’s considerations we feel it is implausible that the health state for active UC would have a utility value of ■■■ (UNIFI utilities) and that the patient experience of the disease suggests that the value of 0.41 from Woehl et al. is more appropriate.

Three hypothetical EQ-5D profiles for active UC and their resultant utility scores are provided below.

**Table 7: EQ-5D profiles for hypothetical active UC health states**

EQ-5D Domain	Profile 1	Utility score profile 1	Profile 2	Utility score profile 2	Profile 3	Utility score profile 3
Mobility	1	0.725	1	0.193	1	0.291
Self-care	1		1		1	
Usual activities	1		1		1	
Pain/discomfort	2		3		2	
Anxiety/depression	2		2		3	

We propose that living with active UC is more closely aligned to scoring an ‘extreme’ level on Domain four or five, than scoring a ‘moderate’ level; we note the patient’s experience in 3.1 of the ACD that *“...in their experience it is extremely challenging.”*

### **2.2.2 The active UC health state in the model does not align with the definition of active UC in the trial**

The active UC health state used in the model represents a health state where no further biologic treatment would be given. Patients remain in this health state until they receive surgery or die. This is markedly different from active UC as defined in the UNIFI trial: not achieving remission or response. In the UNIFI trial, patients not achieving remission or response would either receive further ustekinumab treatment (i.e. placebo patients could receive ustekinumab) or were likely to receive other treatments outside of the UNIFI trial. As such, the active UC definition from the UNIFI trial does not adequately represent the same patient population as the active UC health state in the model.

*There are several other limitations with the utility values from the UNIFI trial that we believe the Committee should further consider:*

#### 2.2.3.EQ-5D collected at multiple timepoints for the same patient resulting in correlation bias

Because EQ-5D data were collected at multiple timepoints in the UNIFI trial, this means that the same patient could have contributed to a health state on multiple occasions whereas a different patient may have contributed only once. This results in correlation bias which has not been adjusted for in the utility values presented.

#### 2.2.4 Clinical assessments (Total or Partial Mayo) were sometimes at different timepoints to EQ-5D collection timepoints

Because clinical assessment were sometimes at different timepoints to the EQ-5D timepoints, assumptions linking the EQ-5D to clinical assessments needed to be made. For example, where the Mayo or partial Mayo scores were missing for an EQ-5D assessment, an approach was taken to impute the missing health state based on the previous health state for the patient. This limits the interpretation of the absolute utility scores for any given health state.

#### 2.2.5 With a chronic disease such as UC there is potential for patients to adapt to the disease, skewing scores upwards (e.g. usual activities domain)

Because UC is a chronic disease, there is the potential that the scores observed from the EQ-5D are subject to adaptation bias. This means that a patient may have scored the EQ-5D differently, had they not have learned to adapt to their disease. For example, on the 'usual activity' domain a patient may have responded that they have 'no problems' with their usual activities because they have learned to adapt to negative consequences that living with UC entails. It is unclear how NICE could address issues of adaptation in EQ-5D scores, but it is likely that adaptation has skewed scores for more severe health states (active UC) upwards.

#### 2.2.6 Selection bias means that patients feeling too unwell will not fill in the EQ-5D

There is a general limitation with EQ-5D collected in trials that arises from selection bias. Because completing EQ-5D was not a mandatory requirement in the UNIFI trial there is the

potential that patients who do not feel well on the day of the EQ-5D collection did not fill in the questionnaire. This selection bias means that the utility values for more severe health states (active UC) are likely to be higher than if every patient had responded.

#### 2.2.7 EQ-5D-5L was collected, and not 3L, therefore there is some potential for the new levels to skew results

The EQ-5D-5L data collected were cross-walked to the 3L scale using the mapping methodology detailed in van Hout et al. (2012) as recommended by NICE. We agree with the Committee's conclusions in the ACD that there are some limitations with this approach.

ACD 3.11 "It noted that the trial data had been 'cross-walked' to the EQ-5D-3L scale and that results from this mapping analysis lacked some face validity because the maximum values for all health states were found to be the same (0.92)."

Further issues arise when interpreting the cross-walked values, in that it remains unclear what patients scoring the 'new' levels 2 and 4 on the EQ-5D-5L would have scored on the 3L. It is possible that this could further limit the interpretation of the utility results from the UNIFI trial, although the direction of bias remains unclear.

Lastly, we suggest that the Committee further consider that when utility values from the UNIFI trial are used in the model, *no NICE-recommended treatment options represent a cost-effective use of NHS resources.*

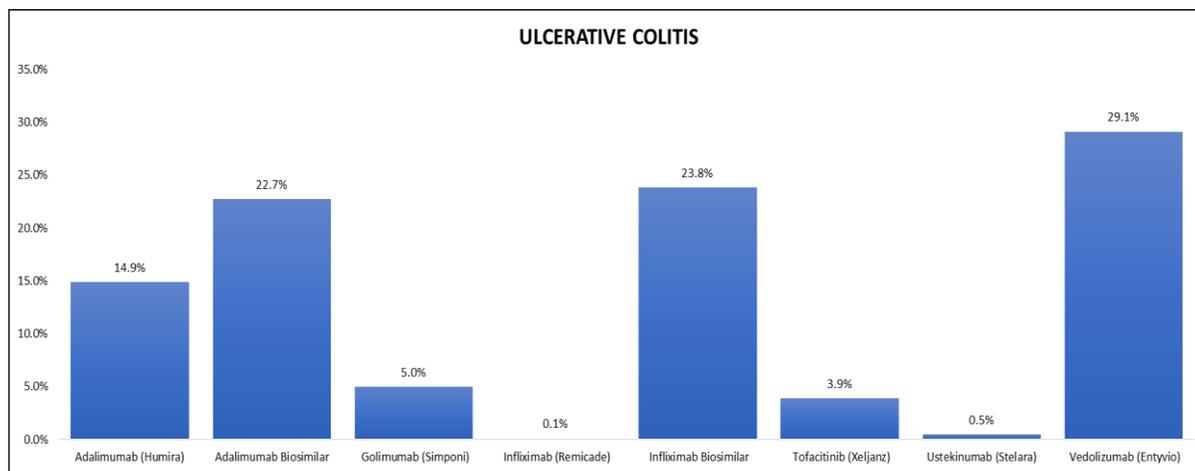
Overall, we strongly suggest that the Woehl et al. utilities reflect the most appropriate and realistic estimates of the utility associated with the active UC health state and these values are consistent with NICE's previous decision making in UC.

## Appendices – Janssen response to the NICE ACD for ustekinumab [ID1511]

### **Appendix 1: Description of Market Research Data**

Market Research data obtained by Janssen in September 2019 supports the Committee’s conclusions in the ACD, 3.2, that treatment with a TNF is commonplace. The Market Research data clearly shows that TNF treatment is the most widely used class of treatment for UC, with two-thirds of all patients being treated with a TNF. The next most commonly used treatment is vedolizumab with a total market share of 30%.

Figure 1: Total Market Share, Ulcerative Colitis, September 2019



This Market share data refers to the proportions of alternative treatments used for moderately to severely active UC. These results are from syndicated, aggregated data survey (Specialist Share Data Report for Ulcerative Colitis) conducted by Wilmington Healthcare Ltd (data collated September 2019, reported October 2019). These data cover the entire UK. The data excel file has been uploaded to NICE docs with the file name: ‘*UC NHIS Data September 2019.xlsx*’

### **Appendix 2: Description of emergent safety concerns with tofacitinib**

“An European Medicines Agency (EMA) safety committee (PRAC) review has found a dose-dependent increased risk of serious venous thromboembolism (VTE), including pulmonary embolism (PE) (some cases of which were fatal) and deep vein thrombosis in patients taking tofacitinib.” This review included data from an open-label clinical trial evaluating tofacitinib compared with TNF antagonists in patients with rheumatoid arthritis.”<sup>1</sup>

As a result, the EMA is “...recommending that tofacitinib should be used with caution in all patients at high risk of blood clots. In addition, the maintenance doses of 10 mg twice daily

should not be used in patients with ulcerative colitis who are at high risk of blood clots unless there is no suitable alternative treatment. Further, EMA is recommending that, due to an increased risk of infections, patients older than 65 years of age should be treated with tofacitinib only when there is no alternative treatment.”<sup>1</sup>

Following this review, the summary of product characteristics (SmPC) for tofacitinib has been updated to include venous thromboembolism (VTE). “Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with ulcerative colitis who have known VTE risk factors, unless there is no suitable alternative treatment available.”<sup>2</sup> “VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.”<sup>2</sup>

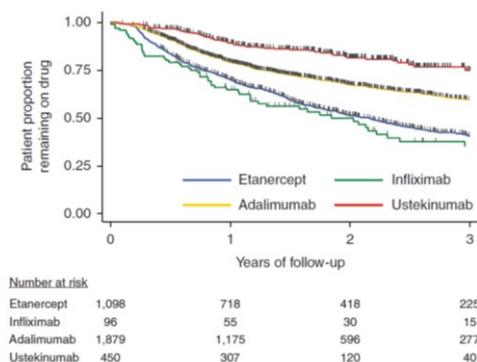
Ref: <sup>1</sup><https://www.ema.europa.eu/en/medicines/human/referrals/xeljanz> Date accessed: 10<sup>th</sup> February;

<sup>2</sup><https://www.medicines.org.uk/emc/product/9410/smpc> Date accessed: 10<sup>th</sup> February 2020

### Appendix 3 – Further evidence on the persistency of ustekinumab in the real-world, psoriasis and Crohn’s disease

#### a) Drug Survival of ustekinumab in Psoriasis – BADBIR and DERMBIO registries

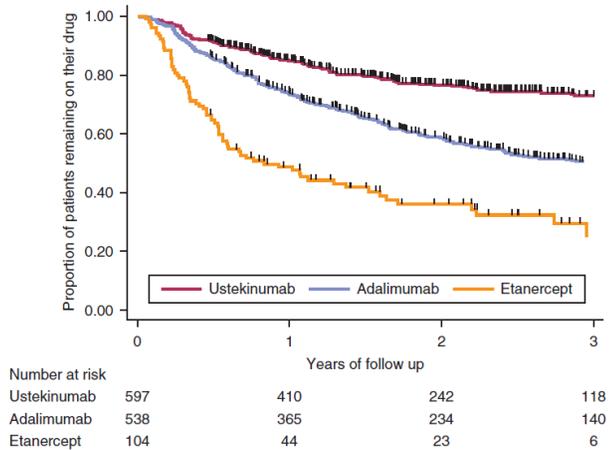
Crude drug survival of the first biologic course showing disaggregated biologic data from the BADBIR data set:



Ref: Warren RB. et al, Differential drug survival of biologic therapies for the treatment of psoriasis: A prospective observational cohort study from the British Association of Dermatologists Biologics Interventions Register (BADBIR), *Journal of Investigative Dermatology*, 2015, 135, pg: 2632-2640

- “After accounting for relevant covariates, ustekinumab had the highest first-course drug survival in biologic-naïve patients.” (Quote from paper conclusion)

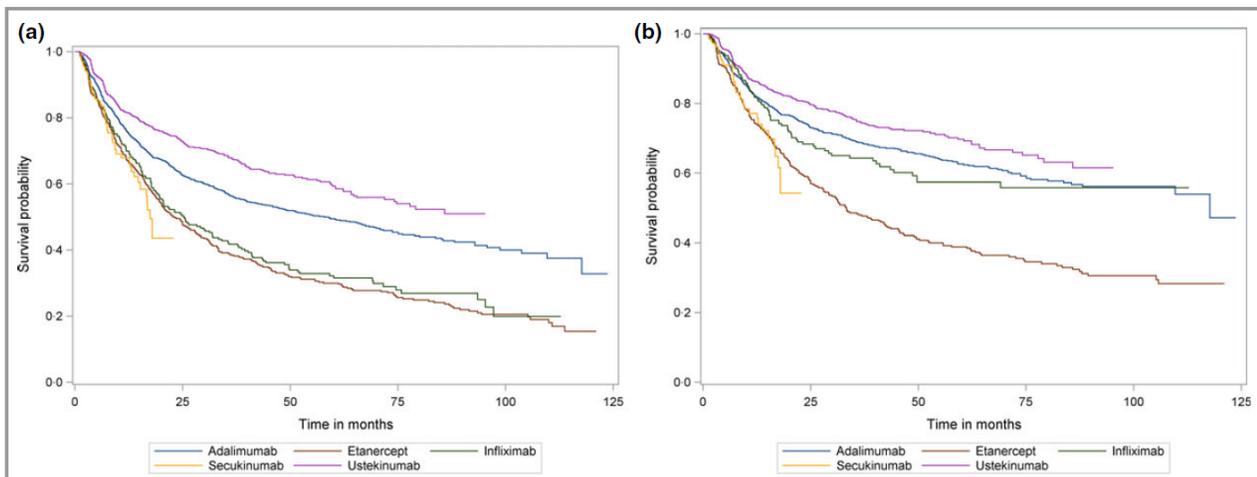
**Crude drug survival of the second biologic course showing disaggregated biologic data from the BADBIR data set:**



*Ref: Iskander IYK. et al, Differential drug survival of second-line biologic therapies in patients with psoriasis: Observational cohort study from the British Association of Dermatologists Biologics Interventions Register (BADBIR), Journal of Investigative Dermatology, 2018, 138, pg: 775-784*

- For patients switched to second-line biologic therapy, “the 1-year survival rate for ustekinumab was 85% (82-87%), for adalimumab was 74% (70-77%) and for etanercept was 49% (39-58%)”. The 3-year survival rates were “73% (68-77%), 50% (46-55%) and 25% (14-37%)” for ustekinumab, adalimumab and etanercept respectively. (Quotations from same paper as above)

**Drug survival rates for all treatment series showing discontinuation because of any cause (A) or lack of efficacy (B) from the DERMBIO registry.**



*Ref: Egeberg A. et al, Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis, British Journal of Dermatology, 2018, 178, pg: 509-519*

- “Overall, ustekinumab was associated with the highest drug survival and lowest risk of drug discontinuation.” (Quotation from paper above)

#### **b) CD RWE Persistency: FINUSTE2 Study:**

A retrospective, non-interventional nationwide chart review at 17 centres in Finland was conducted to review dosing and long-term clinical outcomes in Finnish Crohn's disease patients treated with ustekinumab during 2017 or 2018. Of the 93 patients with follow-up of at least one year, 77 were still on ustekinumab (82.8%).

*Ref: Bjorkesten CG et al, Objectively assessed disease activity during ustekinumab treatment in a nationwide real-life Crohn's disease cohort, P499, ECCO Conference 2020*

#### **Appendix 4: Analysis of Homecare sales data in Crohn's disease**

Janssen receives sales data from its Homecare provider every day. This Homecare service distributes the subcutaneous formulation (SC) 90 mg of ustekinumab to a patient's home, for self-administration. As a result, Janssen has substantial evidence on the administration of the SC dose in the real-world.

For the analysis in the response to the ACD, Janssen analysed the data received from Homecare on the 23<sup>rd</sup> of January 2020. This data was not formatted in manner ready to perform Kaplan-Meier (KM) estimates, so reformatting of the data took place as follows:

##### 1) Estimated start date

As the SC dose is administered 8 weeks after the first administration of the Intravenous dose, an estimated start date for patients in the Homecare data set was created to account for this. When the patient dispatch date (SC dispatch date) was known, the estimated start date was calculated as 8 weeks before the SC dispatch data, to align with the SmPC for ustekinumab in Crohn's disease. When the patient dispatch data was not known, but the Homecare registration date was known, the estimated start date was taken as the average time between known dispatch dates and registration dates, this was approximately 4 weeks (28.4 days).

Patients without an end treatment date were then censored on the date of 23/01/2020, whilst the known treatment end date was used for patients who were not censored. KM survival analysis was then performed to calculate average time on treatment.

##### 2) Handling of patients put on 'hold'

A small proportion of the total patients (<10%) have a treatment status recorded as ON HOLD. This means that they have been registered for the Homecare service, but no treatment dispatch date has been provided. To handle these 'on hold' patients, three scenarios were run:

##### a) Exclude all 'on hold' patients (base case analysis)

- b) Conservative assumption that 'on hold' means that treatment with IV has not been successful and that the patient has ceased treatment
- c) Optimistic scenario that these 'on hold' patients are in fact receiving ustekinumab SC but the data are missing

In all scenarios presented, the median KM estimates for time on treatment are similar, with relatively short medium follow up (~11 months). This shows that the handling of 'on hold' patients has immaterial effects on the conclusions of the analyses. All results can be found in the summary pdf: *'CD Homecare KM\_Allresults.pdf'*

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

**Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 11 February 2020 email: NICE DOCS**

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> <li>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Crohn's &amp; Colitis UK</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p><b>Name of commentator person completing form:</b></p>	
<p><b>Comment number</b></p>	<p style="text-align: center;"><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>

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**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that .....
1	<p><b>We are very concerned by the Committee’s initial recommendation to not make this drug available as a treatment option for this indication on the NHS.</b></p> <p>We note that the Committee agrees with patient and clinical experts that there is significant unmet need and that new medical treatments are needed.</p> <p>In this vein, ustekinumab has shown itself to be clinically effective within its indication for groups of patients. It offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making). This is particularly relevant given how individual a person’s condition can be and consequently how personalised treatments are required to be.</p> <p>It also very importantly has the potential to significantly improve the lives of patients with uncontrolled and unresponsive refractory disease, who are likely to be experiencing an extremely low quality of life.</p> <p>We believe that for this small and defined group of patients —estimated to be <b>&lt;5% of any cohort of patients with ulcerative colitis<sup>1</sup></b> - making this drug available on the NHS would be a good use of finite NHS resources in the circumstances and is in the best interests of these patients. Untreated and unresponsive disease has risks associated with mortality and life-threatening complications. It gives this cohort the ability to avoid costly and traumatic interventions like surgery which have lifelong consequences and ongoing cost both to the NHS and to the individual.</p> <p>As such, our position remains that ustekinumab should be recommended and we urge the Committee to reconsider its initial recommendation.</p> <p><i>“Before I started Stelara, my calprotectin levels were in excess of 2000, and now 5 months on, they have hugely improved and are just 66. I have noticed over this time my pouch function has improved; my output is reduced to an average of 5-6 BMs a day on a good day. I have little or no pressure feeling and no urgency. I can eat better and am only up once at night. This is all on the good days which are about 50% of the time.”</i></p> <p><i>“When I am unwell, I struggle with extreme tiredness and extended periods in the bathroom which makes my working life very difficult. I work in construction so spend a lot of time away from toilets. Vedolizumab, when I first started it, was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.”</i></p> <p><i>“We, as clinicians, are very excited to see the latest data demonstrating the effectiveness of ustekinumab for the induction and maintenance of remission in UC. This will be a very important addition to the therapeutic toolkit for people with UC, particularly given the evidence of remission and mucosal healing in both bio-naive patients and in those previously failing anti-TNF therapy.”</i></p> <p>xxxxx, Gastroenterologist, Edinburgh Western General Hospital Chair, BSG IBD Clinical Research Group CSO Specialty lead for Gastroenterology, Scotland<sup>2</sup></p>

<sup>1</sup> xxxxx, Gastroenterologist  
<sup>2</sup> Previous response

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2	<p><b>Recommending ustekinumab for this indication would give patients and clinicians added options (a) to treat co-morbidities such as skin conditions, (b) the choice of subcutaneous delivery and the ability to be treated at home.</b></p>
3	<p><b>We have concerns that the Appraisal Consultation Document (ACD) conflates the experience of those who experience mild to moderate Ulcerative Colitis with those with moderate to severe / refractory disease.</b></p> <p>The ACD advises that the patient expert was suggesting “effects of the disease and side effects of medication can be moderated, to an extent, by individual circumstances including a patient’s support network and responsibilities.”<sup>3</sup></p> <p>Our understanding was that the patient expert was pointing out the role that self-management and support can play in managing their symptoms, but not in controlling or moderating their disease itself which is quite different. While self-management and support can play an important role in helping to manage symptoms and the emotional impact of the condition, it would be inaccurate to suggest an individual can induce remission or control disease severity through self-management or self-care alone.</p> <p><i>“Uncontrolled or poorly managed acute severe colitis is still a medical emergency requiring effective therapy or life-saving surgery regardless of whether these other factors are in place. It is NOT possible for the natural course of the disease or side effects of medication to be altered in any way by support networks or patients taking responsibility for their overall wellbeing or self-care”.</i><sup>4</sup></p> <p>Given that disease severity is wide-ranging, and while each person has their own individual experience, we would like to take this opportunity to reiterate the impact and experience of the specific cohort of patients this guidance is targeting. It is important to recognise that differences occur not just between those with mild to moderate and moderate to severe disease, but also apply within the group who experience moderate to severe disease.</p> <p>This sub-group is likely to comprise <b>&lt;5% of patients with Ulcerative Colitis</b> who experience <b>more severe</b> flares, weight loss, fever and constitutional symptoms and whose disease has not responded to other treatment options, are unable to tolerate these, and/or can benefit from this treatment in particular</p> <p><b>Truelove and Witts</b> define severe Ulcerative Colitis as six or more stools a day plus at least one of the features of systemic upset (marked with an *): visible blood; pyrexia*; pulse rate greater than 90 BPM*; erythrocyte sedimentation rate (mm/hour)* and anaemia.<sup>5</sup></p> <p>The <b>Mayo Score</b> defines severe Colitis as more than five stools a day, blood passed without stool, obvious blood with stools in most cases and severe disease (spontaneous bleeding, ulceration).<sup>6</sup></p> <p>For this sub-group (&lt;5%) of patients with moderate to severe Ulcerative Colitis, <b>the condition is more than challenging, but frequently overwhelming and detrimentally life altering, as described below:</b></p> <p><i>“it stopped me from being a full-time carer to my son”</i></p>

<sup>3</sup> NICE (2020) Appraisal consultation document: Ustekinumab for treating moderately to severely active ulcerative colitis. Page 5

<sup>4</sup> Nancy Greig, Patient Expert, response to ACD 11 Feb 2020

<sup>5</sup> NICE (2019) NICE Guideline on Ulcerative Colitis: Management (NG130) <https://www.nice.org.uk/guidance/ng130/chapter/Recommendations>

<sup>6</sup> Dignass, A., Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. Journal of Crohn’s and Colitis Vol 6. Issue 10 <https://www.sciencedirect.com/science/article/pii/S1873994612004047#t020>

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	<p><i>"I had my relationship break down"</i></p> <p><i>"I have become isolated and really hid myself away from society"</i></p> <p><i>"Your life is on hold and all normality is replaced by a 'new normal' of pain, distress and sickness"</i></p> <p><i>"The isolation I have felt has been overwhelming. I can't take my children to the park, for a walk or play date, or any of the other simple things that I used to take for granted"</i><sup>7</sup></p>
4	<p><b>We are concerned that this recommendation may imply that for those who cycle through available treatment options without success, steroids are an alternative treatment.</b></p> <p>However, <i>"corticosteroids have no proven efficacy in maintaining remission in IBD and should not be used for this purpose."</i><sup>8</sup> The BSG guidelines set out clear stipulations on the best practice of prescribing of steroid therapies given their diminishing returns, harsh side effects and risk of dependency.<sup>9</sup></p>
5	<p><b>We would strongly urge the Committee to reconsider their position that surgery is an alternative to ustekinumab.</b></p> <p>If ustekinumab was not made available on the NHS, next steps for this small group of refractory patients would be surgery. Yet, for many patients, surgery is unacceptable, but with no other option becomes a very desperate last resort.</p> <p><b>We would draw the Committee's attention to previous discussions on this issue during NICE's consideration of infliximab, adalimumab and golimumab for treating moderately to severely active Ulcerative Colitis after the failure of conventional therapy [TA329].</b> To quote our submission:</p> <p><i>"We welcome the Committee's agreement that surgery is not a relevant comparator for most patients with moderately to severely active disease. While it can offer the individual concerned the feeling they have 'got their life back', for many it is not an option that they want to consider except as a last resort when all available options have been exhausted, and can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult"</i>.<sup>10</sup></p> <p><b>Surgery has both associated risks and an impact on quality of life.</b></p> <p><i>"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life."</i></p> <p><i>"Surgery was on the cards, but my mum, dad and I begged the surgeon not to do it."</i></p> <p><i>"Personally, I'm not prepared for the drastic surgery of having my colon removed."</i><sup>11</sup></p>

<sup>7</sup> Quotes from people living with Ulcerative Colitis following a request via social media (January-Feb 2020)

<sup>8</sup> Barrett, K. (2018) Using corticosteroids appropriately in inflammatory bowel disease: a guide for primary care, British Journal of General Practice. 68 (675): 497-498. <https://bjgp.org/content/68/675/497>

<sup>9</sup> BSG (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. <https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html>

<sup>10</sup> Crohn's & Colitis (2014) UK NICE Appraisal consultation response, October 2014

<sup>11</sup> Ibid

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<p>The most common surgeries are:</p> <p><b>Colectomy with ileostomy (subtotal):</b> The colon is removed, leaving the rectum, with the end of the small intestine brought out through an opening in the wall of the abdomen.</p> <p><b>Restorative proctocolectomy with ileo-anal pouch:</b> This generally requires two or three operations, but in rare circumstances may be done as a single stage.</p> <p><b>Proctocolectomy with ileostomy:</b> The entire colon is removed, together with the rectum and the anal canal. The surgeon then brings out the end of the small intestine through a permanent ileostomy in the wall of the abdomen.</p> <p><b>Colectomy with ileo-rectal anastomosis:</b> The colon is removed and the surgeon joins the end of the small intestine directly to the rectum.<sup>12</sup></p> <p>Surgery has significant associated long- and short-term risks which include:</p> <ul style="list-style-type: none"><li>- general anaesthetic complications</li><li>- infections.</li><li>- anastomosis</li><li>- adhesions</li><li>- pouchitis,</li><li>- pouch leakage,</li><li>- pelvic abscesses</li><li>- pouch fistulae</li><li>- small bowel obstruction,</li><li>- post-operative bleeding</li><li>- sexual dysfunction</li><li>- delayed wound healing</li><li>- nerve damage<sup>13,14</sup></li></ul> <p>A 2011 research study found severe postoperative complications were experienced for 27% of surgeries.<sup>15</sup></p> <p>Additionally, a meta-analysis has shown ‘an approximate threefold increase (from 15% to 48%) in the risk of infertility in women with Ulcerative Colitis as a result of ileal pouch anal anastomosis (IPAA) (Waljee et al. 2006). Johnson et al. reported the infertility rate in females who had pelvic pouch surgery was significantly higher compared to females who were managed medically (38.1 % compared with 13.3 %; p &lt; 0.001).’<sup>16</sup></p> <p>We would also urge the Committee to consider the ‘persistent quality of life issues that impact multiple domains, including psychological and sexual functioning’.<sup>17</sup> A 2015 study found 81% experienced problems in at least one of the following areas: depression, work productivity, restrictions in diet, body image, and sexual function. In the same study, amongst moderate to severe Ulcerative Colitis patients, post-colectomy, 27% of men and 28% of women reported that their sexual life was worse now than before surgery.<sup>18</sup></p>
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<sup>12</sup> Crohn's & Colitis UK (2020) Surgery for Ulcerative Colitis <https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/surgery-for-ulcerative-colitis> (last accessed 4/2/2020)

<sup>13</sup> Ibid

<sup>14</sup> Brown C, Gibson PR, Hart A, et al. Long-term outcomes of colectomy surgery among patients with ulcerative colitis. *Springerplus*. 2015;4:573. Published 2015 Oct 5. doi:10.1186/s40064-015-1350-7

<sup>15</sup> Ibid

<sup>16</sup> Johnson et al. 2004 in Ibid

<sup>17</sup> Ibid

<sup>18</sup> Ibid

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Surgery should not be considered as curative or a one-off. Patients may require multiple surgeries, increasing the risk of complications.

Pouch failure rates in high volume centres have been estimated at 5.7%.<sup>19</sup>

The BSG Guidelines cite research that ‘up to 50% of patients will develop pouchitis at some time after IPAA (as many as 40% in the first year). Typical symptoms of pouchitis include increased bowel frequency, urgency, nocturnal seepage or incontinence, pelvic discomfort and abdominal cramps.’<sup>20</sup>

The Ileoanal Pouch Report 2017 (ACGBI) found that ‘complications occur in about 1 in 5 patients and 1 in 17 patients will need an early second operation to sort out a complication.’<sup>21</sup>

‘The literature suggests that pouch failure over the long term is between 10 and 15%.’<sup>22</sup>

Table 3.04 Patients having primary ileoanal pouch surgery; post-operative complication rates with 95% confidence intervals

	Financial year of operation		
	<2013	2013-2017	All years
None recorded	74.3% (72.9-75.7%)	83.8% (81.7-85.7%)	76.8% (75.6-77.9%)
Any complication	25.7% (24.3-27.1%)	16.2% (14.3-18.3%)	23.2% (22.1-24.4%)
Pelvic sepsis <sup>1</sup>	11.1% (10.1-12.2%)	4.6% (3.5-5.9%)	9.4% (8.6-10.3%)
Anastomotic leak	3.5% (2.9-4.1%)	3.0% (2.2-4.2%)	3.3% (2.9-3.9%)
Fistula	5.9% (5.2-6.7%)	1.2% (0.7-2.0%)	4.7% (4.1-5.3%)
Abscess	3.6% (3.0-4.3%)	1.2% (0.7-2.0%)	3.0% (2.5-3.5%)
Wound infection	3.0% (2.5-3.6%)	1.4% (0.9-2.3%)	2.6% (2.2-3.1%)
Obstruction	6.6% (5.8-7.4%)	1.7% (1.1-2.6%)	5.3% (4.7-6.0%)
Haemorrhage	0.8% (0.5-1.1%)	0.9% (0.5-1.6%)	0.8% (0.6-1.1%)
Pouch failure	6.0% (5.2-6.8%)	1.1% (0.7-1.9%)	4.7% (4.2-5.4%)
Other	8.2% (7.4-9.2%)	10.1% (8.6-11.9%)	8.7% (8.0-9.5%)

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**6 We would urge the Committee to review its initial recommendation taking into consideration the fuller NHS costs associated with surgery.**

We would ask the Committee to consider: the costs of surgery itself; post-operative costs; complications, inpatient stays, emergency admissions, nursing/stoma support and appliances.

*‘Perhaps the most unexpected finding from SWORD is the 27.4% 30-day readmission rate after pouch surgery.’<sup>24</sup>*

<sup>19</sup> BSG guidelines page 24

<sup>20</sup> Ibid

<sup>21</sup> <https://www.acpgbi.org.uk/content/uploads/2016/07/Ileoanal-Pouch-Report-2017-FINAL.compressed.pdf>

<sup>22</sup> Ibid

<sup>23</sup> <https://www.acpgbi.org.uk/content/uploads/2016/07/Ileoanal-Pouch-Report-2017-FINAL.compressed.pdf>

<sup>24</sup> Ibid

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	<p>These include:</p> <ul style="list-style-type: none"> <li>- <b>Potential second or third operations</b> (e.g. restorative proctocolectomy with ileoanal pouch is usually undertaken as two operations; colectomy with ileostomy may be followed by pouch surgery at a later date or permanent ileostomy)</li> <li>- <b>Ongoing stoma care and appliances</b> (estimated at £5,000 per year by Clinical Commissioning Groups for up to 50 years for younger patients)</li> <li>- <b>Potential fertility treatment</b> for young women after surgery</li> <li>- <b>Hospital costs</b> for the treatment of infections and other complications</li> <li>- <b>Psychological support</b> – IBD-related surgery or hospitalisation is associated with a significant risk for depression and anxiety.<sup>25</sup></li> </ul>
7	<p>We would ask the Committee to <b>consider growing evidence that psychological factors have on the impact of surgical outcomes</b>. This is very relevant given that many patients state that they wish to avoid surgery.</p> <p>There are many reasons for this including the impact on their bodies; self-esteem; wishing to complete studies; start or keep up with their young family and those for whom surgery would be considered unacceptable due to cultural or religious factors.</p> <p>Increasingly, evidence suggests <i>‘that psychological factors have an impact on surgical outcomes in both the short and long term. Pre-operative anxiety, depression and low self-efficacy are consistently associated with worse physiological surgical outcomes and postoperative quality of life’</i>.<sup>26</sup></p>
8	<p>We would ask the Committee to <b>consider evidence around the risks and mortality associated with untreated and uncontrolled disease</b> if this treatment option is not made available on the NHS.</p> <p>NICE Guideline on Ulcerative Colitis 130 states: ‘Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person’s social and psychological wellbeing, particularly if poorly controlled.’<sup>27</sup></p> <p>This is echoed by BSG Guidelines that state that ‘acute severe colitis is a potentially life-threatening condition.’<sup>28</sup></p> <p>Acute severe colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).<sup>29</sup> Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare up at some stage. Often this will be the first presentation of their disease.<sup>30</sup></p> <p>When a flare occurs in acute severe colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It’s also vitally important to make decisions quickly to avoid severe complications.</p> <p>The very real risks associated with acute severe colitis include:</p>

<sup>25</sup> Ananthakrishnan AN, Gainer VS, Cai T et al. Similar risk of depression or anxiety following surgery or hospitalization for Crohn’s disease and ulcerative colitis. Am J Gastroenterol. 2013 Apr; 108(4):594-601.

<sup>26</sup> Levett DZH Psychological factors, prehabilitation and surgical outcomes: evidence and future directions. Anaesthesia. 2019 Jan;74 Suppl 1:36-42. doi: 10.1111/anae.14507

<sup>27</sup> NICE Guideline on Ulcerative Colitis: Management

<sup>28</sup> BSG Guideline 2019

<sup>29</sup> Ibid

<sup>30</sup> BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. <https://gut.bmj.com/content/60/5/571.long>

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

**Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 11 February 2020 email: NICE DOCS**

	<ul style="list-style-type: none"> <li>• Life-threatening haemorrhage</li> <li>• Toxic megacolon - can occur in up to 1 in 40 people with Colitis<sup>31</sup></li> <li>• Perforation of the bowel<sup>32</sup></li> </ul>
9	<p>We would ask that the Committee further <b>consider the complications of chronic, uncontrolled, active disease.</b></p> <ul style="list-style-type: none"> <li>- Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity<sup>33</sup></li> <li>- Anaemia is a common complication of IBD. Iron deficiency and anaemia of chronic disease are the commonest causes of anaemia in IBD<sup>34</sup></li> <li>- Increased risk of cancer<sup>35</sup></li> </ul>
10	<p>We would invite the Committee to <b>consider that the regular review of patients and stopping rules (where clinically appropriate) mitigate against inappropriate use of biologics</b> and should allay concerns around inappropriate costs.</p>
11	<p>We would ask the Committee to further <b>consider the impact on social functioning.</b></p> <p>Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. Research shows that young people aged 16-25 with IBD who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. There is a clear associated “productivity loss” by health state, whereby the lowest score for health state (Visual Analogue Score 0-2.5) corresponds with a 71% productivity loss.<sup>36</sup> More recent research supports this.</p> <p>Emotional function is affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness, and fears of needing surgery or developing cancer.<sup>37</sup></p>
12	<p>A number of equalities issues were raised in evidence and discussed by the Committee such as:</p> <ul style="list-style-type: none"> <li>- sexual relationships</li> <li>- pregnancy</li> <li>- fecundity</li> </ul> <p>There are significant equality/diversity issues in terms of effectively compelling patients in this group to having surgery:</p> <ul style="list-style-type: none"> <li>• particularly for young people who have not begun a family and whose fertility may be affected,</li> <li>• and for religious groups such as Muslims, for whom this may impact on religious practices and cause distress.<sup>38</sup></li> </ul>

<sup>31</sup> Parray, F. Q. et al. Ulcerative colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63 (2012)

<sup>32</sup> IBDUK (2019) IBD Standards 2019 www.ibduk.org

<sup>33</sup> Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607.

<sup>34</sup> Ibid

<sup>35</sup> BSG guideline (2019)

<sup>36</sup> Gay M et al. Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK, 2011

<sup>37</sup> Cosnes J, Gowerrousseau C, Seksik P, and Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011; 140(6):1785–1794.

<sup>38</sup> [https://www.researchgate.net/publication/258203344\\_Quality\\_of\\_life\\_after\\_restorative\\_proctocolectomy\\_in\\_Muslim\\_patients](https://www.researchgate.net/publication/258203344_Quality_of_life_after_restorative_proctocolectomy_in_Muslim_patients)

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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	<p>We would ask the Committee to outline to what degree these issues have been taken into consideration when making their final decision.</p>
	<p>Patients have asked us to share the following experiences on their behalf:</p> <p><i>“I was diagnosed with Ulcerative Colitis in 2016. During the first year of treatment, I was given numerous types of drugs, some of which worked for a short amount of time, others for longer, but often my body would begin to react against them. During that first year, I was hospitalised four times due to the severity of the flare ups. Steroids helped to calm the symptoms, but as soon as the dosage was tapered, the flare ups returned. In hospital, the steroid injections were sometimes painful, sometimes distressing. I was given biological drugs for over a year. This entailed 6-weekly trips to hospital and the best part of day hooked up for an infusion. It left me feeling more fatigued than usual, but it seemed to work. Then blood tests revealed my body was reacting against the drug, so they were changed again. A constant has been immune suppressants, which seem to work well, but of course bring their own set of issues.</i></p> <p><i>I have developed side effects that have been worrying and caused even more stress, such as hair loss, joint pains, fatigue, onset of rashes and eczema. My body and face shape changed and I felt generally unwell. Living with UC is unpredictable and soul-destroying. It impacts on your daily life, especially during a flare up. It is messy, painful and depressing. Your life is on hold and all normality is replaced by a “new normal” of pain, distress and sickness. This is borne by sufferers as well as by relatives and friends.</i></p> <p><i>Hope of using a new drug can be a lifeline; something that gives an opportunity to start living life to the full again.”</i></p> <hr/> <p><i>“I was diagnosed with acute severe Ulcerative Colitis at the start of 2018. My condition arrived very suddenly and within three weeks of starting to notice symptoms I was hooked up to a steroid drip in hospital for a week. As I was currently pregnant, I was limited to taking 5ASAs and steroids. Despite taking high dose prednisolone for almost the entirety of my pregnancy, this did little to control my symptoms. I was severely anaemic and struggling to do day to day tasks because of the fatigue. I was visiting the toilet up to 20 times a day. Taking high dose steroids for this length of time was also very difficult - I experienced severe mood swings which were difficult to deal with for me and those around me.</i></p> <p><i>Following the birth of my son I was given the opportunity to start with adalimumab. Unfortunately, this was not successful in controlling my symptoms either and I had to remain on steroids. Following an arthritis diagnosis in 2019, I also started on methotrexate which finally started to control things. However, I have since experienced a further flare up and my consultant is reviewing my options, including possible surgery.</i></p> <p><i>It cannot be underestimated how important it is for patients to have a choice of drug treatments, especially where other initial drug choices have failed. Patients want to be able to continue their lives symptom free for as long as possible, so refusing to back a drug that has already been shown to be effective in some patients is really disappointing. I have one more drug choice left now and otherwise it will be surgery. For many reasons, patients should be able to put off surgery for as long as they can - the general risks associated with surgical procedures and anaesthetics are often forgotten, never mind the procedure specific issues that can occur with bowel surgery. The cost to the NHS of surgeries, hospital stays, and follow up treatments must be more than the possible cost of this drug being available to treat patients who have tried other drugs and whose only other option is surgery.</i></p> <p><i>I hope that, on the basis of the comments received from patients, NICE will reconsider its decision.”</i></p> <hr/>

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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*“Since 2018, I have had a huge flare up, I have taken long term prednisolone and mesalazine. I am a young mum to 4 young children, one of whom is severely disabled. My flare up stopped me from being a full-time carer to my son. My 8-year-old daughter made a comment to me that I was no longer a “proper” mummy anymore because I spent all my time in hospital or in bed or the toilet.*

*In October 2019, I had an emergency operation which resulted in an ileostomy being fitted because no meds were working even after long stints in hospital of IV hydrocortisone and infliximab. The steroids caused me to gain weight which have caused other medical complications and pains in my joints. As well as loss of appetite, I also have severe anxiety due to my looks now due to a massive weight gain. I have become isolated and really hidden myself away from society.”*

*“My daughter has colitis and this was a drug I was reading about only because my niece is on it for Crohn’s and is in remission , I have read some literature that supports this treatment and feel strongly that NICE review this decision.”*

*“I have suffered from ulcerative colitis for 4 years. After the failure of a number of conventional treatments (prednisone/azathioprine/mesalazine) I have been taking regular infusions of infliximab. Whilst this has shown some improvement in the condition, I still experience flare ups and struggle to control the condition on a regular basis. Oral steroid use causes many side effects and no longer brings about any substantial benefit for the condition. My consultant has suggested the next step may be surgery.”*

*“As a father with a young family, with two children under 4, and who works full time, the strain on my mental and physical health has been significant. Should the condition continue to worsen, and surgery be necessary, it is unlikely I would be able to carry on working and support my family adequately. The stress and worry of all of this has a huge impact on myself and my family every day.*

*Any possibility of alternative treatments would be welcome, and I would encourage the NICE panel to support those suffering with this condition by approving any new treatments.”*

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under **‘commercial in confidence’ in turquoise** and all information submitted under **‘academic in confidence’ in yellow**. If confidential information is submitted, please also send a 2<sup>nd</sup> version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> <li>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>[Insert organisation name]</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>[Insert disclosure here]</p>
<p><b>Name of commentator person completing form:</b></p>	<p>[Redacted]</p>
<p><b>Comment number</b></p>	<p style="text-align: center;"><b>Comments</b></p> <p style="text-align: center;">Insert each comment in a new row.</p>

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that .....
1	<p>The summary of the committee discussion notes that:</p> <p>“The patient expert explained that the experience of living with moderately to severely active ulcerative colitis varies on an individual level, but in their experience it is extremely challenging.”</p> <p>Whilst I agree that I did indicate that I found living with the condition extremely challenging, I would say that in its severe form, with the type of symptoms I described, ulcerative colitis can also be life-altering, i.e. ‘normal’ functioning ( socially, emotionally and economically) is on hold indefinitely. This is all encompassing and creates significant disability.</p> <p>With severe UC, a person’s entire life revolves around going to the toilet, pain and loss of function and the emotional impact is severe, frequently triggering anxiety and depression. With severe symptoms they will also be systemically unwell.</p> <p>I may have described going to work and leaving the house with severe symptoms, but I would counter that by explaining that I was doing so while in constant pain and distress, suffering fatigue, nausea, heart palpitations, shortness of breath walking from the station to my office and anxiety about the location of toilets.</p> <p>I continued to work whilst having over 20 bowel movements per day simply because I was worried about taking time off, I was committed to my job and because I saw no point in taking one or two days off when my condition had remained like this for months and would continue to do so without effective treatment ( I was on high doses of steroids and these were having no effect). I saw no end in sight and taking time off would not have helped me to get better in the same way it might help someone recover from a gastric bug.</p> <p>I would therefore disagree that the word “challenging” accurately describes the experience of living with moderate to severe ulcerative colitis. Perhaps alternatives might be something like “life-altering”, “disabling” or even “devastating”?</p>
2	<p>The summary also notes that:</p> <p>“They (the patient expert) commented that the effects of the disease and side effects of medication can be moderated, to an extent, by individual circumstances including a patient's support network and responsibilities.”</p> <p>I would like to point out that there may have been some misinterpretation of my comments in relation to the work I had been involved in, listening to the experiences of many people living with the condition around self-management and how they benefit from support networks to help manage their condition.</p> <p>Whilst a person living with quite severe disease can ‘self-manage’ with the right support in place, i.e. they can develop resilience and coping methods to help them tolerate certain symptoms or employ strategies such as avoiding social activities, taking adequate rest, relaxation techniques, working from home, mapping local toilets etc, the severity of their symptoms and their disease activity itself cannot be moderated without effective treatment.</p> <p>For a more in-depth understanding of the concept of self-management in Inflammatory Bowel Disease please see <a href="https://www.crohnsandcolitis.org.uk/improving-care-services/self-">https://www.crohnsandcolitis.org.uk/improving-care-services/self-</a></p>

**Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

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	<p><a href="#">management/self-management-position-statement</a></p> <p>Medical management of UC is only one component (but an essential one) of self-management, along with:</p> <ul style="list-style-type: none"> <li>-A responsive Inflammatory Bowel Disease service that is easy to access when needed</li> <li>-IBD services with resources to support self-management</li> <li>-IBD Health Care Professionals who are confident and knowledgeable about self-management</li> <li>-Good relationships between people with Crohn's and Colitis and Health Care Professionals</li> <li>-Good quality information and support for people with IBD to feel empowered and in control</li> <li>-Access to emotional and psychological support</li> <li>-Access to e-health and technology resources.</li> </ul> <p>Uncontrolled or poorly managed acute severe colitis is still a medical emergency requiring effective therapy or life-saving surgery regardless of whether these other factors are in place. It is NOT possible for the natural course of the disease or side effects of medication to be altered in any way by support networks or patients taking responsibility for their overall wellbeing or self-care.</p>
3	
4	
5	
6	

Insert extra rows as needed

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## Comments on the ACD received from the public through the NICE Website

Name	
<p data-bbox="252 434 587 463"><b>Comments on the ACD:</b></p> <p data-bbox="252 501 1203 566"><b>There is an unmet need for new treatments that reduce the need for corticosteroids or surgery.</b></p> <p data-bbox="252 602 1310 1099">The committee have made this statement about 'unmet need' and requiring new options however this NICE TAs remit will NOT help address this need. NICE TAs only consider recommendations within the medicines license (ustekinumab is licensed in patients that have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF<math>\alpha</math> antagonist or have medical contraindications to such therapies) yet the unmet need is outside of this ie following failure of 2nd or 3rd line treatments. This is where NICE should be focusing their attention as these are the situations seen in current UK clinical practice. Is there clinical evidence for using these biologics as 2/3/4 line options? What is the cost effectiveness of doing so? These are the very real difficulties commissioner and providers are trying to manage and currently there is a post code lottery as NICE is NOT making recommendations on current practice. National pathways are required as the RMOG guidance on the sequential use of biologics could create a huge cost pressure for the NHS and effectively weaken NICE TA recommendations.</p> <p data-bbox="252 1137 528 1167">1 Recommendations</p> <p data-bbox="252 1205 1326 1270">I assume the company will come back with a PAS price then this will be approved. However points to be made explicit in the final recommendations will be:</p> <p data-bbox="252 1270 740 1299">What is the starting/stopping criteria?</p> <p data-bbox="252 1299 1310 1328">Is the course of ustekinumab a planned course for 12 months the same as TNFi?</p> <p data-bbox="252 1328 1337 1393">Can it be used following failure of tofacitinib? or can tofacitinib be used following failure of ustekinumab?</p> <p data-bbox="252 1393 1337 1458">Can it be used following failure of vedolizumab? or can vedolizumab be used following failure of ustekinumab? etc.....</p> <p data-bbox="252 1458 1337 1487">Is dose escalation of ustekinumab within the cost analysis? If so how may doses?</p> <p data-bbox="252 1487 1337 1603">Is de-escalation an option prior to maintenance escalation dose? NICE TAs need to provide guidance on practical issues encountered by every CCG and provider nationally so these discussions and decisions are not a post code lottery.</p> <p data-bbox="252 1641 1337 1706"><b>The committee accepted the assumption that 30% of patients would have escalated doses of maintenance treatment</b></p> <p data-bbox="252 1744 1337 1939">Clarity on dose escalation is required and needs to be explicitly stated in TAs. Previous NICE TAs have not included dose escalation in the cost calculator yet when NICE are challenged as to whether it is a cost effective recommendation the response is it should be considered if clinically appropriate, this is not a cost evaluated answer. For expensive biologics such as vedolizumab and ustekinumab this is a significant cost pressure.</p> <p data-bbox="252 1977 1337 2042">I have numerous patients that have failed or are contraindicated for all other available treatments and are unsuitable for, or do not want surgery. Some patients</p>	

are not fit for surgery or have much higher risks due to age and/or comorbidities. Some are young men with fears of surgery causing erectile dysfunction, or young women with fears about fertility. Some patients are actually that terrified of surgery and or the idea of living with a stoma they would rather put up with the horrendous daily symptoms of uncontrolled disease.

The majority of hospitals have no psychological support for patients with IBD, or for patients that undergo surgery resulting in a stoma bag (temporarily or permanently), and this is a real issue in helping patients choose surgery as an option.

Until we can offer risk free surgery with psychological support **for everyone, the more medical options we can give patients, the better.**

### **Questions and Answers**

**Has all of the relevant evidence been taken into account?**

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

**Are the recommendations sound and a suitable basis for guidance to the NHS?**

No the remit does not reflect UK clinical practice where 2/3/4 line options are being requested.

Is escalated dose included if so full details, including cost analysis, are required.

No due to the above, in my opinion you are not thinking of the wider cost to the NHS.

**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternit**

<b>Name</b>	[REDACTED]
<b>Comments on the ACD:</b>	
<p><b>Has all of the relevant evidence been taken into account?</b>          Not fully, if you acknowledge that it is an effective drug then you're basing your decision on clinical cost rather than clinical response.</p>	
<p><b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b>          In my opinion no, you must think of the wider picture. I myself am a registered nurse living with Ulcerative Colitis (pan colitis) which I have had for the last 11 years. I'm now on the last drug I can try (Golimumab) which by lab tests and symptoms has shown to be not fully controlling my UC. As a result Ustekinumab would be my last option, without this as an option it would be a case of life changing surgery.</p> <p>If I have to have surgery this is going to mean a considerable amount of time off work, which is going to mean the NHS is paying me in sick pay, whilst having to pay another nurse (likely bank pay) to cover for the length of time I'd be off.</p> <p>Therefore in my opinion for every NHS worker with UC (and I know of many) think about the huge cost that will cost the NHS in surgery, stoma care and equipment, sick pay and additional staff pay that will cost vs cost of Ustekinumab.</p> <p>When I have costed it up from the figures available to me Ustekinumab isn't much more in cost than Vedolizumab and that requires nurses to infuse it, Ustekinumab can be given by the patients themselves at home after initial infusion.</p> <p>Therefore, at present I am unsure how you have come to the conclusion that cost is the main issue with it. I do understand however that the figures I have to hand may not be up to date.</p>	
<p><b>Are the recommendations sound and a suitable basis for guidance to the NHS?</b></p> <p>No due to the above, in my opinion you are not thinking of the wider cost to the NHS.</p>	
<p><b>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</b></p> <p>No</p>	

<b>Name</b>	
<b>Comments on the ACD:</b>	
<p>My friend's daughter says this product has given her life back. As a young mum she couldn't even take her daughter for a walk as she needed to be near a toilet and it got to the stage where she was told. Surgery was inevitable. She would have had an organ irreversibly removed without it and with this new treatment she had a dramatic change of life and the impact on her mental health and on her marriage was dramatic. With this option she not only has convenience herself but with self-injecting the NHS save on staff to visit her house, administer the jab, save costs for hospital staff doing infusions etc. Just basically it's an all-round good thing and well worth a try where things have failed and given the huge similarities between Crohn's and colitis it would probably save a few people from permanently changing their bodies. '</p>	

<b>Name</b>	
<b>Comments on the ACD:</b>	
<p>I have been diagnosed with ulcerative colitis [pan colitis] since 2012. All the drugs I have been subscribed have left me with muscle pain. Azathioprine affected my immune system so that I had to stop taking it after a while. I was then put on infliximab which is excellent at controlling symptoms of colitis but eventually caused symptoms of inflammatory arthritis in my legs and fingers and possibly elsewhere, I am still having investigations. I had to stop that one. I tell you this because those who cannot tolerate drugs need to know that there is hope of others that may work without those side effects. Ulcerative colitis is extremely difficult to live with and destructive of quality of life.</p>	

<b>Name</b>	
<b>Comments on the ACD:</b>	
<p>I am 29, with a good professional career in the City of London, and was diagnosed with ulcerative colitis in July 2019. Having been on steroids from that date until now, in combination with azathioprine, 5-ASAs, and recently Infliximab, my condition has only proceeded to deteriorate. I have been hospitalised for the past month and have had to stop working. The availability of alternative treatments for patients such as me who have not responded to a host of others is critical. Please reconsider this decision.</p>	

**Name**

**Comments on the ACD:**

I would like to highlight a few clinical practice observations as the clinical lead for large IBD unit in norther England. Treating moderate to severe UC remains a challenge and a significant proportion of patients fail to respond or lose response to currently available NICE endorsed therapies. While surgery is a good option many patients struggle to accept surgery and prefer medical treatments.

In general, we would not routinely stop therapy in moderate to severe colitis after 1 year. Many our patients have struggled to achieve remission and we would want to see prolonged and deep remission before considering discontinuation of biological agents and/or tofacitinib. We would apply the same principles to ustekinumab.

We see that many patients with UC lose response to infliximab over time and to a degree also with vedolizumab. These patients with secondary loss of response deserve a trial with a different mode of action biologic in our view. Ustekinumab should be available as one of those agents with a good efficacy and safety profile.

**Questions and Answers**

**Has all of the relevant evidence been taken into account?**

not sure on the model

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

I think the criticism of the model is out of line with clinical observations

Name	
<p><b>Comments on the ACD:</b></p> <ol style="list-style-type: none"> <li>1. <b>The committee lags behind with evidence, as abstracts submitted by various research teams at ECCO and DDW do not support this NICE recommendation</b></li> <li>3. <b>The committee has only looked at cost effectiveness and not at patient well being including the prospect of complications post colectomy. They are also not considering the use in Paediatrics, there has been a Porto study with over 100 patients that needs to be taken into account</b></li> </ol>	
<p><b>Questions and Answers</b></p> <p><b>Has all of the relevant evidence been taken into account?</b>  No, I do not believe that this has been the case, one trial is mentioned, has the committee looked at abstracts from ECCO, DDW, PIBD conferences?  As Paediatric Gastroenterologist, we need to be able to use medication as much as possible to avoid surgery</p> <p><b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b></p> <p>No, as not all published studies taken into consideration</p> <p><b>Are the recommendations sound and a suitable basis for guidance to the NHS?</b></p> <p>No, they are discriminating against patients' needs as funding is found to be more important</p> <p><b>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</b></p> <p>No consideration for children and also not all evidence used from recent conferences</p>	

<b>Name</b>	
<p><b>Comments on the ACD:</b></p> <p>As some-one with Ulcerative Colitis I cannot emphasise enough the difference that biologic drugs have made to my life. Before I was tired and ill most of the time and could not socialise very much and while I held a full time job it was not uncommon for me to be so tired from the illness that I may sleep immediately after work and not get up until it was time to goto work again 12 hours later. In between I had worries about 'accidents' at work or elsewhere and of course nearly constant pain, while it was usually a relief to sleep often I thought I was sleeping my life away. All I actually managed to do was work. I was hospitalised when my symptoms worsened and after I did not respond to IV steroids was given infliximab. Th e same day I was better I can only describe it like a light switch being turned on and straight away I had my life back, I could not only work but play tennis, socialise and even go on dates. In this period when I was healthy the best thing was to forget I had any chronic disease. In this period I met my wife. After around a year or year and a half I started getting ill again and the hospital determined that the Infliximab was no longer working. I was shortly given Vedulizimab and again this got me into remission very quickly and I could continue my life. I got married and my wife is now pregnant. I had thought long and hard about having a child, mostly because if I was ill and tired like I had been in the past I do not think I could care for it, however perhaps optimistically we took the plunge. Now I am healthy but am aware that in the 2 years since starting vedulizimab the first year I was completely symptom free and in this second year I have had increasing symptoms, the disease becomes active but only for very short periods less than 1 week and my quality of life is not generally affected. I would ask the committee to consider what will happen if/when vedulizimab stops working for me and other people in my condition. It sounds as if this new drug has some uncertainties but I would like to have the option to try it if there are no other biologic drugs available and hope the committee can see the difference it can make to my life. I am aware surgery may be an option but this fills me with dread and fear. I am also aware that it may not resolve my symptoms and further surgeries may be required. I would like to avoid that at all costs.</p>	

Name	
<b>Comments on the ACD:</b>	
<p data-bbox="252 300 1059 331"><b>Has all of the relevant evidence been taken into account?</b></p> <p data-bbox="252 333 1308 434">Have costs of surgery been considered (surgical follow up, appliances, stump surveillance, stoma care etc) and cost of psychological morbidity associated with surgery?</p> <p data-bbox="252 468 1155 533"><b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b></p> <p data-bbox="252 535 1310 701">There are flaws and inadequacies in the NMA and the cost-effective modelling. These are acknowledged in the summary document yet the decision not to recommend ustekinumab for use seems to have been heavily influenced by this evidence despite its inadequacies. Even so, the estimated range of efficacy does still seem to sit within the cost effective threshold criteria advocated by the NHS.</p> <p data-bbox="252 736 1331 1037">Ustekinumab has a novel mechanism of action which may offer a treatment option where other mechanisms of action have failed. Factors which may not have been appropriately considered include situations in which drug withdrawal can be achieved once durable remission is achieved (ie at annual review with monitoring of faecal calprotectin and disease activity scores). Ustekinumab has demonstrated good rates of sustainable treatment response in crohn's disease (most often in individuals who have already failed other biologic treatments) and it is logical to anticipate that good rates of sustainable treatment response will also be seen in Ulcerative colitis.</p> <p data-bbox="252 1072 1278 1137"><b>Are the recommendations sound and a suitable basis for guidance to the NHS?</b></p> <p data-bbox="252 1140 1339 1509">No. There is a clear need for a greater range of treatment options with different mechanisms of action in this debilitating and chronic condition. Currently available treatment options have high rates of primary and secondary treatment failure. Treatment failure can occur for many reasons, immuogenicity appears to be key. Evidence available to date suggests ustekinumab is less immunogenic and therefore response to treatment may be better and more durable for some patients. Other biologics (infliximab/adalimumab) often require co-prescription of immunomodulators eg thiopurine/MTX with associated costs of blood monitoring etc. Given the current limitations of the treatment armamentarium and the clinical trial and real world evidence available to date, Ustekinumab should be offered for use in the NHS as it fulfils a currently unmet need in ulcerative colitis</p>	

Name [REDACTED]

**Comments on the ACD:**

Many thanks to the committee for reading this response.  
I am a Gastroenterologist at St George's Hospital, and am CO-LEAD for the Inflammatory Bowel Disease services. Please kindly read the below, and I hope some of this information is useful when the re-appraisal for Ustekinumab is undertaken.

At present we have 3 classes of drugs after immunomodulator treatment for UC, anti-TNFs (infliximab, adalimumab, golimumab), a JAK inhibitor (tofacitinib) and a gut selective alpha-4 beta-7 inhibitor (vedoluzimab).

It could appear that this choice looks extensive, however still frequently there are patients who because of clinical reasons have only one real choice. In the last month, I have had 2 patients referred to my clinic with steroid dependant UC not responding to addition of immunomodulator. 1 was a young lady (29-years) on the combined contraceptive pill, with chronic herpes infection in both her eyes (already having caused partial loss of vision). After complex discussion of this patient on our multi-disciplinary team meeting, our consensus conclusion shared by all the physicians was she has 2 safe-choices; trail vedoluzimab with a steroid wean or opt to have a panproctocolectomy. Triple immunosuppression with infliximab, azathioprine, and temporarily high dose corticosteroids (with attempted wean) or Tofacitinib were considered too high risk with ongoing active herpes infection in the eye. Anti-TNF addition to steroids was deemed inappropriate as more than half patients on this in absence of additional immunomodulator therapy will not maintain response to this 1-year after starting this, and after 2-years, very few patients remain on anti-TNF monotherapy and potentially the severity of her UC could get worse if she developed non-response to this. The risks of prolonged high dose of steroids was also prohibitive because of the known complications of this approach (including worsening of the infection in her eyes). Ustekinumab if available would also have been deemed acceptable, as our preferred 1st line approach (and certainly if she had Crohn's, this would have been the case). In this specific situation, like vedoluzimab, it can be used without an immunomodulator and if there is an initial response, is very likely to allow the patient to wean off steroids, and maintain prolonged response as evidenced by the outcomes in the UNIFI clinical trials. My clinical experience with CD also gives me confidence a steroid wean would be quicker with Ustekinumab compared to vedoluzimab. For a patient like this, at present there is only one real biologic choice available at the NHS where risks are not prohibitive.

The second case is a man in his fifties presenting with high dose steroid dependant UC (25mg prednisolone), diabetes and subsequently his immunosuppressive screen also reveals a new diagnosis of latent TB and HIV. For an individual like this a quick acting single agent allowing a rapid steroid wean is the safest treatment. Monotherapy is specifically very important here both to avoid the interactions of polypharmacy, and to reduce the risks of other septic complications this gentleman is predisposed to. Furthermore, while he remains on steroids, he is also unfortunately requiring insulin to maintain adequate sugar control. In this case, again Ustekinumab if available would have been our preferred 1st line biologic. I highlight these cases as for patients like these who are at heightened risk of sepsis, there remains an unmet need for biologics with are potent, and have a minimal risk of infections.

**Furthermore, Ustekinumab has an excellent track record in Crohn's Disease. I would like to highlight a few of the strengths seen in the Crohn's trials;**

1. The rapid onset of action
2. The durability of the drug after initial response
3. Safety profile with respect to malignancy and cancer (also replicated in Psoriasis studies and real-life Psoriasis experience)
4. The major advantage when compared to anti-TNF that ustekinamab can be used as a monotherapy agent.
5. Once commenced, the high chance of a steroid wean for individuals who are steroid dependant

All the above were seen in the original UNITI / IMUNITI clinical trial programme and have been replicated in real clinical practice. I would like to highlight that all the above has been replicated in the UC UNIFI trial and there is no reason why it should not be replicated in real life. One specific strength of this treatment is the durability after initial response seen in the long-term extension of the clinical trial. To my knowledge, no other treatment has been able to replicate this. Also, please appreciate that because the chance of developing antibodies to ustekinamb is very low, once remission is induced, our practice would be to stop the biologic, and only re-intervene with treatment again if the patient was to flare. Unlike with anti-TNF treatment, we would not worry that an individual would be predisposed to antibody formation with this medication. Also, unlike with tofacitinib, a bridge to immunomodulator therapy where deemed necessary can be done with the safety of overlapping the treatments, not leaving an individual on no therapy as there is no washout required prior to starting the immunomodulator.

Please kindly review my comments. Many thanks for your time.

<b>Name</b>	[REDACTED]
<b>Comments on the ACD:</b>	
<p>The indication under review is ‘treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.’</p> <p>However, the recommendation does not include the full indication under review the part on ‘or have medical contraindication to such therapies’ has not been included. Was this intentional to leave this part of the indication out of the recommendation? Could this be reviewed so that the recommendation is in-line with the indication under review e.g. Ustekinumab is not recommended, within its marketing authorisation, for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or are contraindicated or the disease has responded inadequately or lost response to treatment.</p>	

<b>Name</b>	[REDACTED]
<b>Comments on the ACD:</b>	
<p>This is a disappointing outcome both for UC patients as well as the clinicians who care for them. There exists a clear unmet need in the management of UC (as evidenced by relatively static colectomy rates). I very much hope that an</p>	

agreement can be reached between Janssen and NICE for a price-point that will facilitate approval and allow access for patients who badly need new treatment options.

<b>Name</b>	██████████
<b>Comments on the ACD:</b>	
<b>Has all of the relevant evidence been taken into account?</b>	
<p>The interim decision made by NICE in respect of Ustekinumab is, sadly, grossly mistaken.</p> <p>Having been affected by colitis for more than 20 years, I enjoyed a prolonged period of remission for approximately 10 years after the 'correct' treatment plan was found for me, after trying several drugs which either did not work or did not suit me.</p> <p>Unfortunately, botched NHS appendicitis surgery rather brought that period of remission to an abrupt end.</p> <p>Suddenly, none of the treatments which had worked for me for over 10 years did work.</p> <p>Thankfully I hadn't tried all the treatments which had become available and approved by NICE in the 10 years of my remission.</p> <p>Having needed an extended period of high dose prednisolone, I am now being treated with adalimumab with mixed results. The prednisolone is a great short-term treatment but, for obvious reasons, cannot be prescribed long term. I am so grateful that new treatments had been approved during my period of remission and I was able to be prescribed Humira and then adalimumab; I dread to think of the state I would be in if that weren't the case.</p> <p>The decision to not approve Ustekinumab is plainly wrong for the following reasons:</p> <p>(a) There is no one-size-fits-all approach with colitis and a variety of treatments options are absolutely necessary. I know this from personal experience: azathioprine left me unable to climb stairs; Humira had zero effect on me (not even side effects); I suddenly, without warning, became intolerant to Asacol overnight. It would be amazing if there were one single drug which treated everybody's colitis and put them in remission - that just isn't the case and the availability of alternative treatments is absolutely vital;</p> <p>(b) NICE rightly examines the impact of the costs of a drug. Does it also (rightly) examine the costs of absenteeism from work and the loss to society as a whole by being desperately ill with colitis and unable to work? I am a solicitor. Since my colitis has flared after the botched appendicitis surgery, I had to give up my role as a very highly paid, senior director of legal affairs as I was simply too unwell to run my busy legal team within a highly thought-of private media company. I have not been able to work for nearly 2 years - what is the cost of that on the economy compared to potential successful treatment with Ustekinumab? Of course the cost of a new drug needs to be considered, but it absolutely must be considered within</p>	

the context of the cost of the consequences of not prescribing it and what impact that has on society as a whole, including non-financial consequences;

(c) Ustekinumab will be an alternative in the treatment plan for colitis. It will be used in place of another drug. Have the savings of not prescribing that other drug been fully taken into account or has the cost consideration of prescribing Ustekinumab only been considered as if it would be an additional cost burden, not an alternative cost to other treatment options?

(d) The NICE decision appears to be based on cost vs long term management of colitis. It's almost as if NICE is assuming that should Ustekinumab be approved for use on the NHS, every single gastro consultant and nurse throughout the country will immediately prescribe it to every patient diagnosed with colitis. That's clearly not going to happen. What does need to happen is that NICE properly approves Ustekinumab so that it can form another vital element of the armour in the treatment plan for colitis. As I've already mentioned, there is no one-size-fits-all approach for colitis (sadly), so let the consultants and nurses be able to prescribe Ustekinumab if and when it's actually appropriate. How can NICE deny a treatment that is proven to have some efficacy for certain people? Ustekinumab won't suit everyone, there will not suddenly be an enormous bill owing to every single colitis patient being erroneously prescribed Ustekinumab. Let the consultants and nurses be the judges of the suitability of Ustekinumab, not (forgive me) a committee far removed from the coal face of the clinical environment;

(e) For over 20 years no-one has quite worked out whether I do have colitis or Crohn's - limiting the approval of Ustekinumab to just Crohn's makes no sense. Both illnesses need to have as many interchangeable treatment plans as possible approved for use in order to enable consultants and nurses across the country to find the right treatment for each patient.

For the reasons set out above, I implore you to reconsider your interim decision and, instead, fully endorse and approve Ustekinumab to be prescribed as and when the expertise of the gastro consultants and nurses deem it a suitable treatment option.

Kind regards.

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

**As above**

**Are the recommendations sound and a suitable basis for guidance to the NHS?**

**As above**

**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

**As above**

<b>Name</b>	[REDACTED]
<b>Comments on the ACD:</b>	
<b>Has all of the relevant evidence been taken into account?</b>	
<p>I do not think all the relevant evidence has been taken into account. in particular, the likelihood of persistent response and remission which is likely with ustekinumab as evidenced in the Crohn`s disease studies has not been taken into account.</p> <p>The safety data is not fully appreciated</p>	
<b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b>	
<p>I think a number of aspects needs further exploration. the use of S/C injection will have direct and indirect savings and save resources to already overstretched infusion units.</p> <p>In addition there is chance that patients who achive sustained mucosal healing ustekinumab may be able to be withdrawn</p>	
<b>Are the recommendations sound and a suitable basis for guidance to the NHS?</b>	
<p>In my opinion Ustekinumab needs to be in the armamentarium of agents for UC. This is particularly relevant when taking co-morbidity into question such as in patients who are older age and have co-morbidities which may make use of anti TNF relatively contraindicated</p>	

<b>Name</b>	[REDACTED]
<b>Comments on the ACD:</b>	
<b>Has all of the relevant evidence been taken into account?</b>	
<p>Yes</p>	
<b>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</b>	
<p>I agree that the indirect cost comparisons to adalimumab are a bit tenuous, but the comparisons to placebo are relevant</p>	
<b>Are the recommendations sound and a suitable basis for guidance to the NHS?</b>	
<p>Yes</p>	
<b>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</b>	
<p>No</p>	

Name

**Comments on the ACD:**

**Response rates and remission rates are uncertain for patients with disease that does not respond or loses response to initial therapy.**

I would absolutely agree with this. The initial ERG assumption seems to be based upon historic data suggesting that patients with UC may indeed experience spontaneous remission - this may be true of a general UC population, but when taking a population enriched for refractory disease as a result of active disease despite multiple previous treatment attempts, the expectation of spontaneous remission would be close to 0%.

**The maintenance-phase NMAs are uncertain but provide more robust estimates of relative effectiveness than the company's unadjusted indirect treatment comparison (ITC)**

**Selected text:**

**The company asserted that drug half-life is a cause of the continuing effects of induction treatment being observed during the maintenance phase. But evidence provided by a comparator company suggests there is no correlation between drug half-life and placebo-arm response rates.**

I appreciate the difficulty of interpretation here, but I would respectfully suggest that there is a lack of evidence to support either position - and further more that neither position really matters. What is clear (and what we have known since initial trials of episodic usage of infliximab back in the 1990s) is that there will be patients where a short course of induction therapy can induce a temporary state of remission without necessarily the need for ongoing dosing. However, the duration of this period of remission and the predictors of who will flare and when are absolutely lacking across all drugs in this area, and hence there is now standard acceptance of scheduled maintenance treatment as being appropriate in all responders. The fact that some responder patients re-randomised to placebo did not flare straight away in the IM-UNITI studies should not be used to infer that maintenance treatment with UST is not appropriate in initial treatment responders.

**The utility values are uncertain and the choice of inputs has a large effect on the cost-effectiveness estimates**

The committee is absolutely right to recognise the limitations of the data used from Woehl et al (that were only ever published in abstract form). There is an urgent need to generate better utility data in this condition. There is a delicate balance to be struck, however, when considering that NICE have indeed previously allowed economic appraisals (with very large confidence intervals) based upon these data for drugs that are used to good effect within the NHS - but that, nevertheless, as already highlighted, these drugs are not universally effective and indeed may be inferior in terms of efficacy on indirect comparisons. It would seem inconsistent of NICE to adopt this approach without asking for revised health-care related quality of life data for other drugs already approved.

Specifically, I note that a model based upon Woehl was allowed in the STA for Vedolizumab in UC, but health-care related quality of life data were available from the GEMINI 1 trial that were not used or requested (subsequently published as *Aliment Pharmacol Ther.* 2017 Jan;45(2):264-275 - the committee may find review of these data of interest.

## **Questions and Answers**

### **Has all of the relevant evidence been taken into account?**

It appears that the committee has not considered one recent NMA published by a highly respected independent group. I strongly suggest the committee review Singh et al, published in the peer reviewed literature in *Clinical Gastroenterology and Hepatology* in January 2020 (DOI <https://doi.org/10.1016/j.cgh.2020.01.008>). In this NMA in patients with prior biologic exposure ustekinumab and tofacitinib were ranked highest for use after anti-TNF therapy in ulcerative colitis for induction of clinical remission and were superior to vedolizumab (Odds ratio for UST vs VDZ 5.99 95% CI 1.13-31.76) and superior to adalimumab (Odds ratio for UST vs ADA 10.71 95% CI 2.01-57.20). At same time, during maintenance trials, vedolizumab had the lowest risk of infection.

Taken together this NMA highlights that ustekinumab may represent a valuable addition to the therapeutic option with indirect evidence of potentially superior efficacy. The complexity of balancing efficacy and side effect profiles is also highlighted - further supporting the need for additional treatment options in this patient population, to include ustekinumab.

### **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Please see my particular comment regarding the determining the healthcare related quality of life utility of this drug in the context of the data from Woehl et al, but also the need for consideration of similar approaches which have previously been permitted by NICE despite the availability of better validated health utility data for other drugs.

<b>Name</b>	[REDACTED]
<p><b>Comments on the ACD:</b></p> <p>I have numerous patients that have failed or are contraindicated for all other available treatments and are unsuitable for, or do not want surgery. Some patients are not fit for surgery or have much higher risks due to age and/or comorbidities. Some are young men with fears of surgery causing erectile dysfunction, or young women with fears about fertility. Some patients are actually that terrified of surgery and or the idea of living with a stoma they would rather put up with the horrendous daily symptoms of uncontrolled disease.</p> <p>The majority of hospitals have no psychological support for patients with IBD, or for patients that undergo surgery resulting in a stoma bag (temporarily or permanently), and this is a real issue in helping patients choose surgery as an option.</p> <p>Until we can offer risk free surgery with psychological support for everyone, the more medical options we can give patients, the better.</p>	

# **Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]**

## **ERG comments on the company's response to the Appraisal Consultation Document**

**Produced by** Southampton Health Technology Assessments Centre

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**Date completed** 21<sup>st</sup> February 2020

## **Section 1. Ustekinumab is a cost-effective use of NHS resources when decision rules consistent with previous NICE Appraisal Committee decision making are applied**

### **1.1 The committee's decision making is inconsistent with previous NICE appraisals in UC – ustekinumab is cost-effective vs CT**

The company express concerns regarding how the Appraisal Committee have applied resource allocation decision rules in this appraisal, arguing that this is inconsistent with previous decision making in UC, and immunology appraisals more generally. The company state that “fully incremental analyses have not been utilised for decision-making in previous UC NICE appraisals (TA329 and TA342)”. They note that in particular that in TA329, the Committee concluded that all three anti-TNFs could be considered cost-effective, despite two of the anti-TNFs being dominated or extendedly dominated, and despite the fact that all three anti-TNFs had pair-wise ICERs versus CT exceeding £50,000 per QALY gained using the Assessment Group's base-case results.

#### **ERG response:**

Incremental analysis is a fundamental element of economic evaluation. It is not an academic nicety or procedural convention but a basic requirement to obtain good value for limited NHS resources. However, incremental analysis does have to be applied in the context of judgements about the relevance of comparators for the populations of interest and uncertainties and potential biases in the evidence base and cost-effectiveness model. It is therefore important to understand the reasons underlying committee decision-making in previous NICE appraisals.

With regard to previous NICE appraisals for ulcerative colitis, we suggest that it is not that fully incremental analyses have not been utilised, but that that judgement has been applied in their interpretation. For example, in TA329 discussion of extended dominance shows that incremental analysis must have been considered. However, the Committee chose not to distinguish between the TNF-alpha inhibitors due to uncertainty in the results of the network meta-analysis and shortcomings of the cost-effectiveness models. Similarly, in TA342, the Committee applied judgement to allow for uncertainties over the utilities, costs of surgery and post-surgery care and the impact of a stopping rule. Furthermore, we note that the company do not cite the example of TA547 (tofacitinib), in which it is clear from the guidance that both fully incremental and pairwise analyses were submitted and there is discussion of ICERs relative to all comparators in the Committee's considerations.

## **1.2 Fully incremental analyses are uncertain; a cost-comparison to vedolizumab is appropriate for the Committee to consider**

The company state that reliance on pair-wise comparisons to make decisions in previous NICE appraisals of biologics is due to a large degree to the uncertainty produced in fully incremental analyses, which results from relative treatment effects derived in network meta-analyses. They go on to say that as relative effectiveness estimates between comparators are somewhat uncertain, it is more appropriate to consider the pair-wise ICERs for ustekinumab versus CT.

### **ERG response:**

When incremental and pairwise analyses are both informed by NMAs with inherent uncertainty (due to differences in trial design, data imputation, assumptions and/or data that cannot all be validated), then the results of both the incremental and pairwise analyses are uncertain.

We agree that using direct trial head-to-head comparisons could reduce uncertainty in pairwise comparisons and that the only direct comparison available for ustekinumab is against conventional therapy (CT). However, we suggest that CT is not the most relevant comparator. The market share data shows that TNF inhibitors still predominate for this indication. Advice to the ERG is that biologic treatment is routinely initiated with a TNF inhibitor and other treatments will usually only be used after failure of one or more TNF inhibitor. This is unlikely to change in the absence of clear evidence of superiority for alternative biologics and the availability of low-cost infliximab and adalimumab biosimilars.

We report both fully incremental and pairwise cost-effectiveness results (ustekinumab versus comparators), including all agreed commercial arrangements and price discounts in a confidential addendum (ERG Comparator PAS addendum 4). Tables 2 to 9 report results for the biologic-failure and non-biologic failure subgroups under the four 'key scenarios' requested in the ACD (permutations of the 2 maintenance phase NMAs and 0%/ 1% response and remission rate after initial treatment failure). Tables 10 and 11 also show pairwise comparisons for these scenarios with alternative sources of utility estimates.

The company state that, in order to "pragmatically address" the uncertainty in cost-effectiveness analyses noted in the ACD, a simple cost-comparison against vedolizumab

should be considered. They argue that this is the appropriate comparator as it is the treatment that ustekinumab would most likely displace in the NHS: because vedolizumab has the largest market share after the TNF inhibitors and because it is the only comparator to have shown head-to-head superiority against a TNF inhibitor (in the VARSITY trial). They also argue that tofacitinib is not such a relevant comparator due to emergent safety concerns “meaning it is not suitable for some patients”.

**ERG response:**

We do not agree that this cost-comparison approach reduces uncertainty: it merely ignores it. The uncertainty remains because (i) assessment of whether ustekinumab provides “*similar or greater health benefits*” can only be made using one of the existing maintenance NMA analyses (both subject to uncertainty); and (ii) the direct data for vedolizumab compared with adalimumab cannot be scrutinised since the only sources available are two brief abstracts reporting the VARSITY trial (references 25 and 45 in the ERG report).

We also question whether the criteria for a cost comparison are met, and if so, whether the comparison with vedolizumab alone is appropriate. The cost-comparison addendum to the NICE Guide to the methods of technology appraisal states:

*“A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.”* (Paragraph 1.2)

And:

*“For the acceptance of a cost comparison case, evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes, must be presented in the company’s evidence submission.”* (Paragraph 2.5)

We note the plural ‘technologies’. This raises the question of whether other comparators should be retained.

- TNF-inhibitors are routinely used for initiation of biologic treatment and so are an important and relevant comparator for NHS practice. In the company’s updated base case model and all permutations of scenarios requested in the ACD (ERG cPAS addendum Tables 10 and 11), pairwise ICERs for

ustekinumab compared with the cheapest available biosimilar TNF-inhibitor are above £30,000 per QALY.

- There are safety questions for tofacitinib, but if this remains a treatment option for some patients, tofacitinib may also be a relevant comparator. In the company's updated base case and key scenarios, the ICERs for ustekinumab versus tofacitinib are all above £30,000 per QALY threshold (or ustekinumab is dominated by tofacitinib, or less costly and less effective with an ICER below £30,000 per QALY).

The company have provided an analysis of usekinumab compared to vedolizumab which they refer to as a cost-comparison analysis (Company response Table 1).

**ERG response:**

The reported analysis in Company Response Table 1 and 2 are basic budget impact analysis. We report cost-effectiveness results for ustekinumab compared with vedolizumab in ERG cPAS addendum 4 Tables 12 to 15. These show results for the four key scenarios requested in the ACD and with alternative utility sources (Woehl et al. and UNIFI). In most scenarios, estimated QALYs are greater for ustekinumab than for vedolizumab. The only exceptions are in the biologic failure subgroup with the maintenance-only NMA, in which modelled QALYs for vedolizumab are slightly higher than those for ustekinumab. Modelled cost differences are shown in the ERG addendum.

### **1.3 The updated base-case demonstrates that ustekinumab is cost-effective and that cost-effectiveness estimates are conservative for ustekinumab**

In response to the ACD the company updated their base-case model to reflect the Committee's preference for modelling long-term outcomes via a NMA (as opposed to the "direct trial" unadjusted ITC), with the following assumptions:

- modelled relative effectiveness in maintenance from the Company NMA
- 0% rate for spontaneous remission and response
- utility values from Woehl et al.

The company report ICERs for ustekinumab compared with conventional therapy for this updated base case in Company ACD Response Table 3. They also report results for one scenario, with 1% response/ remission rate after initial treatment failure. They argue that as these ICERs are all below £30,000 per QALY, this means that ustekinumab is a cost-effective use of NHS resources, and cite a number of reasons why they believe this scenario is conservative.

#### **ERG response:**

See Table 1 below for ERG estimates of ICERs for ustekinumab compared with conventional therapy under a wider range of scenarios: including the alternative maintenance phase NMA and different sources of utility estimates.

There appears to be a reporting error in the company's table: we estimate an ICER of £29,920 for the 1% response/remission rate scenario in the biologic-failure subgroup (rather than £29,290, as in company response Table 3).

ICERs are higher in scenarios with the maintenance-only NMA and with different sources for utility estimates (see section 02.2 below).

We do not consider conventional therapy to be the most relevant comparator for ustekinumab. Results versus other comparators are reported in the ERG cPAS Addendum.

**Table 1 ICERs for ustekinumab versus comparator by key scenario and utility source (CMU arrangement for ustekinumab)**

Key scenario (NMA, % in response or remission after initial treatment failure)	Non biologic failure	Biologic failure
<b>Woehl et al. (2008)</b> utilities: remission 0.87, response 0.76, active 0.41		
1 (1-year NMA, 0% res/rem)	£24,849	£28,348
2 (1-year NMA, 1% res/rem)	£26,359	£29,920
3 (maintenance-only NMA, 0% res/rem)	£29,681	£33,624
4 (maintenance-only NMA, 1% res/rem)	£31,512	£35,512
<b>Swinburn et al. (2012)</b> utilities: remission 0.91, response 0.80, active 0.55		
1 (1-year NMA, 0% res/rem)	£32,664	£37,722
2 (1-year NMA, 1% res/rem)	£34,617	£39,758
3 (maintenance-only NMA, 0% res/rem)	£39,349	£44,860
4 (maintenance-only NMA, 1% res/rem)	£41,757	£47,316
<b>Vaizey et al. (2013)</b> utilities: remission 0.86, response 0.77, active 0.66		
1 (1-year NMA, 0% res/rem)	£54,026	£64,079
2 (1-year NMA, 1% res/rem)	£57,148	£67,329
3 (maintenance-only NMA, 0% res/rem)	£66,291	£76,663
4 (maintenance-only NMA, 1% res/rem)	£70,274	£80,622
<b>UNIFI trial (CS 2019)</b> utilities: remission █████, response █████, active █████		
1 (1-year NMA, 0% res/rem)	£82,643	£93,836
2 (1-year NMA, 1% res/rem)	£87,665	£99,029
3 (maintenance-only NMA, 0% res/rem)	£98,424	£110,804
4 (maintenance-only NMA, 1% res/rem)	£104,490	£116,992

### **1.3.1 The committee should consider stopping rules when assessing cost-effectiveness in ulcerative colitis to be consistent with previous NICE decision making**

The company have requested that NICE consider whether a stopping rule would be appropriate. They provide illustrative data on how different stopping rules would impact on ICERs (Company Response Tables 4 and 5).

#### **ERG response:**

TA329 and TA342 guidance do include 'stopping rule' criteria, including an assessment of response a tone year, continuation only if there is clear evidence of benefit and consideration of withdrawal for patients in stable or complete remission. These criteria appear to have been inherited from NICE guidance for TNF-inhibitors for Crohn's disease, rather than modelled cost-effectiveness for UC. The more recent TA547 (tofacitinib for UC), did not include a stopping rule. Clinical experts consulted by the ERG reported variation in practice regarding an annual trial of withdrawal for patients in remission: with one saying that this would be unusual and stopping treatment in this situation would be difficult; and the other saying that a one-year treatment plan is routine.

We question the validity of the company's modelled stopping rule scenarios – the method of implementation and assumptions are not described or justified in the company's submission or response to technical engagement.

- Inspection of the model shows that the stopping rule is applied to patients with a sustained response (with or without remission) at the defined assessment time. But TA329 and TA342 stopping criteria only apply to patients in sustained remission.
- It is not clear if the estimated rates of loss of response after treatment withdrawal are realistic. In the analyses presented in the Company ACD response, these are inferred from trial data on the proportion of induction responders re-randomised to placebo who were in response or remission at the end of the maintenance trial (ustekinumab, golimumab, vedolizumab and tofacitinib only). For ustekinumab the proportions of induction responders re-randomised to placebo in response at the end of maintenance were: 50.6% for patients not previously exposed to a biologic; and 38.6% for patients with prior biologic treatment.

## **Section 2. Additional evidence provides greater certainty on the long-term effectiveness of ustekinumab**

### **2.1 The Committee has not considered all of the relevant evidence in reaching its conclusions on comparative effectiveness**

#### **2.1.1 The Committee should reconsider that both the ERG and the Company prefer the Company NMA to the ERG NMA**

The company refer to several limitations of the ERG maintenance-only NMA, as set out in points numbered 1 to 3 in their Response to the ACD:

##### *1. The ERG NMA violates the similarity assumption required to conduct NMAs.*

The company refer to the CS, [Document B, pages 83-84], stating that the chi-squared test of re-randomised maintenance placebo arms show that these maintenance placebo arms are statistically significantly different. As a result, to assume that they are similar is factually inaccurate. The similarity assumption required to conduct a NMA does not hold in light of the fact that response and remission rates in maintenance placebo arms are statistically significantly different. Therefore, we believe it is not appropriate to conduct such an NMA, as a core assumption is violated. Results should be viewed with caution and we do not believe they provide reliable treatment effects estimates of maintenance outcomes due to the differences in placebo rates.

##### **ERG response:**

The ERG has already responded to this point, as raised by the company at the Factual Accuracy Check stage of the appraisal. The assumption underlying the ERG “scenario” was that the placebo arms were equivalent, subject to normal heterogeneity. That is, that there was no differential carry-over effect between treatments (the ERG concedes this is an unlikely scenario but was conducted for illustrative purposes). Therefore, under this “assumption” we believe the analysis is justified.

##### *2. The data inputs for the ERG NMA and its application in the model are inaccurate*

*The company* comment that the ERG NMA includes data from both the ustekinumab doses in induction – the 130 mg dose (unlicensed) and the ~6 mg/kg dose (licensed). The company claim that this is conservative against the effectiveness of ustekinumab because

the ~6 mg/kg dose achieved better remission and response outcomes in both the induction and maintenance study.

**ERG response:**

The ustekinumab maintenance outcome data reported in the CS combines induction doses. We have been unable to find maintenance outcomes data reported by 6mg/kg and 130mg induction doses, either in the CS documents or the CSR, to enable us rerun the ERG NMA. If the Company can provide these data, the ERG can rerun the maintenance ERG scenario.

In addition, the CSR notes:

*With regard to subgroup analyses by induction treatment received, the maintenance treatment effects were generally consistent with those of the primary analysis population for all induction treatments (ustekinumab ~6 mg/kg IV, 130 mg IV, or placebo IV → ~6 mg/kg IV). However, there is some suggestion of a lower maintenance treatment effect (particularly for the q12w regimen) for subjects who had received the 130 mg IV induction treatment or the placebo IV → ~6 mg/kg IV induction treatment. This finding may be due to the variability in treatment effect estimates, as these analyses are based on relatively small subgroups (about 45-70 subjects per group) of the primary analysis population. (CSR, section 6.2.1.2)*

This would appear to be at odds with the Company's claim in their ACD response that the 6mg/kg dose achieved better outcomes in maintenance compared to the 130mg dose. Again, we were unable to find these outcomes reported in the CSR to support the argument of a lower maintenance treatment effect in the 130mg induction patients.

**3. The ERG NMA has not been incorporated appropriately in the economic model**

The company comment that when the ERG NMA is applied in the model, the odds ratios from each treatment versus the re-randomised placebo are applied in the model to predict long-term outcomes in maintenance. However, the application of these odds ratios in the model is in fact in relation to a common placebo-placebo arm baseline effect, as used in the Company NMA. The placebo-placebo arm baseline effect is substantially lower than the re-randomised placebo arm effects, and so the odds ratios from the ERG NMA are not being applied appropriately in the model. This leads to the underestimation of all treatment effectiveness in maintenance. The company also say that because the Induction NMA appropriately uses only the licensed ~6 mg/kg induction dose for ustekinumab, the

application of the ERG NMA in the model is at odds with the induction modelling approach applied.

**ERG response:**

The CT arm in the model should reflect real-world outcomes with conventional treatment through both 'induction' and 'maintenance' phases (CT-CT), alongside active treatment arms (with continuation after induction period only for responders). In our scenario, the odds ratios from the maintenance-only NMA are to the maintenance period. Given the assumption underlying the ERG maintenance-only NMA scenario that the placebo arms were equivalent, subject to normal heterogeneity but with no differential carry-over effect between treatments, a baseline comparator of placebo-placebo is valid as a proxy for CT-CT. A better baseline for both NMA analyses would be a real-world measure of CT-CT.

**2.1.2 The Committee should reconsider the Company base-case NMA – the 1 year NMA**

The company state that their preference for comparative effectiveness analyses is to use their 1-year NMA, since it explicitly includes both initial and delayed induction responders. However, they state that because this 1-year NMA assesses outcomes at the end of one year of treatment it cannot be incorporated into the economic model. This is because the economic model appropriately reflects SmPC indication wording for all comparators that if a response is not achieved after early or delayed induction then treatment should not continue. Nevertheless, the company believe that the 1-year NMA provides the most complete and comprehensive evidence base for the Committee to consider the relative effectiveness of treatments over both induction and maintenance.

**ERG response:**

The fact remains that the 1-year NMA cannot be used to inform the model because it compares placebo-placebo with active-active, which does not reflect real-world practice.

### **2.1.3 Comparison to other evidence on the long-term effectiveness of ustekinumab**

The company have requested that the long-term extension (LTE) data from UNIFI, as well as long-term data on ustekinumab in psoriasis and Crohn's disease (CD), are considered to inform conclusions on the long-term effectiveness of ustekinumab, as set out in sections 2.1.3.1 to 2.1.3.4 below.

#### *2.1.3.1 Ustekinumab Long-Term Extension data from UNIFI*

The company have provided partial Mayo remission rates from the UNIFI LTE study in Company Response Figure 1. The company comment that the partial Mayo remission scores are maintained through a further year of treatment (up to week 92), suggesting that both the company and ERG NMAs underestimate the treatment effect of ustekinumab.

#### **ERG response:**

As stated in ERG report section 3.1.3.5 the company have not reported any methods for their long-term extension (LTE) study and therefore we cannot comment on the validity of the LTE study results. We note that the proportions of patients in long-term partial Mayo remission at weeks 0-44 in Company Response Figure 1 are higher than those reported in CS Figure 24.

#### *2.1.3.2 Ustekinumab real-world data in psoriasis*

Company Response Figure 2 displays data from the BADBIR register in psoriasis to show the proportions of patients remaining on therapy up to 3 years for ustekinumab, adalimumab, and infliximab. The company argue that these data demonstrate that there are minimal discontinuations of ustekinumab in a real-world setting, with approximately 80% of patients still on ustekinumab at 2 years. Company Response Appendix 3 also provides data from the DERMBIO registry showing rates of discontinuation due to any cause or due to lack of efficacy up to 125 months which indicate that ustekinumab had higher drug survival and lower risk of discontinuation than adalimumab.

#### **ERG response:**

Psoriasis and ulcerative colitis are very different conditions that might have different issues relating to patient compliance. And as noted in ERG report section 3.3.7.3 the dose of ustekinumab in psoriasis may be lower than that used for UC. We are therefore uncertain whether the psoriasis drug survival rate comparisons in Company Response Figure 2 are transferrable to a UC population.

### *2.1.3.3 Ustekinumab real-world data in CD*

Company Response Figure 3 displays data showing the percentage of patients on ustekinumab treatment up to 144 weeks, based on sales data for over 1,700 patients with CD reformatted to enable Kaplan-Meier analysis (explained briefly in Company Response Appendix 4). The company argue that these data suggest that the treatment effect observed in clinical trials for ustekinumab in CD (IM-UNITI) is replicable in the UK practice, in terms of time on treatment as a proxy for treatment effect.

#### **ERG response:**

We are unclear about the validity of using long-term data for CD as a proxy for long-term data for UC, given the differing characteristics of the conditions.

### *2.1.3.4 Comparison of modelled outcomes versus long-term data*

Company Response Table 6 compares outcomes for model predictions from the company NMA and ERG maintenance-only NMA against long-term data at the end of years 1 and 2 from UNIFI and CD. The company argue that the model predictions from both the company and ERG NMAs underestimate the effectiveness of ustekinumab.

#### **ERG response:**

It is unclear in Company Response Table 6 which outcome is being referred to. The 1-year data reported in the table (81.5% for non-biologic failure and 71.3% for biologic failure) do not match the partial Mayo remission data shown in Company Response Figure 1. The source of CD data in Company Response Table 6 is not stated.

## **2.2 The committee's conclusions about health-related quality of life are inconsistent with previous decision making and do not reflect the impact UC has on patients**

The company raise concerns about the modelling of utilities, in particular the sources of utility data (UNIFI versus Woehl et al) (sections 2.2.1 to 2.2.7 below).

- 1) The utility values from UNIFI for the active UC health state do not align with the published utility values or the patient expert's experience of the disease
- 2) The active UC health state in the model does not align with the definition of active UC in the trial
- 3) EQ-5D collected at multiple timepoints for the same patient resulting in correlation bias
- 4) Clinical assessments (Total or Partial Mayo) were sometimes at different timepoints to EQ-5D collection timepoints
- 5) With a chronic disease such as UC there is potential for patients to adapt to the disease, skewing scores upwards (e.g. usual activities domain)
- 6) Selection bias means that patients feeling too unwell will not fill in the EQ-5D
- 7) EQ-5D-5L was collected, and not 3L, therefore there is some potential for the new levels to skew results

### **ERG response:**

We agree with all these points. The company could have done a better job at analysing the trial EQ-5D data: adjusting for repeated measures (point 3). Some problems are unavoidable given the trial design: treatment crossover (point 2); timing of response and quality of life assessment (point 4). And some problems are universal: non-randomness of missing data (point 6); and adaptation for patients with a chronic disease (point 5). Although the latter is less of an issue when health state valuations are obtained from a general population sample (as with the EQ-5D). The use of 'cross-walk' valuations for the EQ-5D-5L is now common in NICE appraisals, and consistent with NICE guidance.

Nevertheless, the above arguments do not negate the methodological and reporting deficiencies with the Woehl et al. study, which is only reported in abstract form and does not specify how and when the patients were recruited. It is impossible to assess how

representative they are of the population of interest in this appraisal. It is also unclear the severity assessment (based on the SCCAI) relates to trial-based Mayo or partial-Mayo classification of response and remission.

Uncertainty over utilities have been extensively discussed in previous NICE appraisals for ulcerative colitis (see Table 2 below). Swinburn et al. (2012) was used for scenario analysis in all previous UC appraisals, and was judged equally plausible as Woehl et al. in TA329 and TA342. The Assessment Group for TA329 also cited a UK study by Vaizey et al. (2013), which was not used because it did not report post-surgery outcomes (Archer et al. HTA 2016). We consider that there is no real basis to distinguish between the Woehl, Swinburn and Vaizey studies in terms of methodological or reporting quality, generalisability of the results or applicability to the current decision problem.

As illustrated in Table 1 above, cost-effectiveness for ustekinumab is very sensitive to the source of utility for the three pre-surgery health states. This is due to the wide variation in the estimates for the 'Active UC' (moderate/severe) health state: with the decrement versus the 'Remission' (mild) state ranging from 0.46 in Woehl down to 0.20 in Vaizey and 0.12 in the UNIFI analysis. This parameter is particularly influential because of the large proportion of time spent with 'Active UC' after failure of the initial treatment option in the ustekinumab model (see Table 3 and Table 4 below).

Differences in the Active UC utility estimates may be a function of the population recruited to the different studies and/or to the timing of when the EQ-5D assessment is made. If the severity of symptoms with moderately/severely active UC fluctuate, then one would expect utility to be worse for patients recruited following a hospital consultation for a disease flare and better when utility is assessed at fixed time points in a clinical trial setting.

This leaves the question of which set of utility estimates is most appropriate for use in the model. We note the company's definition of the 'Active UC' health state after the initial treatment failure as "a health state where no further biologic treatment would be given" where "patients remain until they receive surgery or die". The Committee decision to apply a 0% or 1% rate of response/remission from this state supports this view. We contend that it also has implications for the utility that should be applied to the Active UC state: it should reflect an average utility over a long period of time rather than a point estimate taken

**Table 2 Alternative sources for health state utility estimates**

					<i>Health state, utility (decrement vs. Remission)</i>					
					Remission	Response (without remission)	Active UC	Surgery (6 months)	Post surgery	Post surgery complications
<i>n</i>	<i>Setting</i>	<i>Utility</i>	<i>Severity</i>							
<b>Sources of utility estimates</b>										
Woehl 2008	180	UK	EQ5D	SCCAI	0.87	0.76 (0.11)	0.41 (0.46)		0.715	
Swinburn 2012	230	UK	EQ5D	pMayo	0.91	0.80 (0.11)	0.55 (0.36)		0.59	
Vaizey 2013	173	UK	EQ5D	pMayo	0.86	0.77 (0.09)	0.66 (0.20)			
UNIFI 2019		■	■	■	■	■	■			
Arseneau 2006	48	US	TTO		0.79		0.32	0.614		0.34
<b>Values used in TA models</b>										
<b>Ustekinumab</b> (company base case)					0.87	0.76	0.41	0.614	0.715	0.34
<b>TA329</b> Infliximab, adalimumab & golimumab					Woehl & Swinburn uncertain but most relevant evidence (4.72). Woehl likely to have overestimated value for post-surgery (4.73).					
<b>TA342</b> Vedolizumab					Committee preferred utilities from literature to trial based utilities (GEMINI). Woehl may not fully capture lifelong effect of surgery. Swinburn estimates equally valid (4.14, 4.17 & 4.18).					
<b>TA547</b> Tofacitinib					Committee considered utility values from Weohl et al. appropriate and consistent with previous appraisals (3.9). Trial based estimates not reliable because OCTAVE was re-randomised.					

IBDQ; SCCAI Simple Clinical Colitis Activity Index; pMAYO Partial Mayo (remission 0-2, response decrease ≥2 from induction baseline)

**Table 3 Health outcomes by utility source: conventional therapy, non-biological failure (updated company base case)**

Outcome	Remission	Response w/o remission	Active UC	Surgery, post-surgery & AE	Total
Life years (undiscounted)	■	■	■	■	■
<b>Woehl et al. 2008</b> pre-surgery utilities (0.87, 0.76, 0.410)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>Swinburn et al. 2012</b> pre-surgery utilities (0.91, 0.80, 0.55)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>Vaizey et al. 2013</b> pre-surgery utilities (0.86, 0.77, 0.66)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>UNIFI trial</b> pre-surgery utilities (■, ■, ■)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■

**Table 4 Health outcomes by utility source: conventional therapy, biological failure (updated company base case)**

Outcome	Remission	Response w/o remission	Active UC	Surgery, post-surgery & AE	Total
Life years (undiscounted)	■	■	■	■	■
<b>Woehl et al. 2008</b> pre-surgery utilities (0.87, 0.76, 0.410)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>Swinburn et al. 2012</b> pre-surgery utilities (0.91, 0.80, 0.55)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>Vaizey et al. 2013</b> pre-surgery utilities (0.86, 0.77, 0.66)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■
<b>UNIFI trial</b> pre-surgery utilities (■, ■, ■)					
QALYs (undiscounted)	■	■	■	■	■
QALYs (discounted)	■	■	■	■	■

