Adalimumab

(HUMIRA®)

National Institute for Health and Care Excellence (NICE)

Health Technology Appraisal

Adalimumab, golimumab and infliximab, for the treatment of ulcerative colitis (subacute)

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Submission by AbbVie

Appraisal technology: Adalimumab (HUMIRA®)

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DECLARATION

This submission does not omit any relevant evidence of which AbbVie is aware of and is not currently in the public domain, which could reasonably be considered to be related to the appraisal of adalimumab (HUMIRA®) for the treatment of moderately to severely active ulcerative colitis.

Information within this dossier considered as academic in confidence is underlined and highlighted in yellow and information considered commercial-in-confidence is underlined and highlighted in blue

FOREWARD

The aim of this multiple technology appraisal is to evaluate adalimumab, golimumab and infliximab for the treatment of ulcerative colitis for non-hospitalised patients at the time of treatment initiation with anti-TNF therapy (subacute).

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Executive Summary

Ulcerative Colitis (UC) is a chronic and recurrent condition characterised by inflammation of the colon causing symptoms such as rectal bleeding, urgency, pain, and fatigue. The age of onset is generally between the ages of 15-25 and therefore the condition has long lasting implications for patients' life aspirations. The disease can cause a negative impact on Health-Related Quality of Life (HRQoL), significantly reducing the ability of those affected to perform daily activities. UC patients have been demonstrated to have a significantly worse HRQoL than the population at large. There has been shown to be a clear deterioration of HRQoL associated with increasing disease severity. Patients with the most severe disease report values comparable with colorectal cancer.

Many conventional therapies are proven, licensed, and available in the UK for the treatment of mild to moderate UC. These treatments work by reducing inflammation and alleviating symptoms. Conventional therapies work for many but not all patients suffering from UC. Therefore the only currently recommended option for patients with moderate to severe subacute UC that have failed conventional therapy is surgery. Whilst surgery will remove the colon and may be perceived as curative, surgery is not without complications, for example; reduction in fertility, pouchitis, stoma care, diurnal and nocturnal frequency, and risk of faecal incontinence. Frequency of defecation can be a concern following ileal pouch-anal anastomosis (IPAA), with a study showing a median of 7 (3-12) bowel movements during the day and 2 (0-6) at night. Forty percent of patients reported urgency of defecation requiring a change in lifestyle. A number of patients who undergo a colectomy will undergo a surgical procedure resulting in a stoma. The tip of the lower small intestine is brought through the stoma. An external bag is attached to the stoma. This is called a permanent ileostomy. Stools pass through this opening and collect in the pouch. The pouch must be worn at all times. In addition to having an impact on patient's body image and functional limitations for the patient, stoma care is associated with a financial burden for the NHS. Direct medical costs for the management of UC are increasing and place a substantial burden on health care systems. Bassi *et al* have shown that, the top 10% most costly patients accounted for 62% of total direct UC medical costs in the UK.

Anti-Tumour Necrosis Factor (TNF) therapies including adalimumab are recommended by the European Crohn's and Colitis Organisation (ECCO) clinical guidelines as effective treatment options for patients with UC. Adalimumab was granted a licence by the EMA for the treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Adalimumab has been shown to be effective in the induction and maintenance of remission in patients with moderately to severely active UC in the M06-826 (ULTRA 1) and M06-827 (ULTRA 2) randomised controlled trials. In M06-827, which enrolled anti-TNF naïve and anti-TNF experienced patients, clinical efficacy was demonstrated as early as week-2, with 39.1% responding to the 160mg part of the loading dose alone, using the Partial Mayo Score. At week-8, the percentage of responders was 50.4% using the Mayo Score. While the ultimate aim of anti-TNF therapy in UC is to get patients into remission, achieving remission after 8 weeks of therapy is unrealistic in the majority of patients. Response per Mayo Score however, is an outcome that is achievable in 8 weeks of therapy and is indicative of a patient's likelihood to eventually reach the remission state. Data from M06-827 suggested that patients who did not respond by week-8 would not benefit from further adalimumab treatment, thus should discontinue at this point. For patients who did respond at week-8, by week 52, 30.9% achieved remission and 49.6% achieved response. Caution should be observed in making comparisons of trial results in UC, particularly across countries, due to limitations in the Mayo Score used for defining treatment response, patient population differences, and study design differences.

Adalimumab is the first biologic to indicate an impact in reduction in all-cause hospitalisations (40% reduction compared to placebo; p=0.046). Treatment with adalimumab also resulted in a 50% reduction in the proportion of patients with UC-related hospitalisations compared to placebo (p=0.02). Adalimumab led to a 47% reduction in the number of UC or drug-related hospitalisations compared to placebo (p=0.02). In a post-hoc analysis of M06-827 of IBDQ responders, statistically significantly different changes in the IBDQ score were observed in the adalimumab group at week 8, 20, 32, and 52 compared to placebo.

With the advent of anti-TNF therapy; increasing emphasis is being placed on the achievement of mucosal healing, both in clinical trials and in clinical practice. Achievement of long-term mucosal healing in UC has been associated with a decreased risk of both surgery and colorectal cancer. It is believed that mucosal healing may prevent IBD relapses, minimise hospitalisations, and alter the natural history of the disease to prevent complications such as fistulae, colorectal cancer, and the need for surgery.

Adalimumab is licensed across a broad range of autoimmune conditions. The adverse event profile of adalimumab in randomised controlled trials suggests a favourable benefit risk profile in moderately to severely active UC patients and is consistent with the known profile established in other indications containing over 23,000 patients in clinical trials.

There is currently a high unmet need for patients in England and Wales with moderately to severely active UC (subacute) who have failed on standard of care with no recommended biologic options in this patient population. The limited medical treatment options available has led to increasing clinical variation as individual localities take differing positions on the extent to which anti-TNF therapies are made available through local funding policies.

The cost-effectiveness of adalimumab plus standard of care (SOC) vs. SOC alone was evaluated in moderate to severe UC (subacute) patients over a 10-year treatment time horizon using a Markov model. Base case results suggest that adding adalimumab to SOC gave an incremental cost-effectiveness ratio (ICER) of £34,417/QALY (vs. SOC alone). Deterministic Sensitivity Analyses (DSA) varying key model inputs produced incremental costs per QALY gained in the range of £29,437 to £38,073. The economic evaluation demonstrated that when compared to SOC alone, the addition of ADA to SOC therapy has a reasonable cost-effectiveness ratio and the result was robust to a range of sensitivity analyses.

The availability of anti-TNF therapy for the treatment of moderate to severe UC gives patients and clinicians the opportunity to delay irreversible and life changing surgery. Clinicians should discontinue adalimumab therapy in those patients who fail to achieve a response after 8 weeks of therapy. These patients would then have the option of surgery. AbbVie considers that anti-TNF therapy for moderate to severe UC patients will be an important and final medical option for patients, especially given their preference to avoid surgery.

Section 1: Background and Context

Given the existing guidance available AbbVie has not included a detailed account of the epidemiology, pathophysiology, or aetiology of ulcerative colitis (UC) in this submission other than what is already outlined in the scope.

1.1 Introduction to Ulcerative Colitis

- UC is one of the primary forms of Inflammatory Bowel Disease
- It is a chronic, recurrent, non-transmural inflammatory disease of the rectum and/or colon
- Primary age of onset is between 15 and 25 years of age
- An autoimmune response is thought to be responsible for the condition along with genetic and environmental factors
- UK incidence rate is approximately 10 per 100,000 people annually
- UK prevalence rate is around 240 per 100,000 this amounts to around 146,000 individuals with a diagnosis of UC

Inflammatory bowel diseases are considered autoimmune diseases, in which the body's own immune system attacks elements of the digestive system. The two main forms of inflammatory bowel disease are Crohn's disease and ulcerative colitis (UC). UC is a chronic, recurrent, non-transmural inflammatory disease characterised by inflammation and ulceration of the mucosal and sub-mucosal layers of the rectum and colon. The clinical disease activity of UC is typically classified by activity (active or in remission), severity (mild, moderate, and severe, or acute severe) and anatomic extent (distal or extensive), based on clinical and endoscopic findings. Acute severe disease is also referred to as fulminant in the literature.

Disease activity tends to decrease over time with 40-50% of patients entering prolonged remission after a few years[1,2]. Ulcerative colitis is restricted to the colon and the rectum. Microscopically it is restricted to the mucosa (epithelial lining of the gut). The extent of colonic involvement in UC varies among patients although typically correlates with the severity of a patient's symptoms.

Diagnosis of UC usually involves a colonoscopy or flexible sigmoidoscopy with biopsy. Complete blood and C-reactive protein counts are also often employed. UC patients present with left-sided colitis, pancolitis, ulcerative proctitis, or proctosigmoiditis when diagnosed by a gastroenterologist.

The clinical course of UC fluctuates; with disease exacerbations (relapses) followed by periods of remission, each of which can last weeks or months. UC has a significant negative impact on patients with quality of life being significantly impaired due to its typically early onset and chronic nature. The disease generally appears in early adulthood, most frequently being diagnosed in people between the ages of 15-25 years[3]. The exact cause of the disease has not been determined however, both genetic and environmental factors, coupled with abnormal immune response, are thought to contribute to the incidence of UC. It is fair to say that, to date, the natural history of the disease is not fully understood.

Major symptoms of UC include; diarrhoea, rectal bleeding, the passage of mucus, and abdominal pain. Other symptoms including anaemia, severe tiredness, weight loss, and loss of appetite are also common. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Patients with UC can also present with extraintestinal complications including; arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis).[4] Patients with UC are at increased risk of developing colon cancer - risk increasing with disease duration as well as the extent of colon affected by the disease.[5]

In addition to medical consequences, UC can also have a significant negative impact on Health Related Quality of Life (HRQoL).[6] In comparison to the general population, patients with UC have been shown to have reduced HRQoL and general life satisfaction[7]. Two studies have reported that 53% of UC patients felt the condition was controlling their lives[8,9]. This was a statistically significant result when compared to other chronic conditions such as; asthma, migraine, and rheumatoid

arthritis. Factors that appear to affect HRQoL in patients with UC include the extent, severity and pattern of disease, medical treatment including; efficacy, side effects, and burden of administration, as well as various non-disease-related factors.[10] There has been shown to be a clear deterioration of HRQoL associated with increasing disease severity. Patients with the most severe disease report values comparable with colorectal cancer[51]. The most commonly used disease-specific quality-of-life instrument among patients with UC in clinical trials is the Inflammatory Bowel Disease Questionnaire (IBDQ). However, the IBDQ it is not commonly used in UK clinical practice.

1.1.1 Epidemiology

There is an extensive literature base describing the incidence and prevalence of ulcerative colitis in different regions of the world. In general, the highest incidence and prevalence rates have been reported from northern Europe, the United Kingdom, and North America, which are the geographic regions that have been historically associated with IBD[11]. However; there are reports of increasing incidence and prevalence rates from other areas of the world such as; southern or central Europe, Asia, Africa, and Latin America.[12]

In North America, incidence rates range from 2.2 to 14.3 cases per 100,000 person-years, while prevalence estimates range from 37 to 246 cases per 100,000 persons. In Europe, incidence rates range from 1.5 to 20.3 cases per 100,000 person-years, while prevalence estimates range from 21 to 243 cases per 100,000 persons[12]. From a UK perspective the recent NICE guidelines[3] cite a UK incidence rate of approximately 10 per 100,000 people annually, and with a prevalence of around 240 per 100,000 this amounts to around 146,000 individuals in the UK with a diagnosis of UC.

1.2 Treatment goals

- Primary aims of medical therapy in UC are to end symptoms by reducing the inflammation that triggers signs and symptoms (induce remission); and to prevent symptoms from coming back (maintain remission)
- Additional aims of medical therapy are to reduce symptoms, such as rectal bleeding, to encourage mucosal healing, improve quality of life, limit the amount of steroid exposure, and reduce hospitalisations and the need for surgery
- Achieving mucosal healing may improve quality of life, prevent IBD relapses, minimise hospitalisations, and alter the natural history of the disease to prevent complications such as fistulae, colorectal cancer, and need for surgery
- Avoidance of surgery is of vital importance, especially from the patient's perspective

Primary aims of medical therapy in UC are to end symptoms by reducing the inflammation that triggers signs and symptoms (induce remission); and to prevent symptoms from coming back (maintain remission). Additional aims of medical therapy are to reduce symptoms, such as rectal bleeding, to encourage mucosal healing, improve quality of life, limit the amount of steroid exposure, and reduce hospitalisations and the need for surgery[13], the latter being of primary concern from the patient perspective. Fear of surgery and the potential of lasting complications as a result is a key issue for all UC patients[14].

With the advent of biological therapy, increasing emphasis is being placed on the achievement of mucosal healing, both in clinical trials and in clinical practice[15]. It is also believed that mucosal healing may improve quality of life, prevent IBD relapses, minimise hospitalisations, and alter the natural history of the disease to prevent complications such as fistulae, colorectal cancer, and need for surgery.

Disease severity and response to treatment can be assessed using clinical activity measures such as the Mayo Score or condition specific quality of life assessments such as the IBDQ. The use and implications of the Mayo Score and the IBDQ assessment are discussed in further detail in section 2.11.1 Limitations of the Mayo scoring system and section 2.11.2 Limitations affecting comparability across trials.

1.2.1 Anatomic extent

UC phenotype is determined by the maximal extent of inflammation observed at colonoscopy. Disease extent can broadly be divided into distal and more extensive disease however disease extent can change over time in any 30% of patients.[16] Distal disease includes left-sided colitis, limited

to below the splenic flexure, and colitis confined to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis). In contrast; extensive disease includes left-sided colitis which extends proximal to the splenic flexure, extensive colitis (up to the hepatic flexure) and pancolitis which affects the whole colon. The Montreal classification of disease extent of ulcerative colitis allows extent to be defined into three subgroups: proctitis (E1); left-sided colitis (E2) and extensive disease (E3).

1.2.2 Disease severity

Regardless of the extent of the disease, patients can have any level of disease severity. Four classifications of disease severity exist: mild, moderate, severe, and acute severe. It is generally accepted that a Mayo Score of 6 to 9 is moderate disease and a score of 10 or greater is severe disease. Patients with moderate UC often present with 5 bloody bowel movements a day and are more likely to have abdominal pain during acute attacks[17]. They are often fatigued and may have a chronic low grade fever. In comparison, patients with severe disease are likely to experience 6 or more bloody bowel movements per day and are usually weak from anaemia and weight loss. Fever, tachycardia, and postural hypotension are common and toxic megacolon is possible. Moderately to severely active UC patients are managed in an outpatient setting.

Acute severe disease, while not the focus in this submission, is regarded by physicians as a subset of severe disease. Patients of any severity may flare to acute severe level requiring hospitalisation. This rare, life-threatening form of colitis affects the entire colon and causes severe pain, profuse diarrhoea and, sometimes, dehydration and shock and is best defined by the Truelove and Witts criteria (≥6 bloody stools/day and signs of systemic toxicity; heart rate>90 beats per minute, temperature>37.8C, hemoglobin≤10.5dL or an erythrocyte sedimentation rate>30mm/hour). This is reproduced from the NICE guidance[3] as Table 1 below.

Table 1: Truelove and Witts' severity index

Symptom	Mild	Moderate	Severe
Bowel movements (no. per day)	Fewer than 4	4–6	6 or more plus at least one of the features of systemic upset (marked with * below)
Blood in stools	No more than small amounts of blood	Between mild and severe	Visible blood
Pyrexia (temperature greater than 37.8°C) *	No	No	Yes
Pulse rate greater than 90 bpm *	No	No	Yes
Anaemia *	No	No	Yes
Erythrocyte sedimentation rate (mm/hour) *	30 or below	30 or below	Above 30

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People with acute severe colitis are at risk of serious complications including; colon rupture and toxic megacolon, a condition that causes the colon to rapidly expand. Acute severe ulcerative colitis is considered a medical emergency[16].

According to the ECCO Consensus guidelines[39], the classification of UC based on disease severity is useful for clinical practice and dictates the patient's management. Disease severity influences the treatment modality and determines if oral, subcutaneous, intravenous, or surgical therapy is initiated. Clinical, laboratory, imaging and endoscopic parameters, including histopathology, assist physicians in patient management. AbbVie is not aware of any population-based study that has categorised patients with UC according to both severity of symptoms and extent of disease within the colon simultaneously. Symptom severity is not always indicative of extent of disease, although most studies report a strong positive correlation between the number and intensity of symptoms and the anatomical extent of disease.

1.3 Current treatment options for UC

- Conventional therapies include 5-ASAs, corticosteroids, and immunomodulatory agents
- Approximately 20-35% of patients will ultimately require surgery with risk of lasting post-operative complications
- While surgery is perceived as curative it is associated with significant consequences and complications. HRQoL has been reported to be significantly worse in UC patients who have undergone surgery than those with UC who have not undergone surgery.
- Demand for an effective last-line pharmacological therapy is currently unmet prior to commencing salvage therapy
- In the UK there is currently no recommendation for the use of anti-TNF agents to treat subacute patients
- Anti-TNF therapy offers an important treatment option for those patients currently destined for surgery

Conventional therapies used to treat moderate to severe UC include 5-ASAs, corticosteroids, and immunomodulatory agents. These agents do not completely abate the inflammatory process in all patients and corticosteroids and immunomodulatory agents have significant side effects.[16] For those who do not respond, are intolerant or medically contraindicated to conventional therapies, surgical intervention can be considered.

Whilst surgery will remove the colon and may be perceived as curative, surgery is not without complications which can occur in the short and long term, for example; reduction in fertility, pouchitis and pouch failure, stoma care, diurnal and nocturnal frequency, and risk of faecal incontinence. Fertility considerations are also important in the choice and timing of surgery in UC. Surgery may lead to infertility in women due to abnormal fallopian patency or with presence of occlusion and adherence of fallopian tubes to pelvic floor post-IPAA surgery. Vaginal delivery has also been associated with occult sphincter injury and decreased anal canal pressures, leading to higher rates of Caesarean section post-IPAA than the general population[18]. Therefore, avoiding colectomy, even for a short period, can be beneficial to some patients by providing time to think about surgery, perhaps allowing time to conceive or allowing an elective rather than an emergency procedure.

Frequency of defecation can be a concern following ileal IPAA, with a study showing a median of 7 (3-12) bowel movements during the day and 2 (0-6) at night. 40% of patients reported urgency of defecation requiring a change in lifestyle. A number of patients who undergo a colectomy will undergo a surgical procedure resulting in a stoma. The tip of the lower small intestine is brought through the stoma and a external bag is attached to the stoma. This is called a permanent ileostomy. Stools pass through this opening and collect in the pouch. The pouch must be worn at all times. In addition to having an impact on patient's body image and functional limitations for the patient, stoma care is associated with a financial burden for the NHS. Direct medical costs for the management of UC are increasing and place a substantial burden on health care systems. Bassi *et al*[19] have shown that, the top 10% most costly patients accounted for 62% of total direct UC medical costs in the UK.

Given the typical age of onset of the disease (15-25 years) many patients are not comfortable with the life-altering implications of surgery[14]. Despite recent improvements, surgery is still predominantly regarded as salvage therapy for situations where therapeutic drug management fails. Many people find the idea of surgery and coping with the associated early and long term side effects difficult. Patients with UC who have undergone surgery have reported significantly worse HRQoL than UC patients who have not undergone surgery or age-matched controls[51] (see appendix 3). UC patients who have undergone surgery have reported statistically significant worse scores on the Simple Colitis Activity Index (SCCAI) for the domains of daytime bowel frequency, night time bowel frequency and urgency of defecation ($p<0.01$), when compared to UC patients who have not undergone surgery. General well-being in UC patients who have undergone surgery has been reported to be no better than patients with UC who had not undergone surgery. UC patients who had undergone surgery, and those who had not were asked whether they would be willing to try a new type of drug therapy as an alternative; 87% indicated that they would be willing to do so.

Although some patients may undergo colectomy it is not an appropriate comparator for this submission. This surgery is a downstream consequence of chronic unresponsive moderately to severely active disease and is generally viewed as a last resort option as outlined in the scope.

1.3.1 5-Aminosalicylic Acid [5-ASA]

The 5-aminosalicylic acid derivatives act on epithelial cells by a variety of mechanisms to moderate the release of lipid mediators, inflammatory cells, cytokines, and reactive oxygen species. They can be delivered by a variety of oral tablets, sachets or suspensions, or as topical agents in the form of liquid or foam enemas, or suppositories. Topical agents are more commonly used in milder forms of the disease. Agents available in the UK include sulfasalazine, mesalazine, and olsalazine. The main role for 5-ASAs in UC is maintenance of remission. Maintenance therapy with all 5-ASA drugs may reduce the risk of colorectal cancer by up to 75%, thus favouring long-term treatment for patients with extensive ulcerative colitis[16]. The choice of 5-ASA is debated, but is influenced by tolerability (it is estimated that approximately 20% of patients are unable to tolerate sulfasalazine[20]), dose schedule (single- or twice-daily dosing is associated with better compliance), and cost (sulfasalazine is less expensive than second generation 5-ASAs).

1.3.2 Corticosteroids

Corticosteroids are used to induce remission in UC but have no role as maintenance therapy as they do not prevent relapse and have unacceptable, long-term adverse effects. Adverse effects are an inevitable result of systemic corticosteroid treatment if the dose and/or duration of treatment are sufficient, because most are dose-related biological effects of the hormone: e.g. immunosuppression, metabolic effects, and osteoporosis. Corticosteroids are used in the form of oral prednisolone, prednisone, beclometasone, and budesonide (among others), or intravenous hydrocortisone and methylprednisolone. Topical steroids may also be used. Many strategies attempt to maximise topical effects while limiting systemic side-effects of steroids. Too rapid reduction in steroid dose can be associated with early relapse. Steroid resistance or unresponsiveness should lead to escalation of treatment.

1.3.3 Immunosuppressants (IMM)

Thiopurine immunosuppressant drugs (azathioprine and mercaptopurine) are effective for inducing remission and as maintenance therapy, but have potential adverse effects and take 3 to 6 months to achieve their maximum benefit. Due to this slow onset of action, IMM are often initiated with corticosteroid therapy during acute-phase treatment in an attempt to wean patients from steroids without a gap in medical treatment. Methotrexate may also be used to treat UC, but is less effective than the thiopurines. Azathioprine is more effective than mesalazine at induction of clinical and endoscopic remission in steroid dependent UC patients. Thiopurines also serve as effective maintenance therapy for patients with UC who have failed or who cannot tolerate mesalazine and for patients who require repeated courses of steroids[16].

Although a significant proportion of patients experience adverse effects with thiopurines, when the drug is tolerated for 3 weeks, long-term benefit can be expected. Adverse events occur in up to 20% of patients. The most common events are allergic reactions (fever, arthralgia and rash) that characteristically occur after 2-3 weeks and cease rapidly when the drug is withdrawn.

Ciclosporin is also indicated for use in acute severe UC as an add-on to corticosteroids with the goal of inducing remission. Should a patient fail or be contraindicated for such treatment, surgery may remain the best option; neither of these approaches are free from a risk of severe adverse events.

1.3.4 Surgery

Approximately 20-35% of UC patients will ultimately require surgical intervention due to inadequate relief of symptoms or a complication of the disease.[16] While colectomy is an option for moderately to severely active UC for patients that have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies, many patients are not comfortable with the life-altering implications of surgery and seek more effective alternatives to current last-line pharmacological treatments.

Surgery may be considered curative, considering the colon is removed, but many patients experience high rates of post-operative complications and there is evidence that bowel movement frequency remains high. Early complications that arise from surgery include sepsis, small bowel obstruction and anastomotic leakage while late complications (over 30 days post colectomy) include pouchitis, pouch failure, and pouch-vaginal fistulae. Surgery may also lead to sexual dysfunction in females caused by injuries to nerve plexuses or distortions in the pelvic structure sustained during surgery, or infertility in women. While effective surgery has been shown to generally improve HRQoL

in patients with UC[21,22,23], some patients experience long term complications with significant negative impacts.[6]

The IPAA procedure is the most common surgical treatment for the management of ulcerative colitis. This procedure removes all of the colon and rectum, but preserves the anal canal. The rectum is replaced with small bowel, which is refashioned to form a small pouch. A pouch maintains a normal route of defecation, but most patients experience five to ten bowel movements per day. Andersson *et al*, 2011 reported on the long-term functional outcomes and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis in Norway[24]. Frequency of defecation post IPAA was a median of 7 (3–12) bowel movements during the day and 2 (0–6) at night. The majority had some degree of faecal incontinence (median Wexner score of 8) and 40% reported urgency of defecation necessitating changes in lifestyle. The Wexner score considers 5 parameters that are scored on a scale from zero (absent) to four (daily) frequency of incontinence. These data highlight that there may be some degree of adaptation to what are considered normal symptoms when compared with the general population without UC given that IPAA is perceived as curative. The IPAA patients scored slightly, but significantly, lower in four of six SF-36 health domains than the control subjects, adjusted for age and gender. Multiple regression analysis showed frequency of nocturnal defecation, faecal incontinence and urgency to be independent negative prognostic factors of quality of life. It should also be noted that only patients who still had an intact pouch were included in this study. Quality of life scores for the proportion of patients with pouch failure cannot be established from this study or for patients with surgery other than IPAA procedure.

For patients in whom an IPAA procedure is unsuitable, a stoma would be created. In addition to having an impact on patient's body image and functional limitations, stoma care is associated with a financial burden for the NHS. Further information on post-surgery QoL and complications is available in appendix 3.

1.3.5 Unmet Need

There is a high clinical need for the availability of an effective last line pharmacological therapy option for moderately to severely active UC patients who are refractory, intolerant or contraindicated to conventional therapies prior to salvage therapy. No anti-TNF therapy is currently recommended for the treatment of moderately to severely active UC in the UK for non-hospitalised patients (subacute) by NICE.

Adalimumab, golimumab and infliximab offer an important therapeutic option for the medical treatment of moderately to severely active UC for patients who do not respond, are intolerant or contraindicated to conventional therapies. Without anti-TNF therapy, the only option for these patients is surgery. In other European countries anti-TNF therapy is considered standard care for treatment of moderate to severe UC as per ECCO guidelines outlined in the following section.

1.4 NICE guidance and international treatment guidelines

- In addition to NICE guidance CG166, several international bodies offer treatment guidance for UC
- Infliximab has been recommended by NICE for acute exacerbations of severely active UC where ciclosporin is contraindicated (TA163)
- ECCO guidance provides detailed recommendations based on disease behaviour and location

A number of international guidelines for the management of ulcerative colitis were identified alongside the recent NICE guidance[3] namely the European Crohn's and Colitis Organisation (ECCO) Consensus guidelines[39], the British Society of Gastroenterology guidelines[16] and the American College of Gastroenterology guidelines.[25].

The NICE guidelines (CG166) have laid out key priorities for improving patient care at all stages of the treatment process, focusing on patient engagement and delivery of appropriately tailored treatment across all stages of disease progression with the interventions as detailed in section 1.3. The ultimate goal of these strategies is to induce remission using a progressive treatment approach

and then maintain the patient appropriately to prolong remission status. Ultimately avoidance of surgery is the desired outcome of the treatment approaches recommended therein; this correlates strongly with patient requirements and expectations. NICE also advocates the use of faecal calprotectin testing as an option to provide differential diagnoses between IBS and IBD. The full content of the guidance document has not been paraphrased here due to the reader's familiarity with this guidance document

In addition to this infliximab has been recommended (TA163)[26] as a treatment option for acute exacerbations of severely active UC in patients for whom ciclosporin is contraindicated or clinically inappropriate based on individual patient assessments. It should be noted however that infliximab is currently not recommended for subacute manifestations of UC[27].

The ECCO guidelines provide detailed treatment recommendations based on disease location and disease behaviour. In terms of disease location and according to the Montreal classification system, active ulcerative colitis can be broken down into 3 distinct phenotypes comprising proctitis, left-sided colitis and extensive colitis as defined in Table 2. All types of ulcerative colitis can be classified as mild, moderate to severe and acute severe.

Table 2: Distribution of ulcerative colitis[16]

Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the rectosigmoid junction
E2	Left-sided	Involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis)
E3	Extensive	Involvement extends proximal to the splenic flexure, including pancolitis

The ECCO guidelines advocate use of anti-TNF therapy using infliximab and adalimumab for the treatment of outpatients with moderately active UC refractory to steroids [EL2B, RG C], and patients with moderately active UC who are refractory to thiopurines [EL1b RG B]. Tacrolimus is also recommended for the treatment of outpatients with moderately to severely active UC but this drug is not licensed for this indication in the UK. Other guidelines are generally consistent with the ECCO Consensus statement and NICE has made allowances for the use of tacrolimus where there is a clear advantage following an individual patient risk assessment.

According to the ECCO guidelines, irrespective of the extent of disease, patients with active ulcerative colitis should first be initiated on an optimised course of 5ASAs with or without oral corticosteroids. Following re-assessment and characterisation of the patient's disease, in the case of steroid dependent disease this would be followed by immunomodulators such as azathioprine or mercaptopurine. In steroid refractory or immunomodulator refractory disease, this would be followed by anti-TNF therapy such as adalimumab or infliximab.

1.5 Adalimumab (Humira®)

- Adalimumab is licensed for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
- Adalimumab binds to TNF and inhibits its interaction with p55 and p75 cell surface receptors and modulates biological response that are induced or regulated by TNF
- Adalimumab has been recommended as a treatment by NICE for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, and Crohn's disease.
- The list price for 40mg of adalimumab is £352.14
- Treatment guidance recommends 160mg at week 0, followed by 80mg at week 2, with 40mg being administered every other week henceforth
- Data suggests that clinical response is observed within 2-8 weeks and patients not responding by week 8 should discontinue therapy.
- Adalimumab can be self-administered outside the hospital, for example in the patient's home

Adalimumab binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is

involved in normal inflammatory and immune responses. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1)

1.5.1 Licensed Indications

This section outlines the licensed indications[28] for adalimumab beginning with UC, then lists all other relevant indications for which adalimumab has been licensed.

Ulcerative colitis

Adalimumab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Crohn's disease

Adalimumab is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's Disease

Adalimumab is indicated for the treatment of severe active Crohn's disease in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Rheumatoid arthritis

Adalimumab in combination with methotrexate is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate

Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Polyarticular juvenile idiopathic arthritis

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 2 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. (For the efficacy in monotherapy see section 5.1 in licence).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Adalimumab is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Adalimumab is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs.

Psoriatic arthritis

Adalimumab is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

1.5.2 Mechanism of Action

Adalimumab is a fully human monoclonal antibody that binds specifically to the pro-inflammatory cytokine TNF-α and neutralises the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1 [endothelial leukocyte adhesion molecule-1], VCAM-1 [vascular cell adhesion molecule-1], and ICAM-1 [intracellular adhesion molecule-1] with an IC_{50} of 1-2 X 10^{-10} M).

1.5.3 Presentation and Cost

Adalimumab is available in the following three presentations:

- a 40mg solution for injection in a single-use pre-filled syringe (type I glass) for patient use: packs of 2 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister are provided.
- a single-use automatic injection device with needle-guard that delivers 40mg adalimumab by pushbutton (Humira® Pen). Packs of: 1 pre-filled syringe with needle-guard (0.8 ml sterile solution) in a blister, and 1 alcohol pad are provided.
- 40 mg solution for injection in single-use paediatric vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals: 1 pack of 2 boxes each containing: 1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe, 1 needle, 1 vial adapter and 2 alcohol pads.

The list price for all three presentations of adalimumab is £352.14[29]

The recommended adalimumab induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg adalimumab every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab therapy should not be continued in patients failing to respond within this time period.

1.5.4 Concomitant therapy

No specific therapies are required to be co-administered with adalimumab. Continuation of other drugs to treat moderate to severe ulcerative colitis may be appropriate. These include topical and oral aminosalicylates, oral corticosteroids, and immunosuppressants. During maintenance treatment, when a patient is responding to adalimumab, it is expected that these other therapies, particularly corticosteroids and possibly immunomodulators, will be tapered.

Adalimumab is available for delivery to the patient's home. Patients or their carers can be trained in injection technique to allow delivery of the drug direct to their home. This reduces burden on NHS services and reduces the impact of receiving treatment on work productivity or activities of daily living for those who are not working. VAT is also not payable on any drug delivered outside the hospital setting.

Section 2: Clinical Evidence

2.0 Overview of clinical evidence

- Two randomised trials have been identified as relevant to this submission; M06-826 and M06-827
- Adalimumab has been shown to be effective in the induction and maintenance of remission in patients with moderately to severely active UC
- A third open-label extension study provides long-term data on patients from both these trials
- In M06-827 clinical efficacy was demonstrated as early as week 2, with 39.1% responding to the 160mg part of the loading dose alone.
- In M06-827 at week 8, the percentage of responders, naive to prior anti-TNF use was 58.7%. Data suggested that patients who did not respond by week 8 would not benefit from further adalimumab treatment, thus should discontinue at this point. For the anti-TNF naive patients who did respond at week 8, by week-52, 39.8% achieved remission and 64.8% achieved response.
- In a post-hoc analysis of M06-827 of IBDQ responders, statistically significantly different changes in the IBDQ score were observed in the adalimumab group at week 8, 20, 32, and 52 compared to placebo.

This section of the submission presents a summary and evaluation of clinical evidence relevant to a comparison of adalimumab (ADA) and placebo (PBO), both administered against a common background standard of care (SOC), in the proposed patient population of patients with moderately to severely active UC. The evaluation is based primarily on results from two key randomised controlled trials (M06-826[30] and M06-827[31]) and a long term, single arm, open label extension study which included patients from both of these key trials (M10-223).

Results of these studies indicate that adalimumab is an effective treatment for the induction and maintenance of remission and/or response in patients with moderately to severely active UC despite prior treatment with conventional medical therapies including; 5-ASAs, corticosteroids and/or immunosuppressants. In addition, patients on adalimumab achieve mucosal healing, and experience reduced hospitalisations and rates of colectomy, as well as improved quality of life, which are all important patient relevant outcomes. An extended assessment of comparative safety is also presented, which looks beyond the key randomised trials in UC to provide a broader evaluation of comparative safety.

2.0.1 Summary of literature search conducted

A literature search was conducted to identify published literature related to the efficacy of adalimumab in the treatment of UC in the following databases using the search providers detailed in brackets:

- Embase (OVID)
- Medline (OVID)
- Cochrane Library; including NHS EED and the HTA database (WILEY)
- Science Citation Index (Thomson Reuters)

In addition to this a web based search was also conducted using the clinical research network study portfolio in the UK, the US based ClinicalTrials.gov, and the WHO trials registry.

All searches were carried out between 4th and 5th February 2014, covering the following dates:

- Embase 1980 – January week 4, 2014
- Medline 1946 – 4 February 2014
- Cochrane Library – up to and including Issue 1 of12; 2014
- Science Citation Index 1965 – 4 February 2014

The syntax used to conduct these searches, along with the search results, is provided as **Error! Reference source not found.**.

The search identified a total of 160 positive hits. Of these; 142 were excluded as not relevant. The remaining 18 citations referred to three unique trials judged as being relevant to this submission; M06-826, M06-827, and the long term extension of these (M10-223). A manual search of the reference lists of included publications did not yield any additional publications. The search results are summarised below as Table 3.

Table 3: Summary results of literature review

	Embase & Medline	Cochrane	SCI	Trials Registries	Total
CITATIONS	**23**	**10**	**107**	**20**	**160**
Abstract review					
a) not a randomised trial	18	5	101	14	138
b) wrong comparison	0	0	0	0	0
c) wrong population	0	0	1	2	3
d) exact duplicate	0	0	0	0	0
e) incomplete	0	0	0	0	0
SUBTOTAL	**18**	**5**	**102**	**16**	**141**
Full text review					
a) not a randomised trial	0	0	0	0	0
b) wrong comparison	0	0	0	0	0
c) wrong population	0	0	0	0	0
d) exact duplicate	0	0	0	0	0
e) incomplete	0	0	0	1	1
SUBTOTAL	**0**	**0**	**0**	**1**	**1**
TOTAL EXCLUDED	**18**	**5**	**102**	**17**	**142**
Citations included	5	5	5	3	18
Consolidated number of trials	**3**				

Results were recently released for an ongoing Japanese registration study (M10-447), which appeared in the US Clinical Trial registry. No clinical study report or full publication was identified for this study at the time of searching since the publication was released online in the ahead of print format on 24 December 2013 and as such would not have been identified by the searches carried out. Being mindful of this discrepancy AbbVie has incorporated the study into the literature review component and can confirm that this has been published fully as of February 2014[32].

Data presented in this study has been excluded from the current meta-analyses and the reasons for this are discussed in further detail in section 2.6.

2.1 RCT data for adalimumab

- Induction Data taken from 8-week induction study M06-826 and M06-827
- Maintenance data taken from M06-827; reporting at 52 weeks
- Supportive data taken the from long-term, open-label extension study; M10-223
- Data from a recently published RCT, conducted exclusively in Japan, was excluded from the meta analyses

A master list of trials and associated reports included in the submission is presented in Table 4 below. No relevant randomised controlled trials were excluded from the submission. The trials presented include a pivotal induction study (Study M06-826), a pivotal maintenance study (Study M06-827), and a supportive long-term open label extension study (Study M10-223). Study M06-826 and Study M06-827 are complete, and Study M10-223 is currently ongoing, with interim results available. A brief overview of the design and interaction between the studies is provided below.

As discussed in the previous section; the final identified study was conducted exclusively in Japan and has been presented at the end of this section. There are difficulties in cross country comparison of UC studies which are outlined in section 2.11.

Table 4: Master list of trials included

Trial ID	Brief description and list of associated reports
Included	
M06-826	Description: A multicenter, randomized, double-blind, placebo-controlled study of Adalimumab for the induction of remission in patients with moderate-to-severe ulcerative colitis.
	Main report: Clinical Study report R&D/09/143. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis. 16 March 2012. Abbott Laboratories (Abbott) **Additional citations:** Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. 2011. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011; 60:780-787.[30] Reinisch W, Sandborn WJ, Panaccione R, Huang B, Pollack PF, Lazar A, Thakkar RB. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis. 2013 Jul; 19(8):1700-9.[33] Other ID: ULTRA-1; NCT00385736
M06-827	**Description:** A multicenter, randomized, double-blind, placebo controlled Study of Adalimumab for the induction and maintenance of clinical remission in patients with moderate-to-severe ulcerative colitis.
	Main report: Clinical study report R&D/10/236. A Multicenter, Randomized, Double-blind, Placebo controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis. 16 March 2012. Abbott Laboratories (Abbott) **Additional citations:** Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D'haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. 2012. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012; 142:257–265.[31] Sandborn, WJ; Colombel, JF; D'Haens, G; Van Assche, G; Wolf, D; Kron, M; Lazar, A; Robinson, AM; Yang, M; Chao, JD; Thakkar, R One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther. 2013 Jan; 37(2):204-13.[37] Other ID: ULTRA-2; NCT00408629
Pooled data of M06-826 and M06-827	Feagan BG. Sandborn WJ. Lazar A. Thakkar RB. Huang B. Reilly N. Chen N. Yang M. Skup M. Mulani P. Chao J. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. Gastroenterology. 146(1):110-118.e3, 2014 Jan. [34]
M10-223	**Description:** Multicenter, Open-Label extension study is to evaluate the long-term maintenance of response, safety, and tolerability of repeated administration of adalimumab in patients with ulcerative colitis who participated in and successfully completed Study M06-826 or Study M06-827.
	Main report for Quality of Life data: Clinical Study Report (Interim) R&D/13/180. A Multicenter, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Patients With Ulcerative Colitis. Abbott Laboratories (Abbott). M10-223 Clinical Study Report - Interim 3 Year Reference for efficacy and safety data up to 4 years: J-F Colombel, WJ Sandborn, S Ghosh, DC Wolf, R Panaccione, B Feagan, W Reinisch, AM Robinson, A Lazar, M Kron, B Huang, RB Thakkar. Adalimumab Maintains Remission for up to 4 Years in Patients with Ulcerative Colitis. 2014; Poster presented at the 9th ECCO Congress in Copenhagen, February 20-22, 2014 (P571) [35] Other ID: NCT00573794
Excluded – NA	

2.1.1 Overview of the clinical development program

Study M06-826 was originally designed as a 12 week randomised study using an induction dose of adalimumab 160/80/40, followed by 40mg every other week (EOW), as per the EMA licensed indication. The primary efficacy analysis was conducted on the data set from the double blind period through to Week 8. Protocol amendment 3 created an additional treatment arm for adalimumab with

an alternative induction dose schedule of 80/40, followed by 40mg EOW and also changed the duration of the randomised treatment period (See Figure 1 and Figure 2). Subjects enrolled under this amended protocol had a double blind treatment period of just 8 weeks, with assessment of the primary efficacy analysis at Week 8. Subjects in M06-826 were all anti-TNF naïve.

Figure 1: Study Design of M06-826 (Prior To Amendment-3)

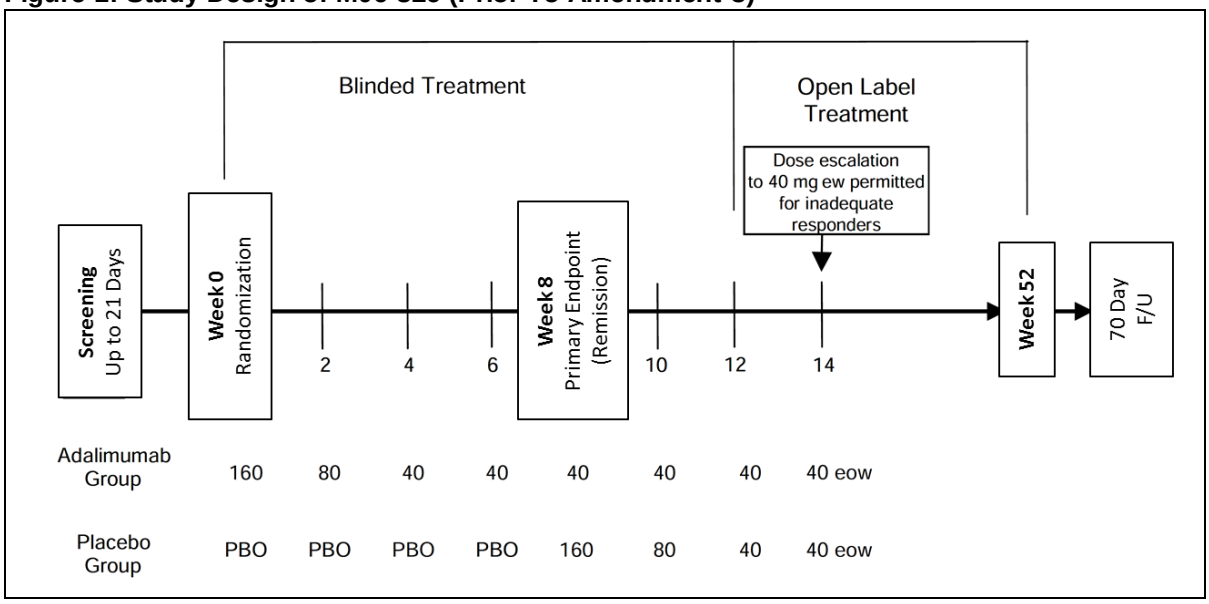
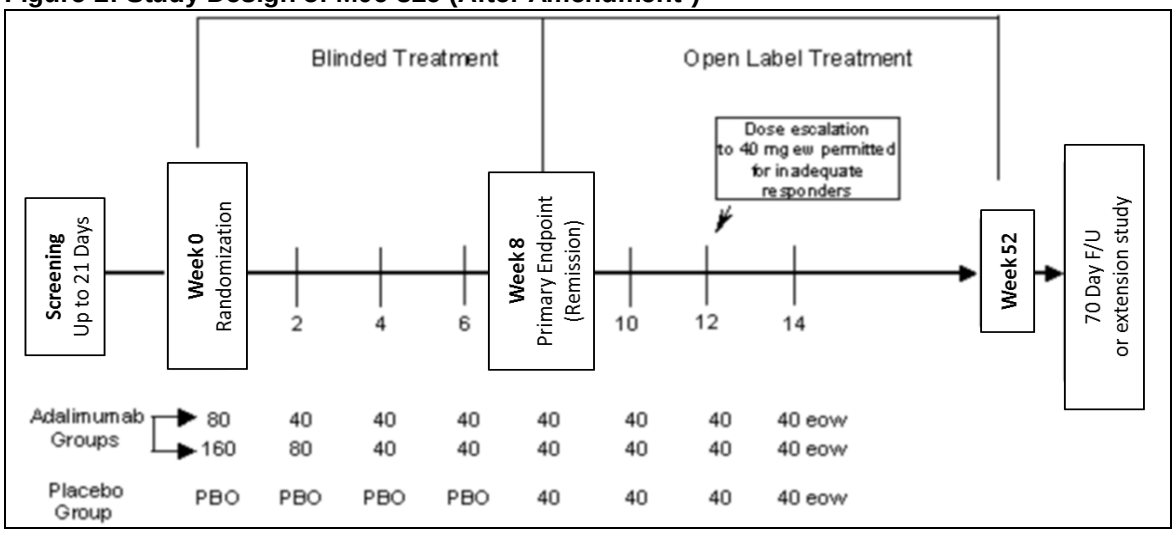
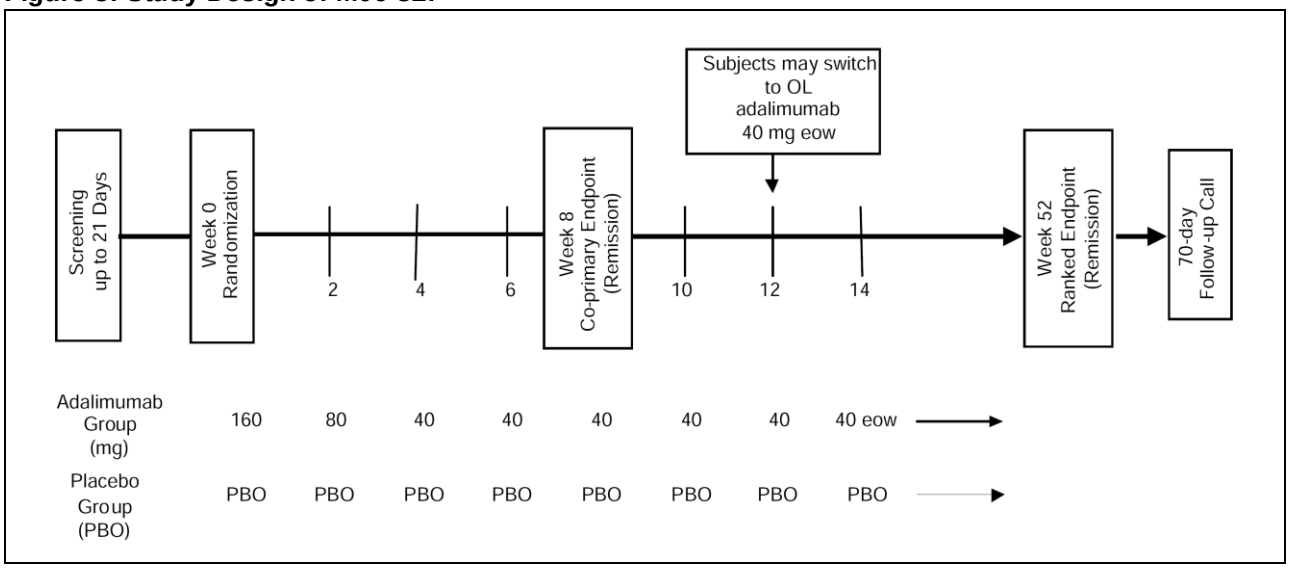


Figure 2: Study Design of M06-826 (After Amendment-)



Patients in Study M06-827 completed an 8 week double-blind treatment period, and continued double-blind treatment until week 52, unless they crossed-over to open-label (OL) adalimumab, which was permitted after week 12 for patients with inadequate response (Figure 3).

Figure 3: Study Design of M06-827



Patients in both studies who completed the 52-week visit had the option of enrolling in an extension study (M10-223) where they continued to receive OL adalimumab.

2.1.2 Comparative summary of trials

A comparative summary table of the study characteristics is provided as Table 5. The primary outcome of M06-826 was evaluated at week 8. The primary outcome of M06-827 was evaluated at both week 8 and week 52. Patients in M06-826 were switched to open label adalimumab after 8 or 12 weeks and could increase their dose to every week if they met a pre-defined inadequate response definition. Subjects in M06-827 remained on double blind therapy through 52 weeks unless they met the pre-defined inadequate response criteria, after which they could switch to open label adalimumab or escalate their adalimumab dose. M10-223 is an on-going open label extension study in which every other week or every week dosing is permitted. Only interim results from this study are currently available for inclusion in the submission.

Table 5: Comparative summary of characteristics of the included trials

			M06-826 (post-amend. # 3)		M06-827		M10-223
Design			DB period, followed by OL		DB; Subjects could cross to OL		OL
Treatments		ADA 160/80 (N=130)	ADA 80/40 (N=130)	PBO (N=130)	ADA (N=248)	PBO (N=246)	ADA 40 mg EOW or EW. (N=588)
	Week 0	ADA 160mg	ADA 80mg	PBO 160mg	ADA 160mg	PBO 160mg	
	Week 2	ADA 80mg	ADA 40 mg	PBO 80mg	ADA 80mg	PBO 80mg	
	Week 4	ADA 40mg	ADA 40mg	PBO 40mg	ADA 40mg	PBO 40mg	
	Week 6	ADA 40mg	ADA 40mg	PBO 40mg	ADA 40mg	PBO 40mg	
	Week 8	ADA 40mg	ADA 40mg	ADA 40mg	ADA 40mg	PBO 40mg	
	Week 10	ADA 40mg	ADA 40mg	ADA 80mg	ADA 40mg	PBO 40mg	
	W. 12-52	OL ADA 40mg EOW; dose escalation to 40mg EW if inadequate response	OL ADA 40mg EOW; dose escalation to 40mg EW if inadequate response	OL ADA 40mg EOW; dose escalation to 40mg EW if inadequate response	ADA 40mg EOW; dose escalation to 40mg EW if inadequate response	PBO 40mg EOW; dose escalation to 40mg EW if inadequate response	
Population		Adult subjects with moderate to severe active UC (MS 6 to 12 points with endoscopy sub-score of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy failed CS and/or IMM. Biologic agent naive			Adult subjects with moderate to severe active UC (MS 6 to 12 points with endoscopy sub-score of 2 to 3 points), confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy; failed CS and/or IMM. Previous anti-TNF exposure permitted.		Subjects who successfully completed Study M06-826 or M06-827
Main primary outcomes		Proportion of subjects with remission at W8			Ranked co-primary; Proportion of subjects who 1. Achieved remission at W8 and 2. Achieved remission at W52		Efficacy: PMS, MS and Mayo sub-scores (absolute score and change from BL); colectomy rates; QoL using IBDQ, SF-36, and WPAI; health care resources utilisation (physician visit, emergency room visits, hospital admissions, days in hospital). Safety: Adverse events, physical examination, vital signs, laboratory data.
Main secondary outcomes		Proportion of subjects with: 1. Clinical response per MS at W8 2. Mucosal healing at W8 3. Proportion with RBS ≤ 1 at W8 4. PGA sub-score ≤ 1 at W8 5. SFS ≤ 1 at W8 6. IBDQ responders at W8			Proportion of subjects with: 1. Remission (sustained) per MS at both W8 and W52. 2. Response per MS at W8 3. Response per MS at W52 4. Response (sustained) per MS at both W8 and W52 5. Mucosal healing at W8 6. Mucosal healing at W52 7. Mucosal healing (sustained) at both W8 and W52; 8. Discontinued CS use for ≥90 days before W52 & remission at W52 9. PGA sub-score ≤ 1 at W8 10. SFS ≤1 at W8 11. RBS ≤1 at W8 12. Discontinued CS use for at least 90 days before W52 & remission at W52 13. Discontinued CS use & remission at both W32 & W52 14. IBDQ responders at W8 15. IBDQ responders at W52		

Abbreviations: BL=baseline; CS=corticosteroid; DB=double-blind; EOW=every other week; EW=every week; IMM=Immunomodulator; IBDQ=Inflammatory bowel disease questionnaire; MS=full Mayo Score; OL=open label; PGA=physician's global score; PMS; partial Mayo Score; QOL; quality of life; RBS=rectal bleeding sub-score; SFS=stool frequency sub-score; W=week; WPAI; Work Productivity and Activity Impairment Questionnaire.

M06-826 ULTRA 1 (8 week induction study post-Amendment-3)

Following an amendment to the study protocol (Amendment 3), at the request of the European Regulatory Agencies, the objective of this study was to assess the efficacy and safety of two dosing regimens of ADA 160/80/40 and 80/40/40 for the induction of clinical remission in subjects with moderately to severely active ulcerative colitis (Mayo Score 6 to 12 points with endoscopy sub-score of 2 to 3 points) who had failed prior or concurrent therapy with systemic corticosteroids and/or immunosuppressants (azathioprine or 6-mercaptopurine). The original study contained one adalimumab arm (ADA 160/80: 160mg at week zero, 80mg at week 2, 40mg EOW subsequently) and a placebo arm, which recruited 186 patients before Amendment-3. All efficacy endpoints were measured in the intention-to-treat population enrolled under Amendment-3 or later (ITT-A3). The

safety population included all patients enrolled under the original protocol or later amendments and had received at least one dose of study drug or placebo.

Subjects received DB therapy from Baseline until week 8 and OL therapy from week 8 until the end of the study. Starting at week 12, subjects with inadequate response could dose escalate to adalimumab 40mg every week (EW); inadequate response was defined as:

- For subjects with a Partial Mayo (PM) score of 4 to 7 at Baseline: PM score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart
- For subjects with a PM score of 8 or 9 at Baseline: PM score ≥ 7 on 2 consecutive visits at least 14 days apart

Subjects on aminosalicylates, azathioprine or 6-MP who qualified for enrolment in the study were required to continue these doses unchanged through the entire study. No dose adjustments of other UC-related concomitant treatments was allowed, with the exception of oral corticosteroids which could be tapered between week 8 and week 52 for patients with acceptable clinical response, according to investigator assessment, unless there was a treatment-related toxicity considered moderate to severe by the investigator.

This study is used as the primary evidence for induction of remission to week 8 (supported by evidence from M06-827 described below). The primary efficacy endpoint was the proportion of subjects with remission at week 8. Remission was defined as a total Mayo Score ≤ 2 and no individual sub-score > 1. Secondary endpoints were ranked so that a statistically significant result needed to be achieved in order to initiate the next comparison in the lower rank.

The overall duration of this study was up to 65 weeks, including a Screening Period of up to 21 days, 52-week study treatment duration, and a 70-day follow-up phone call for subjects who prematurely discontinued or who did not enrol in the extension study.

M06-827 (52 week maintenance study)
The primary objective of study M06-827 was to assess the efficacy and safety of adalimumab for the induction (8 weeks) and maintenance (52 weeks) of clinical remission in subjects with moderately to severely active UC (Mayo Score 6 to 12 points with endoscopy sub-score of 2 to 3 points) who had failed prior or concurrent therapy with systemic corticosteroids and/or immunosuppressants (azathioprine or 6-mercaptopurine). Patients enrolled in M06-827 could also have received prior treatment with infliximab. Study M06-827 is used as the primary evidence of the effect of adalimumab therapy to week 52 (as well as to week 8). The breakdown of the overall duration was identical to that for study M06-826.

Subjects were stratified by prior exposure to infliximab and/or other anti-tumour necrosis factor (TNF) agents, and randomised in a 1:1 ratio to receive ADA or PBO by subcutaneous (SC) injection. The regimen was as per that intended in clinical practice: 160 mg at week 0, 80 mg at week 2, 40 mg at Week 4 and then 40 mg EOW. At or after week 10, subjects who met the criteria for inadequate response could be switched to open-label (OL) ADA beginning at week 12. Inadequate response was defined as for study M06-826.

Subjects were not permitted to change the dosage of UC-specific concomitant medications throughout the study with the following 2 exceptions: decrease in corticosteroid dose between week 8 and week 52 for patients with acceptable clinical response, per the Investigator's discretion, and a dose decrease of any UC-related concomitant treatments in the event of UC treatment-related toxicities considered moderate to severe in the opinion of the investigator. There were two ranked co-primary endpoints:

- The proportion of subjects who achieved remission at week 8; and
- The proportion of subjects who achieved remission at week 52

Secondary endpoints were both ranked and non-ranked.

M10-223 (long-term supportive evidence)
Study M10-223 provides supportive evidence. The objective of this study was to evaluate the long-term maintenance of response, safety, and tolerability of repeated administration of ADA in subjects

who participated in and successfully completed either study M06-826 or study M06-827. Subjects who entered this study from a blinded cohort were assigned to OL ADA 40 mg EOW and those who entered from an OL cohort continued their previous dosing regimen. Any subject who was an inadequate responder or showed response and then had a disease flare could have their ADA dose increased to 40 mg every week, but no earlier than the week 12 visit, or the week 2 visit if already on OL ADA. Inadequate response was defined identically to that for study M06-826 and M06-827. Disease flare was defined as any subject who presents with a partial Mayo Score difference ≥ 3 compared to the Day 1/Baseline (extension study M10-223) partial Mayo Score on 2 consecutive visits at least 14 days apart. Subjects could participate in the study for up to 240 weeks.

2.1.3 Randomisation and blinding

The measures taken to minimise bias in the included studies are summarised in Table 6 below. Both M06-826 and M06-827 were appropriately randomised and blinded. M10-223 is an open label extension study. All three studies were analysed on an ITT or ITT LOCF basis.

Table 6: Summary of the measures undertaken to minimise bias

Trial ID	Randomisation	Blinding Subjects	Blinding Investigators	Blinding Assessors	Basis for analysis	Report source
M06-826	Telephone/ internet	Yes	Yes	Yes	ITT	CSR M06-826
M06-827	Telephone/ internet	Yes	Yes	Yes	ITT	CSR M06-827
M10-223	No	No	No	No	ITT LOCF	CSR M10-223

M06-826: ITT: Missing or incomplete data were to be handled using the non-responder imputation method. The LOCF method was also to be used as a sensitivity analysis. M06-827: ITT missing data or patients who discontinued the study early (including those switching to OL) were classified as “no” for remission. LOCF was used for sensitivity analysis. M10-223: ITT LOCF where the last non-missing value after the baseline visit is carried forward, and as observed as sensitivity analysis.

M06-826
Subjects enrolled in the study under the original protocol or Amendments 1 and 2 were randomised in a 1:1 ratio to receive ADA or PBO during the 12-week DB induction period. Subjects received 160 mg of ADA or PBO at baseline; 80 mg ADA or PBO at week 2; and 40 mg ADA or PBO at weeks 4 and 6. At week 8, subjects randomised to PBO received 160 mg ADA followed by 80 mg ADA at week 10. Subjects randomised to ADA continued to receive 40 mg ADA at weeks 8 and 10. All subjects continued to receive 1 injection of open-label (OL) ADA 40 mg EOW beginning at week 12 up to week 52 (or the early termination visit). All subjects were centrally randomised at baseline using the interactive voice recognition system (IVRS), which was to assign a treatment group according to the randomisation scheme generated before the start of the study. This treatment group assignment was maintained by the IVRS and not provided to the site, as the subject was referred to by the subject number assigned at Baseline.

M06-827
Subjects were stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomised in a 1:1 ratio to receive ADA or PBO by SC injection. Subjects assigned to the ADA treatment arm received an induction dose of 160 mg at week zero and 80 mg at week 2, and 40 mg every other week (EOW) starting at week 4. Subjects assigned to the PBO treatment arm received a matching PBO during the same period of time. At or after week 10, subjects who met the criteria for inadequate response could have been switched to open-label (OL) ADA 40 mg EOW beginning at week 12. Inadequate response was defined as: Partial Mayo Score greater than or equal to Baseline score on two consecutive visits at least 14 days apart (for subjects with a partial Mayo Score of 4 to 7 at Baseline); or partial Mayo Score ≥ 7 on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo Score of 8 or 9 at Baseline).

All subjects were centrally randomised at baseline using the IVRS, which assigned a treatment group according to the randomisation scheme generated by Abbott before the start of the study. The treatment group assignment was maintained by the IVRS and was not provided to the site.

In Study M06-827 problems were identified with GCP compliance at three sites. Consequently, the ITT analysis set excluded patients from these three sites (n=14 ADA; n=10 PBO). These sites were non-compliant with GCP and protocol requirements. Data for patients from these sites were excluded from the efficacy analysis, but retained in the safety analysis.

The ITT analysis set (N=494) was the basis for the confirmatory primary efficacy analysis and the ranked and non-ranked secondary efficacy analyses. The exclusion of similar small numbers of patients from each treatment group prior to database lock and un-blinding is not expected to have any meaningful effect on the validity of the study.

2.1.4 Flow of participants

M06-826
This study evaluated the efficacy of two adalimumab induction regimens compared to placebo in 575 subjects with moderately to severely active UC, as well as the maintenance of remission in subjects who were followed to 52 weeks in the open-label phase of the study.

Owing to changes in study design introduced by Protocol Amendment-3, in which the ADA 80/40 treatment group was added, separate analysis sets were used for the induction and maintenance phases of the study. The primary analysis population for the induction phase of the study (DB period through week 8) was the ITT-A3 Set (N = 390), a population comprising all randomised and treated subjects enrolled after Protocol Amendment-3. The primary analysis population for the maintenance phase of the study (OL period through week 52) was the ITT-E Set (N=575), a population comprising all subjects who received long term ADA regardless of randomisation group and amendment. Safety analyses were performed separately for the DB, PBO-controlled period (week zero to week 8) and the OL period. The safety analysis set included all patients in the ITT-E set as well as one subject who did not have confirmed UC at screening/BL, but was randomised and dosed.

M06-827
A total of 518 patients were randomised into the study; 24 patients (10 ADA and 14 PBO) were excluded from the ITT analysis due to site noncompliance with GCP.

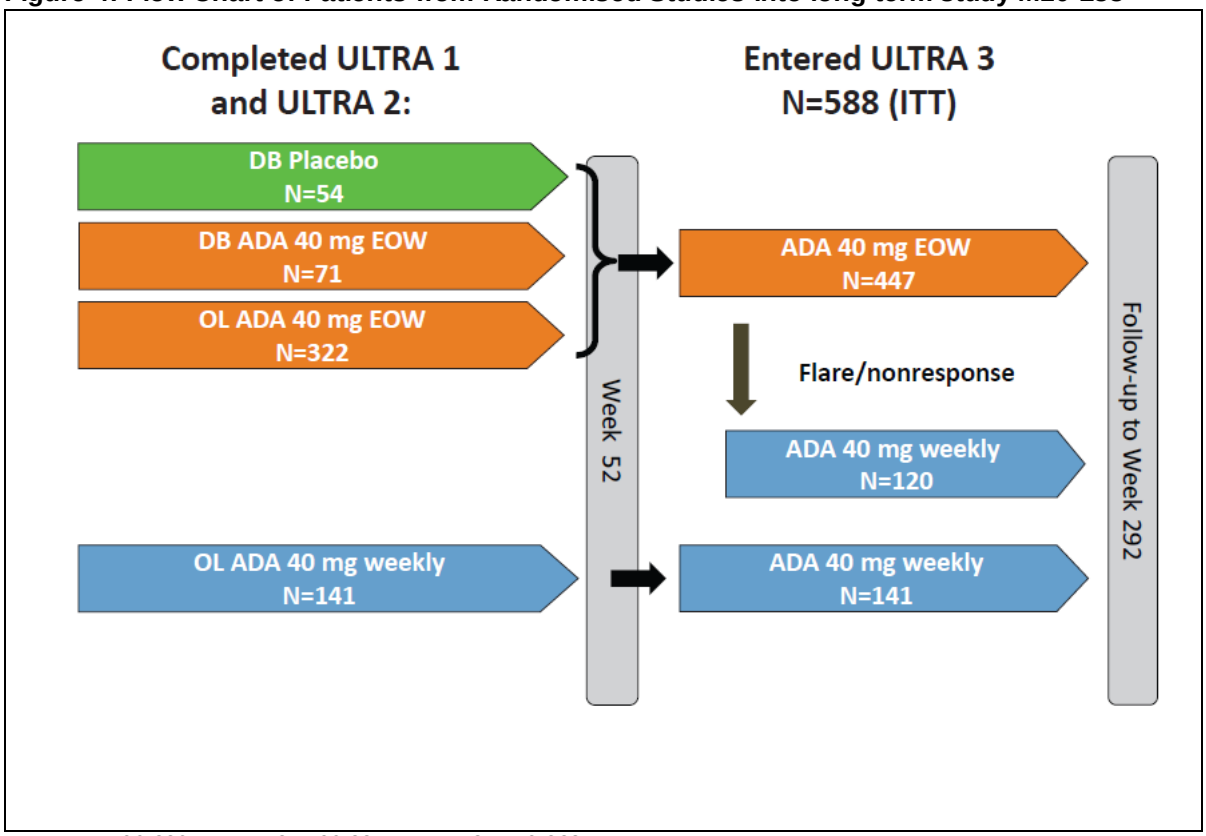
At or after Week 10, patients who met the criteria for inadequate clinical response could have been switched to OL ADA 40mg EOW beginning at week 12. In the ITT analysis set, a total of 251 patients switched to OL administration (135 who had been randomised to PBO and 116 who had been randomised to ADA). Patients who demonstrated inadequate clinical response at two consecutive visits at least 14 days apart while on OL ADA 40mg EOW were permitted to dose escalate to ADA 40mg EW. A total of 152 patients dose-escalated from EOW to EW ADA (84 who had been randomised to PBO and 68 who had been randomised to ADA). The per protocol (PP) analysis set consisted of patients in the ITT analysis set after excluding patients with major protocol deviations (N=424). Exploratory efficacy analyses were performed on the PP analysis set. The Safety analysis set consisted of patients who received at least one dose of study drug, including noncompliant sites (N = 517).

M10-223
There were 592 patients enrolled who were previously randomised; 334 (56.4%) from Study M06-826 and 258 (43.6%) from Study M06-827.

From these; four patients were excluded from ITT-1 because of non-compliance with GCP protocol and 50 additional patients were excluded from the ITT-2 Analysis Set because they had a between-study dosing gap >17 days. All patients were included in the Safety Analysis Set, defined as all patients who received at least 1 dose of study drug. Fifty-five patients (9.3%) had received only PBO treatment before entering this study; all other patients were receiving ADA treatment at the time they enrolled in this study. Most patients (394 subjects; 66.5%) were receiving EOW dosing (264/334 from study M06-826 and 130/258 from study M06-827). As of April 2012, 367 patients were still active in the trial with discontinuation most frequently due to lack of efficacy, AEs, and withdrawal of consent. All other reasons were reported by < 10 patients each.

A summary of participant flow from the two included randomised controlled trials into the open label extension study is shown below in Figure 4; note the figure takes the view of the ITT-1 population (N=588).

Figure 4: Flow Chart of Patients from Randomised Studies into long-term study M10-233



ULTRA 1=M06-826; ULTRA 2=M06-827; ULTRA 3=M10-223

2.1.5 Characteristics of the RCTs

Overall, the M06-826 and M06-827 trials were highly similar in terms of inclusion and exclusion criteria with one notable exception. M06-827 allowed patients who were anti-TNF experienced to be included in the study, whereas M06-826 did not. A summary of the main eligibility criteria is provided in Table 7 below

Table 7: Main eligibility criteria in the included studies

Inclusion criteria	Exclusion criteria
Study ID M06-826	
1. Male or female ≥ 18 years of age. 2. Diagnosis of UC for > 90 days prior to BL 3. Diagnosis of active UC confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of Infection. 4. Active UC: -MS 6 to 12 points and endoscopy sub-score of 2 to 3 points, despite concurrent treatment with at least 1 of the following: -Stable oral corticosteroid dose (prednisolone or equivalent): a) ≥ 20 mg/day for ≥14 days prior to BL or b) < 20 mg/day for ≥40 days prior to BL. And/or - At least a consecutive 90 day course of azathioprine or 6-MP prior to BL, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the patient during that time. Patient was to be on a stable dose for at least 28 days prior to BL. Note: If patients were on both oral corticosteroid and immunosuppressants, only 1 of the drugs had to meet the above criteria. Concurrent therapy was not required for patients who were previously treated with corticosteroids or immunosuppressants during the previous 5 years and, in the judgment of the investigator, have failed to respond to or intolerant.	1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for UC or planning bowel surgery. 2. Received anti-TNF agent or biological therapy in the past. 3. Received recent ciclosporin, tacrolimus, or mycophenolate mofetil, IV corticosteroids, therapeutic enema or suppository (other than required for endoscopy) 4. Current diagnosis of fulminant colitis and/or toxic megacolon. 5. Disease limited to the rectum (ulcerative proctitis). 6. Current diagnosis of indeterminate colitis. 7. Current diagnosis and/or history of CD. 8. Currently receiving total parenteral nutrition. 9. Discontinued use of azathioprine or 6-MP within 28 days or corticosteroid within 14 days of BL. 10. Patients using aminosalicylates for less than 90 days prior to BL, not on a stable dose for at least 28 days prior to BL, or discontinued use within 28 days of BL. 11. History of malignancy, infection (including C. difficile stool assay), poorly controlled medical condition(s). 12. Pregnant or breast-feeding. 13. Patients currently taking both budesonide and prednisone (or equivalent) simultaneously.
Study ID M06-827	
1. Male or female ≥ 18years of age. 2. Diagnosis of UC for > 90 days prior to BL. 3. Diagnosis of active UC confirmed by colonoscopy with biopsy	1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for UC, or planned bowel surgery.

Inclusion criteria	Exclusion criteria
or flexible sigmoidoscopy with biopsy during the Screening Period 4. Active UC -MS of 6 to 12 points and endoscopy sub-score 2 to 3 points, despite concurrent treatment with at least 1 of the following: -Stable oral corticosteroid dose (prednisone or equivalent): a) ≥ 20 mg/day for ≥14 days prior to BL or b) < 20 mg/day for ≥40 days prior to BL. And/or - At least a consecutive 90 day course of azathioprine or 6-MP prior to BL, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the patient during that time. Patient was to be on a stable dose for at least 28 days prior to BL. Note: If patients were on both oral corticosteroid and immunosuppressants, only 1 of the drugs had to meet the above criteria. Concurrent therapy was not required for patients who were previously treated with corticosteroids or immunosuppressants during the previous 5 years and, in the judgment of the investigator, have failed to respond to or intolerant. 5. Previous use of anti-TNF agents other than adalimumab permitted if discontinued use due to a loss of response or intolerance	2. Received recent ciclosporin, tacrolimus, mycophenolatemofetil IV corticosteroids, therapeutic enema or suppository, investigational agent. 3. Current diagnosis of fulminant colitis and/or toxic megacolon, indeterminate colitis, and/or history of CD 4. Disease limited to the rectum (ulcerative proctitis). 5.Currently receiving total parenteral nutrition. 6. Patients using aminosalicylates for less than 90 days prior to BL, not on a stable dose for at least 28 days prior to BL, or discontinued use within 28 days of BL 7. History of malignancy, infection (including C. difficile stool assay), poorly controlled medical condition(s). 8. Previously used infliximab or any anti-TNF agent within 56 days of BL or at any time without clinical response (unless experienced treatment-limiting reaction.) 9. Pregnant or breastfeeding 10. Prior exposure to natalizumab, abatacept or any other biological therapy other than anakinra and anti-TNF agents. 11. Currently taking both budesonide and prednisone (or equivalent) simultaneously.
Study ID M10-223	
1. Successfully enrolled in and completed either Study M06-826 or M06-827. 2. Judged to be in generally good health based upon clinical evaluations performed during the preceding Study M06-826 or M06-827.	1. Patient has not responded to weekly adalimumab from Study M06-826 or M06-827. 2. History of malignancy, infection, poorly controlled medical conditions or current diagnosis of fulminant colitis and/or toxic megacolon 4. Pregnancy 5. Received ciclosporin, tacrolimus, or mycophenolate mofetil within 30 days prior to BL; prior concomitant medication requirements.

Abbreviations: BCC = basal cell carcinoma; BL = baseline; CD = Crohn's disease; IV = intravenous; MS=Mayo Score; SCC = squamous cell carcinoma; UC = ulcerative colitis; 6-MP = 6-mercaptopurine;

2.1.6 Baseline demographic characteristics

The baseline characteristics of included patients in study M06-826 are summarised in Table 8. The majority of study subjects in the ITT-A3 and ITT-E Sets were male, white, and < 45 years old. The groups were relatively well balanced with respect to all baseline characteristics (Table 8). Subjects in the ITT-A3 and ITT-E Sets had a mean duration of UC of around 8 years, with disease comprising primarily pancolitis (52.1% and 55.0%, respectively).

Table 8: Baseline characteristics in M06-826, ITT Analysis Sets

	ITT-A3		ITT-E	
	ADA 160/80/40 N=130	PBO N=130	ADA 160/80/40 N=223	PBO N=222
Female n(%)	47 (36.2)	48 (36.9)	85 (38.1)	83 (37.4)
White n(%)	119 (91.5)	117 (90.0)	206 (92.4)	202 (91.0)
Age mean (SD) years	38.2 (13.46)	38.9 (12.68)	38.5 (13.06)	39.7 (12.72)
Duration of UC; mean (SD) years	8.11 (7.247)	7.48 (7.159)	8.41 (7.284)	7.89 (7.524)
Site of UC – Pancolitis n(%)	60 (46.2)	73 (56.2)	114 (51.1)	132 (59.5)
Site of UC – Descending colon n(%)	61 (46.9)	42 (32.3)	87 (39.0)	67 (30.2)
Site of UC – Other n(%)	9 (6.9)	15 (11.5)	22 (9.9)	23 (10.4)
Mayo Score; mean (SD)	8.8 (1.61)	8.7 (1.56)	8.9 (1.65)	8.8 (1.58)
Mayo Score; median (Range)	9 (6-12)	9 (6-12)	9 (6-12)	9 (6-12)
Partial Mayo Score; mean (SD)	6.4 (1.51)	6.2 (1.41)	6.4 (1.51)	6.3 (1.41)
Endoscopy sub-score; mean (SD)	2.4 (0.50)	2.5 (0.52)	2.5 (0.51)	2.5 (0.51)
RBS sub-score; mean (SD)	1.7 (0.88)	1.6 (0.79)	1.7 (0.86)	1.6 (0.86)
PGA sub-score; mean (SD)	2.2 (0.57)	2.2 (0.50)	2.2 (0.60)*	2.2 (0.50)*
Stool frequency sub-score	2.5 (0.78)	2.4 (0.74)	2.5 (0.75)	2.5 (0.75)
IBDQ score	131.9 (35.07)	125.2 (31.94)	126.0 (35.01)	125.2 (32.18)
SF-36 physical component score	41.99 (8.793)	40.30 (7.947)	40.89 (8.699)	40.70 (8.143)
SF-36 mental component score	36.84 (12.767)	36.68 (11.006)	36.00 (8.699)	37.61 (11.217)
Any UC-related medications; n (%)	121 (93.1)	125 (96.2)	211 (94.6)	209 (94.1)

Source CSR M06-826; Abbreviations: ITT-A3 = all randomised and treated subjects enrolled after Protocol Amendment 3 ITT-E = all subjects who received long term ADA regardless of randomisation group and amendment; *Significant difference between treatment groups (p=0.009)

The baseline characteristics of patients included in study M06-827 are summarised in Table 9. The groups were well balanced with respect to all baseline characteristics. The majority of subjects were male, white, and < 45 years old. Subjects in the ITT analysis set had a mean duration of UC of 8.1 to 8.5 years, with the primary disease site of pancolitis (48%). Among the baseline outcomes questionnaires, the adalimumab treatment group had a statistically significantly higher SF-36 physical component summary score, role-emotional functioning component score, and mental health component score compared with placebo (P = 0.012, 0.004, and 0.037, respectively). There were no other statistically significant differences observed between treatment groups (ITT analysis set).

Table 9: Baseline characteristics in M06-827, ITT Set

	ADA N = 248	PBO N = 246
Female n (%)	106 (42. 7)	94 (38. 2)
White n (%)	236 (95. 2)	234 (95. 1)
Age; mean (SD) years	39.6 (12.47)	41.3 (13.22)
Duration of UC; mean (SD) years	8.1 (7.09)	8.5 (7.37)
Site of UC – Pancolitis n(%)	120 (48.4)	120 (48.8)
Site of UC – Descending colon n(%)	96 (38.7)	96 (39.0)
Site of UC – Other n(%)	32 (12.9)	30 (12.2)
Mayo Score; N; Mean (SD)	246; 8.9 (1.50)	245; 8.9 (1.75)
Mayo Score; N; Median (Range)	246; 9 (6-12)	245; 9 (5-12)
Partial Mayo Score; N; Mean (SD)	247; 6.5 (1.39)	245; 6.5 (1.55)
Endoscopy score (mucosal healing) N; Mean (SD)	247; 2.5 (0.50)	246; 2.5 (0.50)
RBS subscrore; N; Mean (SD)	247; 1.7 (0.85)	245; 1.7 (0.94)
PGA sub-score score; N; Mean (SD)	247; 2.2 (0.55)	245; 2.2 (0.57)
Stool frequency sub-score	247; 2.5 (0.71)	245; 2.6 (0.66)
IBDQ score	230; 127.7 (28.68)	230; 123 (33.26)
SF-36 physical functioning component score	245; 45.7 (9.53)*	239; 44.6 (9.79)*
SF-36 mental component summary	245; 39.0 (10.67)*	237; 36.5 (11.57)*
WPAI – overall work impairment	168 (50.1 (31.98)	155; 52.9 (31.34)
Any UC-related medication at BL; n (%)	224 (90.3)	218 (88.6)
Prior infliximab therapy	97 (39.1)	101 (41.1)

Source CSR M06-827; *Significant difference between treatment groups

Table 10 includes baseline details of all subjects in M10-223 for completeness. However this study is a composite of patients previously enrolled to studies M06-826 and M06-827 and was not randomised or controlled. Interestingly, the table highlights the improvement in Mayo Score achieved by patients on adalimumab over time when compared to baseline scores from M06-826 and M06-827. The ITT-1 analysis set (N = 588) is defined as subjects who received at least one dose of study drug; this excludes four subjects due to noncompliance with GCP and protocol requirements. The safety analysis set (N = 592) consists of all subjects who received at least one dose of study drug, including subjects from the two noncompliant sites.

Table 10: Baseline characteristics in M10-223, ITT-1 Analysis Set

Characteristic	ADA 40mg EOW or EW
Sex female; n (%)	216 (36.7)
Race; white n(%)	549 (93.4)
Age; Mean (SD) years	41.6 (12.83)
Weight; Mean (SD) years	78.1 (16.15)
Partial Mayo Score; Mean (SD)	2.5 (2.02)
Mayo Score; Mean (SD)	3.5 (2.73)
Endoscopy sub-score; Mean (SD)	1.0 (0.94)
Rectal bleeding sub-score; Mean (SD)	0.4 (0.69)
Physician Global Assessment of Disease Severity sub-score; Mean (SD)	0.8 (0.81)
Stool Frequency sub-score; Mean (SD)	1.3 (1.00)

Source: CSR M10-233

2.1.7 Comparability of patient populations enrolled in the trials

Based on the available information in Table 8 and Table 9, the two trial populations are very similar in terms of age, race, and duration of disease irrespective of analysis set. Both studies enrolled patients that were similar in terms of Mayo Score, Partial Mayo Score, endoscopy, and other sub-scores. The proportion of patients receiving other UC-related medications was consistent across all analysis sets. The baseline prior therapies also appear to be reasonably similar across the studies, with the exception of infliximab, prior treatment which was disallowed in M06-826, but allowed in M06-827. The studies did not include the acute severe hospitalised patient population. Patients receiving intravenous corticosteroids within 14 days of screening or during the screening period were excluded

from trial inclusion. Patients with toxic megacolon or fulminant colitis or planned UC surgery were also excluded.

2.1.8 Details of intervention and follow up

For both studies, the study drug was provided as a SC injection solution in 1 mL, pre-filled syringes containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. The packaging design of the study drug was identical for all versions of the protocol. All subjects were randomised to receive adalimumab or placebo SC at week zero. Subjects randomised to the adalimumab treatment group received 160 mg at baseline (week zero), 80 mg at week 2 (M06-826 had an additional arm with an 80mg/40mg algorithm), and 40 mg EOW starting at week 4. Subjects randomised to the placebo treatment group received 4 injections at baseline (week 0), two injections at week 2, and one injection EOW starting at week 4.

Assessments to identify subjects who were inadequate responders could be started at week 10 (week 12 after Amendment-3 for study M06 826). In study M06-826, if a subject met the definition of an inadequate responder (outlined below), the subject could dose-escalate to adalimumab 40 mg weekly starting at week 12 (week 14 after Amendment-3). In study M06-827, at or after week 10, subjects who met the criteria for inadequate response could have been switched to OL adalimumab 40 mg EOW beginning at week 12. Subjects who demonstrated inadequate response at two consecutive visits at least 14 days apart while on OL administration 40 mg EOW were permitted to dose escalate to adalimumab 40 mg weekly.

Inadequate Responder Definition:

- Subjects with a baseline partial Mayo Score of 4 to 7 who presented with a score greater than or equal to their baseline score on 2 consecutive visits at least 14 days apart
- Subjects with a partial Mayo Score of 8 or 9 at baseline who presented with a score of ≥ 7 on 2 consecutive visits at least 14 days apart

Doses were selected based on a combination of expert clinical advice, clinical data from the adalimumab development program in CD, and extensive pharmacokinetic data accumulated in the adalimumab rheumatoid arthritis and CD development programs along with pharmacokinetic modelling. For study M06-826, the adalimumab 160/80/40 mg and 80/40 mg dosing induction regimens were selected based on results from the adalimumab CD development program and were in accordance with the dosage recommendations in the US product label approved in 2007 and the EU-SmPC for induction therapy for CD. In clinical studies conducted in subjects with CD, induction regimens comprising 160 mg adalimumab at week zero and 80 mg adalimumab at week 2 (ADA160/80/40 regimen) or 80 mg adalimumab at week zero and 40 mg adalimumab at week 2 (ADA80/40 regimen) produced higher rates of remission at week 4 than PBO (35.5% and 24.0% vs. 12.2%, respectively).

Subjects on aminosalicylates, azathioprine, or 6-MP who qualified for enrolment into the studies were to continue their medication doses. Doses of these medications were to remain unchanged during the entire course of the studies. Subjects who entered the study on probiotics could continue this therapy provided the dose remained unchanged. No dose adjustments of UC-related concomitant treatments were allowed, with the exceptions of; 1) an oral corticosteroid taper between week 8 and week 52 (at investigators discretion) and; 2) a dose decrease of any UC-related concomitant treatments in the event of UC treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator. Corticosteroids (prednisone or equivalent) were permitted. Subjects were not allowed to adjust the corticosteroid dose during the first 8 weeks of the study. At week 8 and thereafter, subjects who, in the opinion of the investigator, had a satisfactory clinical response were permitted to undergo corticosteroid taper according to the schedule described below, or per investigator discretion, as defined by local standards.

For doses > 10 mg/day of prednisone (or equivalent) start with a weekly dose decrease of 5 mg/day until a 10 mg/day dose is reached. Thereafter, decrease weekly by 2.5 mg/day until discontinuation. If the subject experienced a loss of satisfactory clinical response, the subject could have their corticosteroid dose increased per the investigator's discretion, up to a maximal dose equivalent to the dose used at Baseline.

The use of ciclosporin, tacrolimus, mycophenolate mofetil, and investigational agents was prohibited 30 days or 5 half-lives prior to baseline and during the study. Intravenous corticosteroid use was prohibited within 14 days prior to screening, during the screening period, and during the study. Subjects who took these medications during the study were to be discontinued. Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, were prohibited within 14 days prior to the screening endoscopy, during the remainder of the screening period, and during the study.

In the open label extension study M10-223, all subjects received OL study drug, ADA 40 mg EOW or ADA 40 mg EW, administered as a single SC injection using sterile technique. Subjects who entered the study from a blinded cohort were assigned to OL ADA, 40 mg EOW. Subjects who entered the study from an OL cohort continued their previous dosing regimen of ADA, 40 mg EOW or EW. As in the randomised studies, if a subject met the definition of an inadequate responder the subject could dose-escalate to ADA 40 mg weekly starting at week 12 (or at week 2 for subjects who entered the study from an OL cohort).

2.1.9 Outcome measures and methods of analysis

Table 11 summarises the main end-points used across the studies. Detailed information relating to the individual end-points (definition and methods of statistical analyses) is presented subsequently.

Table 11: Outcome measures in the included studies

Endpoints	M06-826	M06-827	M10-233	Definition
Remission per Mayo Score Week 8	✓ (Primary)	✓ (Co-Primary)		Total Mayo Score ≤ 2 and no individual sub-score > 1.
Clinical response Week 8	✓	✓		Decrease in Mayo Score of ≥ 3 points and a ≥30% decrease from Baseline plus a decrease in the RBS ≥ 1 or an absolute RBS of 0 or 1
Mucosal healing Week 8	✓	✓		Endoscopy sub-score of 0 or 1
Mucosal healing Week 52		✓		Endoscopy sub-score of 0 or 1
Sustained mucosal healing Week 8 and 52		✓		Endoscopy sub-score of 0 or 1
RBS ≤1 Week 8	✓	✓		
PGA ≤1 Week 8	✓	✓		
SFS ≤1 Week 8	✓	✓		
Sustained remission per Mayo Score Week 8 and Week 52		✓		Total Mayo Score ≤ 2 and no individual sub-score > 1 at both visits
Remission per Mayo Score Week 52	✓	✓ (Co-Primary)		Total Mayo Score ≤ 2 and no individual sub-score > 1.
Response per Mayo Score Week 52	✓	✓		
Partial Mayo Score (all visits) and change from BL	✓ BL, Week 2, 4, 6, 8	✓	✓	
Mayo Score (BL, Week 48) and change from BL	✓ Week 8	✓	✓	
Endoscopy score (every 48 weeks)			✓	
RBS (All visits)			✓	
PGA (All visits)			✓	
Stool frequency (All visits)	✓	✓	✓	
IBDQ response	✓ Week 8	✓ Week 8, 32, 52	✓	
SF-36 score	✓	✓	✓	
Healthcare resource utilisation	✓	✓	✓	
Work Productivity and Activity Impairment	✓	✓	✓	

Abbreviations: BL = baseline; RBS = rectal bleeding score; PGA = physician global assessment; SFS = stool frequency sub-score; IBDQ = Inflammatory Bowel Disease Questionnaire

A summary of the definitions and methods of statistical analysis for the outcome measures in the individual trials is provided below in Table 12, Table 13, and Table 14.

Table 12: Outcome measures and methods of analysis in M06-826

Endpoint	Statistical Analysis
Primary endpoint – ITT-A3 population	
Remission rate of ADA and PBO groups at Week 8. Defined as proportion of patients with a total Mayo Score ≤ 2 and no individual sub-score > 1.	Non-responder imputation (NRI) was used for calculations of remission rate. Patient discontinuation for any reason and missing Mayo Scores were counted as "no" to remission. NRI was also applied to the ITT-A2 Population and the Per Protocol Population to provide supportive evidence. The LOCF method was used for sensitivity analyses. The two sided 95%CI for the difference in the remission rates was calculated by normal approximation to binomial distribution
Principal secondary endpoint – ranked: ITT-A3 population	
1. Proportion of patients with clinical response per Mayo Score at Week 8; defined as a decrease in Mayo Score of ≥3 points and a ≥30% decrease from Baseline plus a decrease in the RBS ≥ 1 or an absolute RBS of 0 or 1 2. Proportion of patients with mucosal healing (Endoscopy sub-score of 0 or 1) at Week 8 3. Proportion of patients with RBS ≤1 (indicative of mild disease) at Week 8 4. Proportion of patients with PGA sub-score ≤ 1 (indicative of mild disease) at Week 8 5. Proportion of patients with Stool Frequency sub-score ≤1 (indicative of mild disease) at Week 8 6. Proportion of IBDQ responders at Week 8. Defined as those with a ≥ 16 point increase from BL in total IBDQ	Difference in proportion of patients achieving response between ADA and PBO assessed using chi-square, or Fisher's exact test as appropriate. Statistical comparisons for ranked secondary endpoints carried out in hierarchical order, P-value ≤ 0.05 had to be achieved for higher rank to initiate next comparison in lower rank.
Other secondary endpoints – non-ranked	
Proportion of patients with response per Partial Mayo Score at Week 8. Defined as a decrease in Partial Mayo Score ≥ 2 points and ≥ 30% from BL PLUS a decrease in the RBS ≥ 1 or absolute RBS of 0 or 1 Remission per Mayo Score for OL period to Week 52 Response per Mayo Score for OL period through Week 52	Analysed using the same methods listed above applicable to the ITT-E population. Response rate based on Mayo Score and colectomy rate tabulated and tested using chi-square test or Fisher's exact test, as appropriate.
Health Outcome Assessments	
Proportion of IBDQ responders at week 8 Change from Baseline in SF-36 at Weeks 8 and 52	Analysed as for other non-ranked dichotomous efficacy variables using descriptive statistics.
Safety Assessments	
AEs, TEAs, SAEs, laboratory data, vital signs	DB and OL period analysed separately, descriptive statistics
Sample size calculation	
Assuming 15% of patients in the PBO group achieved clinical remission at Week 8, a sample size of 125 in each treatment group in the ITT-A3 population would be adequate to detect a 15% difference using a chi-square test with 80% power at a 0.05 two-sided significance level. Thus, a total of 375 patients were to be randomised following Amendment 3 of the study.	

Source: CSR M06-826; Abbreviations: ADA = adalimumab; BL = Baseline; CI = confidence interval; DB = double blind; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT-A3 = all randomised and treated subjects enrolled after Protocol Amendment 3 ITT-E = all subjects who received long term ADA regardless of randomisation group and amendment; LOCF = last observation carried forward; OL = open label; PBO = placebo; RBS = rectal bleeding sub-score; AEs = adverse events; TEAEs = treatment emergent adverse events; SAEs = serious adverse events.

Table 13: Outcome measures and methods of analysis in M06-827

Endpoint	Statistical Analysis
Co-Primary endpoints	
1. Proportion of patients who achieve remission at Week 8. Remission defined as a Full Mayo Score ≤2 and no individual sub-score>1. 2. Proportion of patients who achieve remission at Week 52	Hypothesis testing for ranked co-primary endpoint carried out in a hierarchical order using a two-sided CMH test adjusted for prior exposure to anti-TNFs, with difference in proportions given corresponding two-sided 95% CI. If the null hypothesis of no difference between ADA and PBO in remission rate at Week 8 was rejected at alpha = 0.05, then the same was done at Week 52. In order to claim maintenance of remission it was necessary to reject not only both hypotheses on the two ranked co-primary endpoints but also to reject the hypothesis on the first ordered secondary endpoint (proportion of patients in remission at both Week 8 and Week 52). Non-responder imputation (NRI) calculated the remission rate. Patient discontinuation for any reason and missing Mayo Scores were to be counted as "no" to remission. Patients switching to OL drug were counted as "no" for remission from the time of switching onward. For patients switching to OL drug, the non-missing value at the visit when a subject switched to the OL drug was to be carried forward in the LOCF method. The LOCF method was also used for sensitivity analyses.
Principal secondary endpoints (ranked)	
Proportion of subjects: With remission (sustained) at Week 8 & 52 With clinical response at Week 8 and/or Week 52 With clinical response (sustained) at Week 8 & 52; With mucosal healing at Week 8 and/or Week 52 and sustained week 8 & 52. Who discontinued corticosteroids before Week 52 & achieved remission at Week 52. PGA score ≤ 1 at Week 8 SFS ≤ 1 at Week 8 RBS ≤ 1 at Week 8 Who discontinued corticosteroid use for ≥90 days before & achieved remission at Week 52. Who discontinued corticosteroid use & achieved remission (sustained) at Weeks 32 & 52.	Hypothesis testing as above only if statistical significance in primary endpoints shown.
Health Outcome Assessments	
IBDQ responder at Week 8 *(ranked 2° endpoint)* IBDQ responder at Week 52 *(ranked 2° endpoint)* Change in SF-36 score from baseline over time Change in Work Productivity and Activity Impairment from baseline over time Cumulative healthcare resource utilisation over time	Change from BL in IBDQ, SF-36, WPAI analysed using ANCOVA model including factors of treatment, prior exposure to infliximab/other anti-TNFs, and BL values. Ratio of total utilisations and the time under DB observation calculated across all subjects. Cumulative HCRUs analysed with a Poisson-normal model specifying different intercepts and time slopes for each treatment group and adjusting for stratum defined by prior exposure to infliximab or other anti-TNF agents.
Safety Assessments	
AEs, TEAs, SAEs	Tabulated by number and percentage
Lab data, vital signs	Described by descriptive statistics.
Sample size calculation	
Assuming that 5% of the patients in the PBO group achieved clinical remission at Week 52 or Week 8, a sample size of 250 in each treatment group was adequate to detect a difference of at least 7 percentage points from the ADA group using Chi-square test with 80% power at a 0.05 two-sided significance level. Thus, a total of 500 patients were to be randomised in this study.	

Source: CSR M06-827; Abbreviations: ADA = adalimumab; CMH = Cochran-Mantel-Haenszel; BL = Baseline; CI = confidence interval; DB = double blind; IBDQ = Inflammatory Bowel Disease Questionnaire; LOCF = last observation carried forward; OL = open label; PBO = placebo; RBS = rectal bleeding sub-score. ; AEs = adverse events; TEAEs = treatment emergent adverse events; SAEs = serious adverse events

Table 14: Outcome measures and methods of analysis in M10-223

Endpoint	Statistical analysis
Efficacy	
Partial Mayo Score (all visits) Mayo Score (Baseline, Week 48) Endoscopy score (Baseline, Week 48) RBS (all visits) PGA of disease severity (all visits) Stool frequency (all visits) Mayo Score change from Baseline Change from Baseline in partial Mayo Scores	Descriptive statistics. Continuous variables are summarised by the number of observations, mean, standard deviation, median, minimum, and maximum; whereas discrete variables are summarised by counts and percentages.
Health Outcomes assessments	
Change in IBDQ from Baseline; remission defined as score above 170 Change in SF-36 from Baseline over time Change in Work Productivity and Activity Impairment from Baseline over time	Descriptive statistics.
Safety	
Cumulative no. of unscheduled outpatient visits (physician, emergency room, hospital admissions, days of hospitalisation) AEs (including severity, relation to study drug), SAEs, lab data	Descriptive statistics.

Source CSR M10-223

All meta-analyses were carried out using Review Manager Version 5.2 and the outcomes are presented using the mean and 95% confidence intervals (CI) for the risk difference (RD) and relative risk (RR). A chi squared test for heterogeneity was performed on each analysis and was considered significant if $p < 0.05$. Where there was significant heterogeneity between the studies, a random-effects model was used to control for between study variance. The forest plots of the most clinically relevant comparisons are presented. The fixed-effects model was used unless significant heterogeneity was demonstrated.

2.1.10 Discussion of the outcome measures employed across the studies

Efficacy outcomes

Before the efficacy outcomes are discussed, a description of how these outcomes are measured and evaluated via the Mayo Score, are described below.

In clinical trials, disease activity is evaluated objectively using a clinical activity index, such as the Mayo Clinic disease activity index (or Mayo Score)[16]. The symptoms of UC however undoubtedly affect a patients' perceived quality of life beyond the symptoms of the disease captured by the Mayo Score and as such using a clinical indicator alone will not give physicians the complete picture surrounding the benefits of a given treatment option to the patient. To capture the improvement of the patients' quality of life alongside the symptomatic clinical improvements an HRQoL assessment tool should be used to assess disease improvements. The inflammatory bowel disease questionnaire (IBDQ) is used to capture not only clinical improvements as a result of treatment but also quality of life improvements pertinent to the overall health improvements of the patient.

The Full Mayo Score is an indicator of UC disease activity which covers both clinical and endoscopic parameters. The Full Mayo Score is based on a total composite score comprising of four sub-scores: endoscopy; stool frequency (SFS); rectal bleeding (RBS) and physician's global assessment (PGA), each of which is rated from 0 (least active disease) to 3 (most active disease), for a maximum total score of 12. The Partial Mayo Score omits endoscopy from the patient work-up and results in a maximum possible score of 9. Elements of the Mayo Score and Partial Mayo Score are summarised in Table 15 below.

The Mayo Score has been widely used in clinical trials of UC since it was first published in 1987[36]. In the adalimumab UC studies, the worst sub-score from the past 3 days of the patient diary for SFS and RBS was entered into the database and used to calculate the Mayo sub-score at each visit (i.e. worst case methodology). For example, if a patient was determined to have stool frequency sub-scores of 3, 0, and 0 over the 3 days prior to the visit, a sub-score of 3 would be entered into the database. Likewise, a patient with sub-scores of 3, 3, and 3 on 3 consecutive days would also receive a score of 3 in the database. In this setting, these patients would be considered to be equivalent in terms of stool frequency sub-score, even though the degree of their symptoms differs. If average sub-scores are considered for this same scenario, the first patient would instead receive a stool frequency sub-score of 1 for that visit, compared to 3 for the second patient. The utilisation of

worst-case methodology in scoring may have a disproportionate influence on active therapy efficacy outcomes, particularly if the treatment benefits led to improvement but not 100% control of symptoms, as outlined in the example above. For calculation of the stool frequency sub-score the patient's "normal stool frequency" value was documented in the source documentation at the beginning of the study (each patient served as his/her own control). The adalimumab trials captured normal stool frequency as the number of stools for an individual patient when not in flare

The use of the Mayo Score to define patient groups according to disease activity has gained widespread acceptance, and has been used in the majority of significant clinical trials of UC over the past two decades. In practical terms, it is not feasible to use either the full Mayo Score repeatedly in clinical practice, or indeed the partial Mayo Score since patients do not complete daily diaries for stool frequency or rectal bleeding events. First and foremost it would be a concern for the patient and there are lengthy wait lists for endoscopy. It is more likely that a full Mayo Score is taken at baseline and a partial Mayo Score, without the endoscopy, taken at additional time points. Due to the invasive nature of endoscopy, clinicians have advised that they would take a full Mayo in the initial assessment of disease activity, and only undertake an additional endoscopy in any one year if they felt there was a significant change in the disease. It should be noted that the less invasive partial Mayo Score, which excludes the endoscopy component, is considered a good surrogate for the full Mayo Score[37, 38].

In addition to its utility in therapeutic decision making by categorising disease activity, the Mayo Score may also be used to assess disease remission and to determine response to therapy. A total Mayo Score less than or equal to 2 points may be considered remission, consistent with the ECCO Consensus Statement[39] where remission is defined as a combination of clinical parameters (i.e. stool frequency ≤3/day more than normal with no bleeding) and a normal mucosa at endoscopy. The specificity and sensitivity of a cut-off point of 2 or less to determine remission was in the mid to high 80th percentile in 2 separate studies[40, 41].

Table 15: Mayo scoring system for assessment of UC patients

Symptom	Score	Description
Stool frequency	0	Normal no. of stools for this patient
	1	1-2 stools more than normal
	2	3-4 stools more than normal
	3	5 or more stools more than normal
Rectal bleeding	0	No blood seen
	1	Streaks of blood with stool less than half the time
	2	Obvious blood with stool most of the time
	3	Blood alone passed
Findings of flexible proctosigmoidoscopy (***not included for partial scoring system***)	0	Normal or inactive tissue
	1	Mild disease (erythema, decreased vascular pattern, mild friability)
	2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
	3	Severe disease (spontaneous bleeding, ulceration)
Physicians Global Assessment	0	Normal
	1	Mild disease
	2	Moderate disease
	3	Severe disease

Reproduced from Schroeder *et al* [36]

Clinical response is defined as a decrease in Mayo Score of ≥ 3 points, which may be considered a clinically significant change in disease activity. According to Lewis JD 2008[41] the maximum product of sensitivity and specificity to identify patient reported improvement of disease activity is achieved with a reduction in the Mayo Score of ≥ 3 points. However, it should be noted that further validation of this definition of clinical response in larger datasets would be of value

The Mayo Score is noted in international guidelines as an accepted scoring system.[16,39,25] The Mayo Score is accepted as an appropriate outcome measure in UC by the FDA[42] and meets the

description of appropriate outcome measures for treatment of UC as defined by the EMEA (CHMP 2009).

Both the Full Mayo Score and the Partial Mayo Score methodologies of assessing response are consistent with those identified in CHMP's January 2008 Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006). Nevertheless there are limitations to the use of the Mayo Score as an endpoint which are outlined in detail in section 2.9.

The trials presented in this submission employ the worst-rank methodology whereby the worst sub-score from the past three days of the subject's diary for stool frequency and rectal bleeding are used to calculate the overall score. There are other methodologies available to calculate the total Mayo Score, such as the simple average of the past three days for stool frequency and rectal bleeding, as used in the infliximab and golimumab UC trials[43] and in other trials of UC[44]. The Japanese study; discussed in the section 2.6 employs both these methodologies.

Importantly, this difference in methodologies has the potential to impact the absolute differences in remission rates observed. The trials presented in this submission employed a highly conservative approach that biases against the adalimumab results in the calculation of the Mayo Score by employing the worst rank method. Unfortunately, due to lack of access to individual patient diary records in M06-826 and M06-827 these scores are unable to be re-analysed to calculate the impact of adopting the worst rank methodology compared to, for example, the simple average over the last three days.

Remission
Remission was defined equally for both M06-826 and M06-827 trials. Remission was achieved when the Mayo Score was less than or equal to 2 points and there was no individual sub-score greater than 1. Patients could only score a maximum of 1 point for two sub-scores. This definition of clinical remission is consistent with the recent literature in management of UC[42]. A Mayo Score less than or equal to 2 points may be considered remission, consistent with the ECCO Consensus Statement[39] where remission is defined as a combination of clinical parameters (i.e. stool frequency ≤3/day with no bleeding) and a normal mucosa at endoscopy. The specificity and sensitivity of a cut-off point of 2 or less to determine remission was in the mid to high 80th percentile in two separate studies[40].

Remission was evaluated after induction therapy (8 weeks) in trials M06-826 and M06-827, and after maintenance therapy (52 weeks) in trial M10-223 alone. Subjects were said to be in sustained remission if they were in remission at all-time points specified (week 8 and week 52) as defined by the Mayo Score. The trial criteria for remission are consistent with the definition in the previous paragraph.

Response
Response was defined in the same way for both the M06-826 and M06-827 trials. Clinical response was defined as a decrease in Mayo Score of ≥ 3 points and a ≥ 30% decrease from baseline Mayo Score plus a decrease in rectal bleeding sub-score of ≥ 1 or an absolute RBS of 0 or 1. This corresponds with the views from the literature on what constitutes a clinically significant change in disease activity. According to Lewis, *et al*, the maximum product of sensitivity and specificity is achieved with a reduction in the Mayo Score of ≥ 3 points.

Response was evaluated after induction therapy (8 weeks) in trials M06-826 and M06-827, and after maintenance therapy (52 weeks) in trial M06-827 alone. An adequate response was defined as a decrease in Partial Mayo Score of > 2 points AND > 30% from baseline. Subjects were said to be in sustained response if they were in response at all-time points specified (week 8 and week 52) as defined by the Mayo Score.

Mucosal healing
With the advent of biological therapy, increasing emphasis is being placed on the achievement of mucosal healing, both in clinical trials and clinical practice[15].

Mucosal healing was defined in the studies as endoscopy sub-score of 0 or 1. In order to assign an endoscopy sub-score (which ranges from 0 to 3 points) for the Mayo Score calculation, regardless of the type of endoscopy performed, only the last 30 cm on retraction of the scope was to be used for scoring as follows: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular

pattern, mild friability), 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions), 3 = severe disease (spontaneous bleeding, ulceration). Scoring was conducted against standardised photographs by trained endoscopy specialists. The endoscopy sub-score rating system of the Mayo Score has been assessed as having a good degree of concordance for expert endoscopists in terms of inter- and intra-observer agreements (mean weighted kappa values ~0.74)[45] although it has been debated whether this is the case for multinational studies[42]. Subjects were said to have sustained mucosal healing if they were in remission at all-time points specified (week 8 and week 52) as defined by the endoscopy sub-score of the full Mayo Score.

Healthcare resource utilisation
The healthcare resource utilisation (HCRU) questionnaire utilised in the trials documented unscheduled outpatient visits (with physician or other healthcare professional), emergency room visits, and hospitalisations during the study. For HCRU, the ratio of the total number of utilisations and the total time under DB observation (for physician visits, emergency room visits, hospital admissions, and the total number of days in hospital) was calculated across all subjects in each treatment group. The individual cumulative number of HCRUs during the time under DB observation was analysed with a Poisson-normal model adjusted for stratum defined by prior exposure to infliximab or other anti-TNF agents. Parameter estimates with 95% CI and P values were provided.

Health related quality of life outcomes
In addition to medical consequences, UC can also have a significant negative impact on HRQoL[6]. In comparison to the general population, patients with UC have been shown to have reduced HRQoL and general life satisfaction.[7,8] Quality-of-life outcomes assessed in the trials included the IBDQ and the Short Form 36-item Health Survey (SF-36; version 2).

The IBDQ is a disease-specific 32-item questionnaire which captures how the patient felt during the 2 weeks before the measurement time point. Questions relate to symptoms, feelings in general, mood, social, and work problems resulting from UC. A higher score indicates less impact of disease.

Clinical importance of the outcome measures
The efficacy outcome measures used across the studies are well established in the assessment of UC; both in routine clinical practice and clinical trial settings. Historically, most clinical trials in UC have been designed specifically to assess the ability of a drug to induce and/or maintain a response or remission of disease.[46] Of the various indices available which have been used to assess disease severity and associated response and remission outcomes in UC, the Mayo Score used in the adalimumab trials is among the best established and most widely used.

The clinical relevance of the remission and response definitions used in the adalimumab studies has been demonstrated by showing that both definitions correlate with significant improvements in disease specific health related quality of life as measured by the IBDQ and generic quality of life as measured by the SF-36.[47] The outcomes capture the immediate positive impact of treatment on HRQoL through the alleviation of symptoms. These HRQoL instruments have in turn been extensively and independently validated as measures of health related quality of life in various gastroenterological disease states across diverse treatment and healthcare settings.

In recent years, there has been increasing evidence that treating symptoms alone may not be sufficient to achieve optimal long-term outcomes and that targeting mucosal inflammation and associated tissue damage may be equally important.[48] Achievement of long-term mucosal healing in UC has been associated with a decreased risk of both surgery and colorectal cancer, and long term improvements in quality of life, prevention of IBD relapses, and minimising hospitalisations. The importance of mucosal healing is now acknowledged in guidelines, which recommend it is incorporated alongside primary endpoints of remission in future clinical studies[48,47]. The definition for remission used in the adalimumab studies takes into account that the patients should have mucosal healing. However, it should be noted that in the short term endoscopic scores do not necessarily correspond to patient reported severity.

2.2 Efficacy data from pivotal RCT studies

Adalimumab has been shown to be effective in the induction and maintenance of remission in patients with moderately to severely active UC in the M06-826 and M06-827 randomised controlled trials. Clinical efficacy was demonstrated as early as week 2, with 39.1% responding to the 160mg part of the loading dose alone. At week8, the percentage of responders, naive to prior anti-TNF use,

was 58.7%. Data from M06-827 suggested that patients who did not respond by week-8 would not benefit from further adalimumab treatment, thus should discontinue at this point. For the anti-TNF naive patients who did respond at week 8; by week 52, 39.8% achieved remission and 64.8% achieved response

2.2.1 Efficacy

- The pivotal registration trials presented in the submission demonstrate the superiority of ADA over PBO for induction and maintenance of clinical remission and response. In addition, patients achieve mucosal healing, and experience reduced hospitalisations and rates of colectomy, as well as improved quality of life.

Induction of clinical response/remission:

- Study M06-826 shows patients receiving ADA 160/80/40 are two times more likely to achieve clinical remission per full Mayo Score (18.5% versus 9.2% for ADA vs. PBO; RR: 2.0; [95% CI 1.05, 3.83], p=0.031) at week 8 compared to PBO.
- Study M06-827 demonstrated a statistically significantly greater proportion of subjects in the ADA group were in clinical remission per full Mayo Score at week 8 compared to PBO (16.5% versus 9.3%; RR: 1.77; [95% CI 1.10, 2.86]; p=0.019).
- Patients receiving ADA are 1.5 times more likely to achieve clinical response per full Mayo at 8 weeks (50.4% versus 34.6%; RR: 1.5 [95%CI 1.18, 1.80], p<0.001) based on results from M06-827 compared to PBO.
- Results from a meta-analysis of efficacy at 8 weeks (M06-826 and M06-827) were consistent with those from the individual trials (remission: 17.0% versus 8.8%; RR: 1.85 [95% CI 1.26, 2.72], p=0.002); (response: 51.7% versus 37.0%; RR: 1.36 [95% CI 1.16, 1.60], p<0.001).
- Results of a meta-analysis at 8 weeks demonstrates significantly more patients treated with ADA were assessed to have mucosal healing compared to PBO (43.1% vs. 35.1% RR: 1.23 [95% CI 1.03, 1.47], p = 0.02.
-

Maintenance of clinical response/remission:

- Study M06-827 shows patients receiving ADA are two times more likely to achieve clinical remission per full Mayo Score (17.3% versus 8.5%; RR: 2.03 [95% CI 1.24, 3.32]; p =0.004) at week 52 and are also 2 times more likely to achieve sustained remission per full Mayo Score at week 8 and week 52 (8.5% versus 4.1%; RR: 2.08 [95% CI 1.01, 4.33], p=0.047).
- Study M06-827 also demonstrates ADA patients are 1.7 times more likely to achieve clinical response (30.2% versus 18.3%; RR 1.66 [95% CI 1.20, 2.29], p=0.002) at week 52 and almost 2 times more likely to achieve sustained response per full Mayo Score at week 8 and week 52 (23.8% versus 12.2%; RR: 1.95 [95% CI 1.30, 2.92], p<0.001).
- In study M06-827 of the ADA-treated patients who achieved clinical response at week 8, 30.9%, 49.6%, and 43.1% achieved clinical remission, clinical response, and mucosal healing, respectively, at week 52. Of the week 8 responders using corticosteroids at baseline (N = 90), 21.1% achieved steroid-free remission and 37.8% were steroid-free at week 52.
- A statistically significant proportion of subjects achieved corticosteroid-free remission at week 52 in the ADA group compared to PBO (13.3% vs. 5.7%; p=0.035).
- ADA provides clinically significant improvement in patient quality of life as measured by IBDQ and SF-36.

2.2.2 Remission results

The primary outcome for both studies was the remission per Mayo Score. In the induction study M06-826, this was assessed at week 8 and for the maintenance study M06-827; it was assessed at week 8 and 52 (Table 16). After 8 weeks of therapy the meta-analysis showed, treatment with adalimumab was almost twice as likely to induce remission compared with placebo treatment (RR [95%CI]: 1.85 [1.26, 2.72]; Figure 5). Furthermore, patients treated with adalimumab for up to 52 Weeks were twice as likely to be in remission compared with patients treated with placebo (RR [95%CI]: 2.03 [1.24, 3.32]). Patients treated with adalimumab were also twice as likely to have sustained remission, remission at week 8 and also at week 52 when compared with patients treated with placebo. While

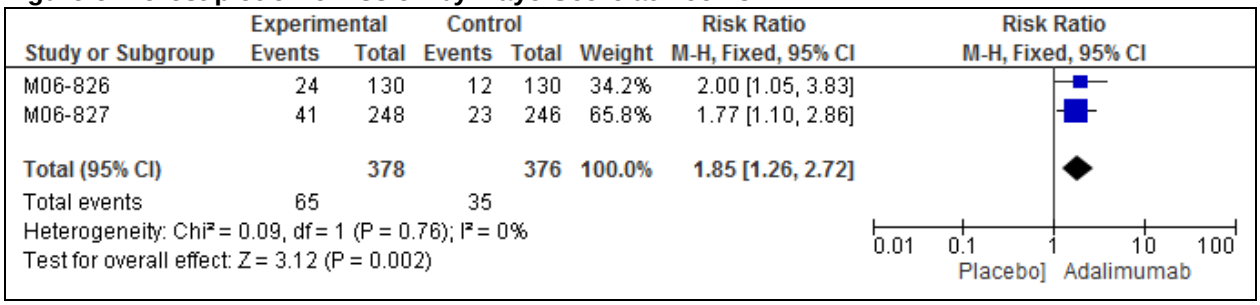
not the primary outcome, remission per partial Mayo Score was also assessed in study M06-827. The partial Mayo Score is the Mayo Score minus the endoscopy outcome. This is of clinical relevance as it is impractical for a clinician to perform an endoscopy at every clinical assessment of their patients. Remission rates based on the partial Mayo Score are similar to those using the full Mayo Score, with patients treated with adalimumab being almost twice as likely to be in remission at week 8 compared with patients treated with placebo (RR [95%CI]: 1.72 [1.22, 2.42]).

Table 16: Proportion of patients in remission by full and partial Mayo Score at week 8 and week 52 across the randomised trials

Trial ID	Remission per Mayo Score				
	ADA n/N (%)	PBO n/N (%)	Risk difference [95% CI]	Relative risk [95% CI]	p-value
Remission per MS week 8					
M06-826	24/130 (18.5)	12/130 (9.2)	9.3 [0.9, 17.6]	2.00 [1.05, 3.83]	0.031
M06-827	41/248 (16.5)	23/246 (9.3)	7.2 [1.3, 13.1]	1.77 [1.10, 2.86]	0.019
TOTAL	65/378 (17.2)	35/376 (9.3)	7.9 [2.4, 16.0]	1.85 [1.26, 2.72]	0.002
Remission per MS week 52					
M06-827	43/248 (17.3)	21/246 (8.5)	8.8 [2.9, 14.7]	2.03 [1.24, 3.32]	0.004
Sustained remission per MS week 8 and 52					
M06-827	21/248 (8.5)	10/246 (4.1)	4.4 [0.1, 8.7]	2.08 [1.01, 4.33]	0.047
Remission per partial MS week 8					
M06-827	71/248 (28.6)	41/246 (16.7)	11.9 [4.7, 19.3]	1.72 [1.22, 2.42]	0.002

NRI=non-responder imputation; p-values for ADA vs. PBO; MS= Mayo Score; Source: CSR M06-826; CSR M06-827

Figure 5: Forest plot of remission by Mayo Score at week 8



2.2.3 Response

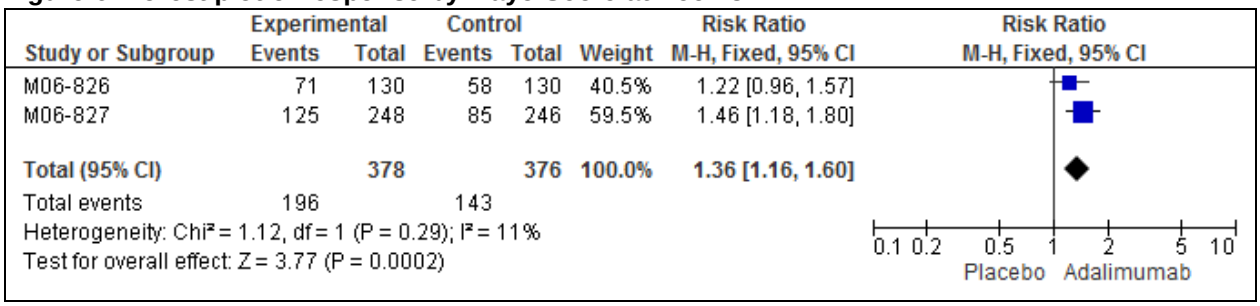
While the ultimate aim of anti-TNF therapy in UC is to get patients into remission, achieving remission after 8 weeks of therapy is unrealistic in the majority of patients. Response per Mayo Score however, is an outcome that is achievable in 8 weeks of therapy and is indicative of a patient's likelihood to eventually reach the remission state (Table 17). According to the meta-analysis, after 8 weeks of therapy, patients treated with adalimumab were 1.36 times more likely to have responded compared with patients treated with placebo (RR [95%CI]: 1.36 [1.16, 1.60]; Figure 6). After 52 weeks of therapy, patients treated with adalimumab were more than 1.5 times more likely to have responded to therapy compared with patients treated with placebo (RR [95%CI]: 1.66 [1.20, 2.29]). In terms of sustained response, patients treated with adalimumab were almost twice as likely to have responded at both the week 8 and week 52 time-points compared with placebo treated patients. As with remission, it is not practical to assess response based on the full Mayo Score including endoscopy in clinical practice and the partial Mayo Score is more relevant. The response rates based on the partial Mayo Score are almost identical to those based on the full Mayo Score with patients being treated with adalimumab 1.37 times more likely to have responded after 8 weeks of therapy compared with patients treated with placebo demonstrating the high correlation between the full and partial Mayo Scores.

Table 17: Proportion of responders by full and partial Mayo Score at weeks 8 and 52 across the randomised trials

Trial ID	ADA n/N (%)	PBO n/N (%)	Risk difference [95% CI]	Relative risk [95% CI]	p-value
Response per MS week 8					
M06-826	71/130 (54.6)	58/130 (44.6)	10.0 [-2.0, 22.0]	1.22 [0.96, 1.570	0.107
M06-827	125/248 (50.4)	85/246 (34.6)	16.0 [7.0, 24.0]	1.46 [1.18, 1.80]	<0.001
TOTAL	196/378 (51.9)	143/376 (38.0)	13.9 [7.0, 21.0]	1.36 [1.16, 1.60]	<0.001
Response per MS week 52					
M06-827	75/248 (30.2)	45/246 (18.3)	11.9 [4.5, 19.4]	1.66 [1.20, 2.29]	0.002
Sustained response per MS at week 8 and week 52					
M06-827	59/248 (23.8)	30/246 (12.2)	11.6 [4.9, 18.3]	1.95 [1.30, 2.92]	<0.001
Response per partial MS week 8					
M06-826	72/130 (55.4)	56/130 (43.1)	12.3 [0.0, 24.0]	1.29 [1.00, 1.65]	0.047
M06-827	123/248 (49.6)	86/246 (35.0)	14.6 [6.0, 23.0]	1.42 [1.15, 1.75]	0.001
TOTAL	195/378 (51.6)	142/376 (37.8)	13.8 [7.0, 21.0]	1.37 [1.16, 1.61]	<0.001

NRI=non-responder imputation; p-values for ADA vs. PBO; MS= Mayo Score; Source CSR M06-826; CSR M06-827

Figure 6: Forest plot of response by Mayo Score at week 8



The validity of using the outcome of response by Mayo Score as a marker for longer term benefits is highlighted in a post-hoc analysis of study M06-827[37]. The aim of this analysis was to assess week 52 efficacy, safety and benefit/risk balance of adalimumab treatment in patients with moderately-to-severely active UC failing conventional therapy who achieved clinical response at week 8 in the trial. Of the adalimumab treated patients who achieved clinical response at week 8, 30.9%, 49.6%, and 43.1% achieved clinical remission, clinical response, and mucosal healing, respectively, at week 52. Of the week 8 responders using corticosteroids at baseline (N=90), 21.1% achieved steroid-free remission and 37.8% were steroid-free at week 52. There was also high concordance between the patients identified as having clinical response whether the full or partial Mayo Score definitions were used with 93.6% and 95.1% of responders achieving clinical response respectively. In addition to this, the analysis found that early response was predictive of a positive outcome at one year. This highlights the importance of the EMA licence recommendations regarding stopping adalimumab therapy for patients not responding by week 8.

2.2.4 Mucosal healing

Mucosal healing is an important and clinically relevant endpoint for patients with ulcerative colitis as mucosal healing has been associated with a decreased risk of surgeries and colorectal cancer, as well as improved quality of life, prevention of relapses, and minimised hospitalisations over time. Patients who improve in other domains are likely to improve in mucosal healing. The results for mucosal healing in the included studies are presented in Table 18. After 8 weeks of therapy, the meta-analysis showed significantly more patients treated with adalimumab were assessed to have mucosal healing compared with patients treated with PBO (RR [95%CI]: 1.23 [1.03, 1.47]).

Table 18: Proportion of patients with mucosal healing at week 8 across the randomised trials

Trial ID	ADA n/N (%)	PBO n/N (%)	Risk difference [95% CI]	Relative risk [95% CI]	p-value
Mucosal Healing at week 8					
M06-826	61/130 (46.9)	54/130 (41.5)	5.4 [-7.0, 17.0]	1.13 [0.86, 1.49]	0.382
M06-827	102/248 (41.1)	78/246 (31.7)	9.4 [1.0, 18.0]	1.30 [1.02, 1.64]	0.032
TOTAL	163/378 (43.1)	132/376 (35.1)	8.0 [1.0, 15.0]	1.23 [1.03, 1.47]	0.02

p-values for ADA vs. PBO; Source CSR M06-826; CSR M06-827

2.2.5 Individual sub-parameters of the Mayo Score

The Mayo Score is an indicator of UC disease activity based on a total composite score of four sub-scores added together: endoscopy; stool frequency (SFS); rectal bleeding (RBS) and physician's global assessment (PGA). A significantly greater proportion of patients treated with adalimumab compare with those treated with placebo met the endpoints of rectal bleeding sub-score ≤ 1 at Week 8 (p<0.001), Physician's Global Assessment sub-score ≤ 1 at Week 8 (P = 0.005) as well as stool frequency sub-score <1 at Week 8 (p=0.005) (

Table 19).

Table 19: Individual sub-parameters of the Mayo Score at week 8 across the randomised trials

Trial ID	ADA n/N (%)	PBO n/N (%)	Risk difference [95% CI]	Relative risk [95% CI]	p-value
RBS ≤1 at week 8					
M06-826	101/130 (77.7)	86/130 (66.2)	12.0 [1.0, 22.0]	1.17 [1.01, 1.37]	0.038
M06-827	174/248 (70.2)	143/246 (58.1)	12.0 [4.0, 20.0]	1.21 [1.06, 1.38]	0.006
TOTAL	275/378 (72.8)	229/376 (60.9)	12.0 [5.0, 19.0]	1.19 [1.08, 1.32]	<0.001
PGA ≤1 at week 8					
M06-826	78/130 (60.0)	61/130 (46.9)	13.0 [1.0, 25.0]	1.28 [1.02, 1.61]	0.035
M06-827	114/248 (46.0)	92/246 (37.4)	9.0 [0.0, 17.0]	1.23 [1.00, 1.52]	0.058
TOTAL	192/378 (50.8)	153/376 (40.7)	10.0 [3.0, 17.0]	1.25 [1.07, 1.46]	0.005
SFS ≤1 at week 8					
M06-826	63/130 (48.5)	49/130 (37.7)	11.0 [-1.0, 23.0]	1.29 [0.97, 1.71]	0.080
M06-827	94/248 (37.9)	70/246 (28.5)	9.0 [1.0, 18.0]	1.33 [1.03, 1.72]	0.028
TOTAL	157/378 (41.5)	119/376 (31.6)	10.0 [3.0, 17.0]	1.31 [1.09, 1.59]	0.005

P-values for ADA vs. PBO; Abbreviations: RBS Rectal Bleeding Score; PGA Physician's Global Assessment; SFS Stool Frequency sub-score; Source CSR M06-826; CSR M06-827

2.2.6 Sub-group analysis by prior exposure to infliximab

Forty percent of patients in study M06-827 had prior experience with infliximab (Table 9). A sub-group analysis by prior anti-TNF therapy was pre-determined in the statistical analysis plan. The analysis of response by prior anti-TNF therapy was reported for the co-primary endpoint and first ranked secondary endpoints (Table 20).

Among anti-TNF naive subjects, both co-primary endpoints significantly favoured adalimumab. At week 8, 21.3% of patients receiving adalimumab achieved clinical remission compared to 11% in the placebo group (p=0.017). The corresponding values at week 52 were 22% and 12.4% (p=0.029). Among the anti-TNF experienced patients, 9.2% of patients receiving adalimumab achieved clinical remission at week 8, compared to 6.9% on placebo (p=0.559). The corresponding values at week 52 were 10.2% and 3%, respectively (p=0.039). For the ranked secondary endpoints, differences also favoured adalimumab or PBO, with all but three of the comparisons being statistically significant. Numerically, comparisons on the secondary endpoints mostly favoured adalimumab over placebo. Furthermore, the proportion of patients achieving a clinical response at week 52, and sustained clinical response at both week 8 and week 52 was statistically in favour of adalimumab. In summary,

adalimumab treated patients were more likely than placebo treated patients to achieve clinical remission or clinical response, particularly for patients with no prior experience with anti-TNF therapies.

Table 20: Subgroup analysis of M06-827 by Prior Anti-TNF strata (ITT Analysis Set; NRI)

	No Prior Anti-TNF			Prior Anti-TNF		
	ADA N = 150	**PBO N = 145**	**p-value**	**ADA N = 98**	**PBO N = 101**	**p-value**
Ranked co-primary endpoints, n (%)						
Clinical remission per Mayo Score at W8	32 (21.3)	16 (11.0)	0.017	9 (9.2)	7 (6.9)	0.559
Clinical remission per Mayo Score at W52	33 (22.0)	18 (12.4)	0.029	10 (10.2)	3 (3.0)	0.039
Ranked secondary endpoints, n (%)						
1. Sustained clinical remission per Mayo Score at W8 & W52	16 (10.7)	9 (6.2)	0.169	5 (5.1)	1 (1.0)	0.115
2. Clinical response per Mayo Score at W8	89 (59.3)	56 (38.6)	< 0.001	36 (36.7)	29 (28.7)	0.228
3. Clinical response per Mayo Score at W52	55 (36.7)	35 (24.1)	0.019	20 (20.4)	10 (9.9)	0.038
4. Sustained clinical response per Mayo Score at W8 & W52	44 (29.3)	24 (16.6)	0.009	15 (15.3)	6 (5.9)	0.032
5. Mucosal healing at W8	74 (49.3)	51 (35.2)	0.014	28 (28.6)	27 (26.7)	0.772
6. Mucosal healing at W52	47 (31.3)	28 (19.3)	0.018	15 (15.3)	10 (9.9)	0.250
7. Sustained mucosal healing at W8 & W52	36 (24.0)	20 (13.8)	0.025	10 (10.2)	6 (5.9)	0.269
8. Discontinued CS use before W52 & achieved clinical remission at W52	N = 110 15 (13.6)	N = 81 5 (6.2)	0.096	N = 40 5 (12.5)	N = 59 3 (5.1)	0.263
9. PGA ≤ 1 at W8	88 (58.7)	63 (43.4)	0.009	26 (26.5)	29 (28.7)	0.731
10. SFS ≤ 1 at W8	69 (46.0)	43 (29.7)	0.004	25 (25.5)	27 (26.7)	0.844
11. RBS ≤ 1 at W8	116 (77.3)	86 (59.3)	< 0.001	58 (59.2)	57 (56.4)	0.695
12. Discontinued CS use for ≥ 90 days before W52 & achieved clinical remission at W52	N = 110 15 (13.6)	N = 81 5 (6.2)	0.096	N = 40 5 (12.5)	N = 59 3 (5.1)	0.263
13. Discontinued corticosteroid use & sustained clinical remission at W32 and W52	N = 110 11 (10.0)	N = 81 1 (1.2)	0.014	N = 40 4 (10.0)	N = 59 1 (1.7)	0.155

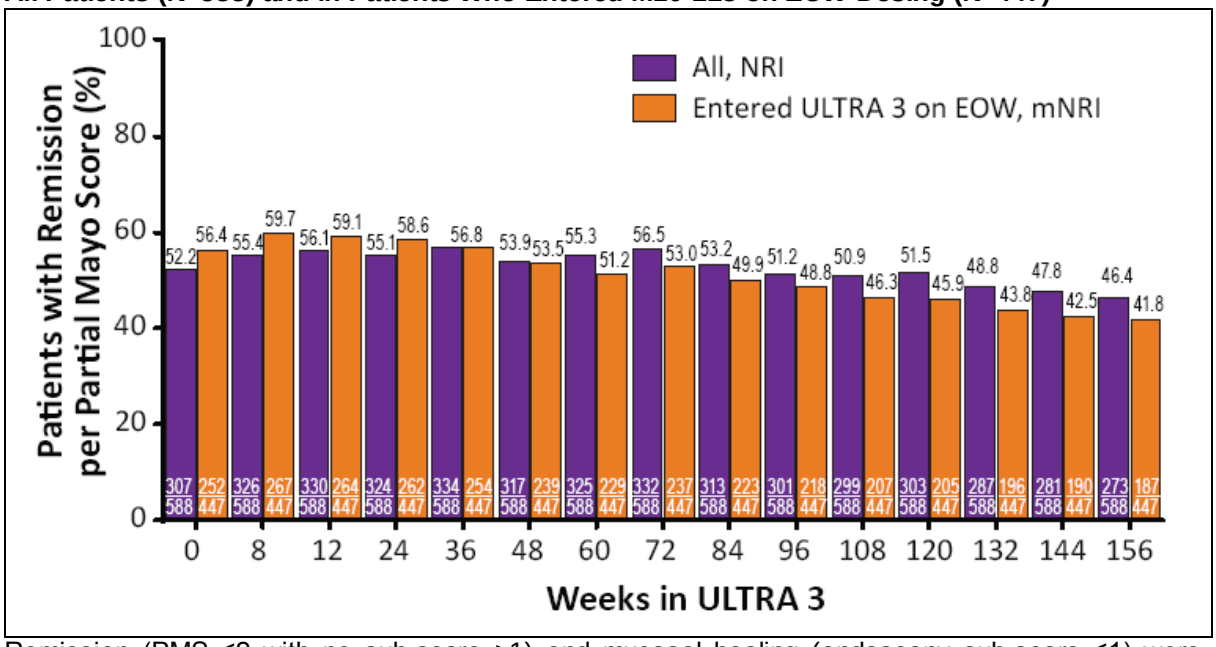
Source; CSR M06-827; NRI=Non-responder imputation; W=week

N.B. the week 8 responder analysis showed that subjects with week 8 responses had similar outcomes at week 52 regardless of prior anti-TNF use

2.2.7 Long-term efficacy

A post-hoc analysis of the maintenance of remission over time in M10-223 has been published[35]. Of the 588 patients who entered the extension study, 52.2% (307/588) were in remission upon entry according to partial Mayo Scores. Partial Mayo Scores were calculated at each study visit and at week 156, 46.4% (273/588) of patients had achieved clinical remission. Therefore, suggesting sustained clinical remission rates over time as seen in Figure 7.

Figure 7: Efficacy of ADA Over Time in Patients Who Entered M10-223; Remission per PMS in All Patients (N=588) and in Patients Who Entered M10-223 on EOW Dosing (N=447)



Remission (PMS ≤2 with no sub-score >1) and mucosal healing (endoscopy sub-score ≤1) were assessed in the ITT patients who entered ULTRA 3 from ULTRA 1 or 2 (N=588). A modified NRI (mNRI) was used to calculate remission per PMS for patients who entered ULTRA 3 on EOW dosing, whereby NRI was used for missing data and at the point of moving to weekly dosing.

2.3 Healthcare resource utilisation from pivotal RCT studies

- ADA is the first biologic to date to indicate an impact in reduction in all-cause hospitalisations (40% reduction compared to PBO; p=0.046) at week 8.
- Treatment with ADA resulted in a 50% reduction in the proportion of patients with UC-related hospitalisations compared to PBO (p=0.02) at week 8.
- ADA led to a 47% reduction in the number of UC or drug-related hospitalisations compared to PBO (p=0.02) at week8.
- Treatment with ADA also led to a 17% reduction in the rate of colectomy compared to PBO at week 8. Statistical significance was not reached due to low colectomy event rates.

Health care resource utilisation throughout the studies is summarised in Table 21. During double-blind treatment, subjects in the adalimumab group reported fewer physician visits compared with placebo, in both studies, although this result only reached statistical significance in the longer M06-827 study (1.663 versus 1.347 incidences/PYs, respectively; P=0.035). Incidence rates were not statistically significantly different between placebo and adalimumab groups for emergency room visits, hospital admissions or total number of days in the hospital, although the adalimumab group had a numerically lower rate of hospitalisation and shorter durations of hospitalisation than placebo. In terms of the open-label study, utilisation of various health care resource items for patients receiving adalimumab was low.

Table 21: Unscheduled health care resource utilisation across the randomised trials

	ADA No. events (events/PY)	PBO No. events (events/PY)	P-value
M06-826	(N=223); (PYs =34.0)	(N=222); (PYs = 19.6)	
Physician visits	15 (0.441)	21 (0.619)	0.559
Emergency room visits	2 (0.059)	8 (0.236)	NA
Hospital admissions	5 (0.147)	7 (0.206)	NA
Days in hospital	26 (0.764)	73 (2.153)	0.297
M06-827 – ITT set	(N=248); (PYs = 125.5)	(N=246); (PYs = 101.6)	
Physician visits	169 (1.347)	169 (1.663)	0.035
Emergency room visits	12 (0.096)	10 (0.098)	0.847
Hospital admissions	13 (0.104)	13 (0.128)	0.418
Days in hospital	120 (1.181)	105 (0.837)	0.467
M10-223 – ITT-1 set	(N=588); (PYs = 1307.0)		
Physician visits	445 (0.34)	NA	NA
Emergency room visits	38 (0.029)	NA	NA
Hospital admissions	50 (0.038)	NA	NA
Days in hospital	347 (0.266)	NA	NA

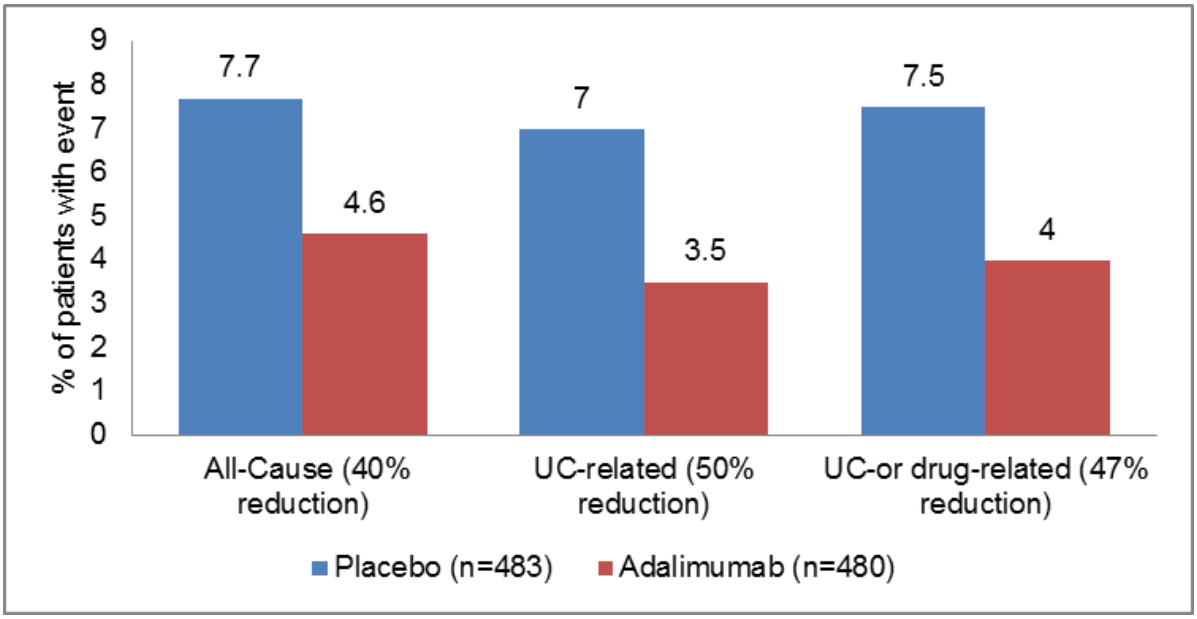
Source: CSR M06-826; CSR M06-827; CSR M10-223 Interim 3 year; Abbreviations: ADA = adalimumab; PBO = placebo; PYs = patient years; ITT = intention to treat; NA = Not available

2.3.1 Surgery and hospitalisation

Thirteen subjects (2.3%) underwent colectomies during the course of the induction study M06-826; 8 (3.6%) from the placebo group and 5 (1.4%) from the adalimumab group. No colectomies were performed on any subjects while on treatment. None of the subjects who underwent colectomies following the last dose of study drug enrolled in the open-label extension study. In the maintenance study M06-827, 12 (4.9%) and 10 (4.0%) subjects in the placebo and adalimumab groups, respectively, had a colectomy; all of them were performed during the follow-up phase of the study. None of the subjects who underwent colectomies following the last dose of study drug enrolled in the OL extension study (Study M10-223). A total of 16 subjects (1.2%) underwent colectomies during the long-term study M10-223.

A post-hoc, pooled analysis of patients enrolled in studies M06-826 and M06-827 excluding the 80/40 mg induction dose patients was also conducted which compared the proportion of patients with hospitalisation events and the number of hospitalisations between the adalimumab and placebo treatment groups at week 8[34]. There was a 40% reduction in the rate of all cause hospitalisations in the adalimumab group; a 50% reduction in the rate of UC-related hospitalisations (p=0.02); and a 47% reduction in the rate of UC-related or drug-related hospitalisations compared to placebo (Figure 8).

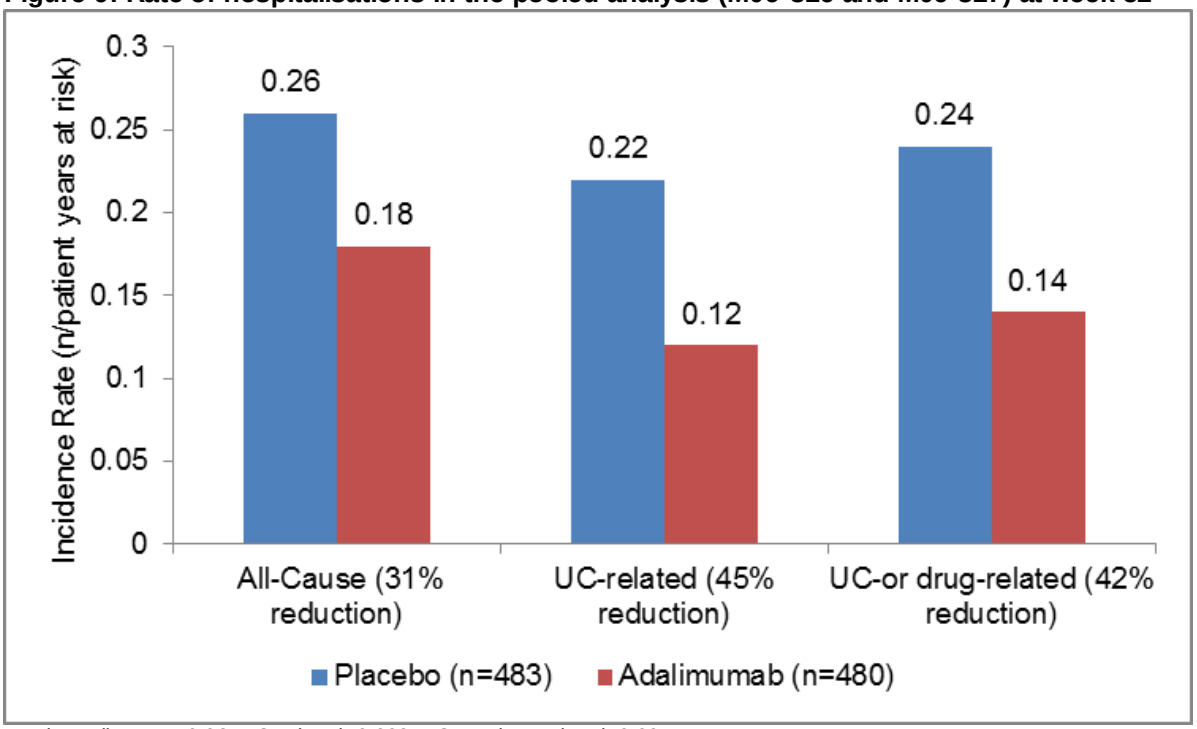
Figure 8: Proportion of patients hospitalised in the pooled analysis (M06-826 and M06-827) at week 8



P value: All-cause=0.046; UC-related=0.02; UC- or drug-related=0.02

In the pooled 52 week results, when considering the rate of hospitalisations, there was a 31% reduction in all cause hospitalisations for adalimumab patients; a 45% reduction in UC-related hospitalisations (p=0.001) and a 42% reduction in UC- or drug related hospitalisations (Figure 9)[34].

Figure 9: Rate of hospitalisations in the pooled analysis (M06-826 and M06-827) at week 52

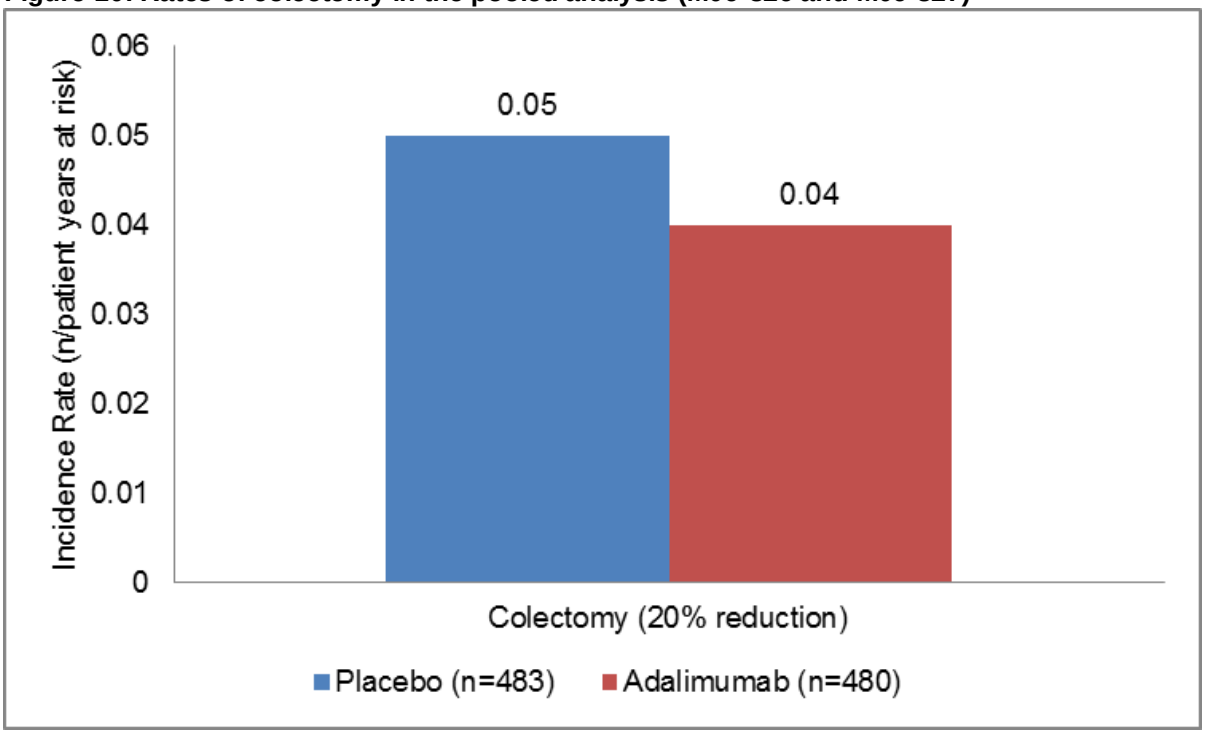


P value: All-cause=0.03; UC-related=0.002; UC- or drug-related=0.005

UC-related hospitalisations were defined as hospital admissions due to AEs or complications that were related to UC and included the following categories: UC-related surgery; hospitalisations for nonsurgical UC-related events, such as UC-related flares; and hospitalisations related to the complications / extra-intestinal manifestations of UC. A reduction in hospitalisations due to flares effectively means adalimumab worked to prevent some patients being admitted into hospital for treatment of acute severe disease. Adalimumab is the first biologic to indicate an impact in reduction in all-cause hospitalisations.

Incidence rates of colectomy were also numerically lower in the adalimumab group compared with the placebo group (4% vs. 5%), representing a 20% reduction at week 52 (Figure 10). Week 8 results showed a 17% reduction. Statistical significance was not reached at either time point due to low event rates.

Figure 10: Rates of colectomy in the pooled analysis (M06-826 and M06-827)



Serious adverse events were further evaluated to determine how many led to hospitalisation. Events of hospitalisation were identified by a retrospective review of de-identified narratives from Studies M06-826 and M06-827. All-cause hospitalisations were defined as SAEs resulting in admission to the hospital for any reason. UC-related hospitalisations were defined as hospital admissions due to SAEs or complications that were related to UC and included the following categories: UC-related surgery; hospitalisations for nonsurgical UC-related events, such as UC-related flares; and hospitalisations related to the complications/extra-intestinal manifestations of UC. Two external independent gastroenterologists who were blinded to the treatment assignment performed the review and resolved any discrepant opinions.

2.4 Quality of Life data from pivotal RCT studies

- ADA provided greater improvement in patients' quality of life compared with PBO as measured by IBDQ.
- In a post-hoc analysis of M06-827 of IBDQ responders, statistically significantly different changes in the IBDQ score were observed in the ADA group at week 8, 20, 32 and 52 compared to PBO. The proportion of IBDQ responders was greater in the ADA than the PBO group at both week 8 (58.1% vs. 45.5%; p =0.006) and week 52 (26.2% vs. 16.3%; p=0.007).
- In extension study M10-223, patients generally had good quality of life at baseline, as assessed by IBDQ and SF-36, which was generally maintained through up to 108 weeks of follow up.

A number of instruments were used to assess quality of life in patients in the trials including the IBDQ, an IBD specific HRQoL questionnaire; and the SF-36, a generic HRQoL questionnaire. A summary of the proportion of IBDQ responders across the randomised studies is presented in Table 22. After 8 and 52 weeks of therapy, more patients treated with adalimumab were classified as IBDQ responders compared with patients treated with placebo.

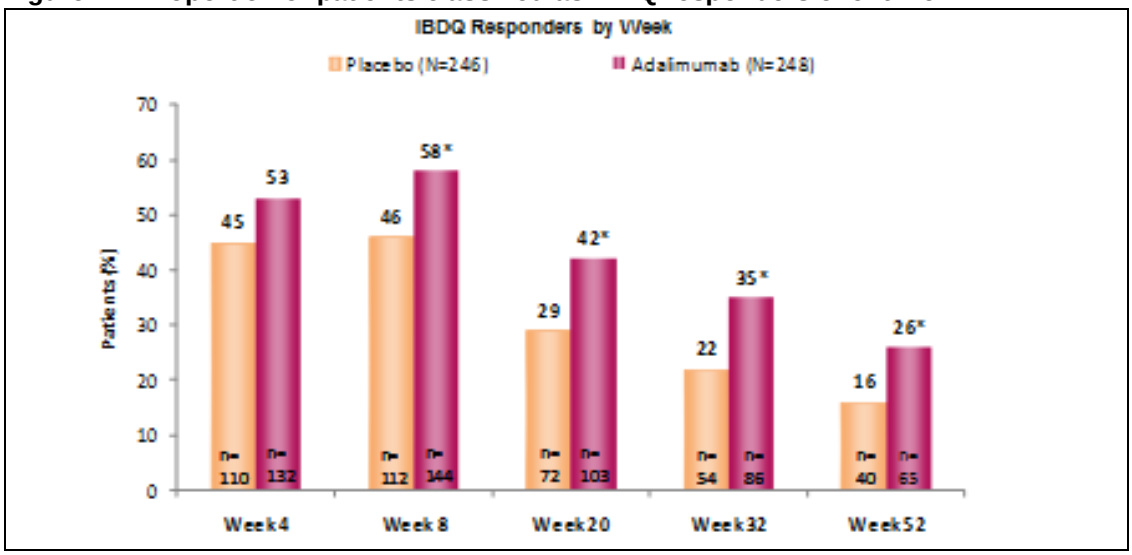
Table 22: Proportion of patients classified as IBDQ responders across the randomised trials

	ADA n/N (%)	PBO n/N (%)	P-value
IBDQ responders at Week 8			
M06-826	79/130 (60.8)	75/130 (57.7)	0.614
M06-827	144/248 (58.1)	112/246 (45.5)	0.006
IBDQ responders at Week 52			
M06-827	65 (26.2)	40 (16.3)	0.007

Source: CSR M06-826; CSR M06-827

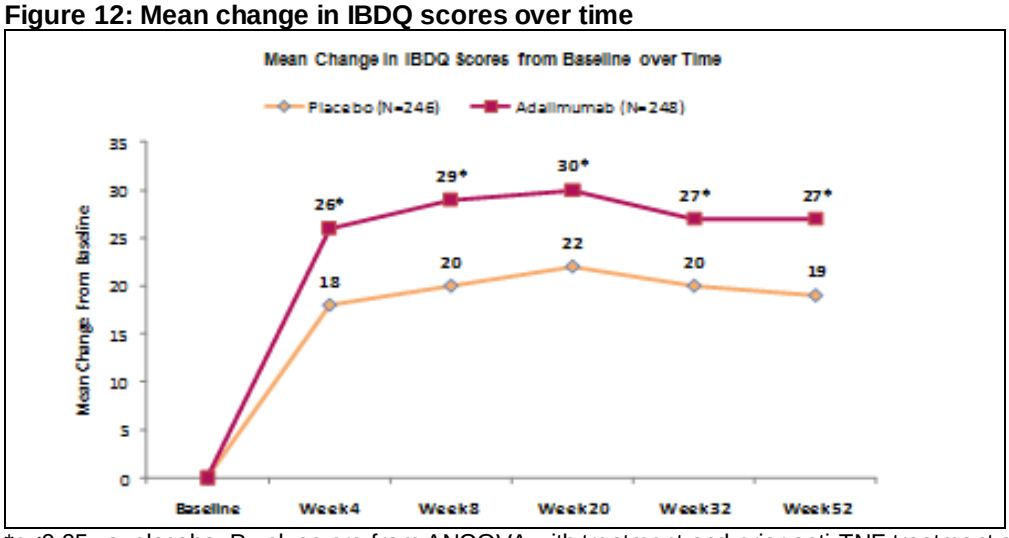
In a post-hoc analysis of M06-827[49] of IBDQ responders, statistically significantly different changes in the IBDQ score were observed in the adalimumab group at week 8, 20, 32, and 52 compared to placebo (Figure 11). Mean changes from baseline IBDQ scores were consistently and significantly greater for adalimumab treated versus placebo treated patients (Figure 12). The mean change from baseline by week 8 in the adalimumab treatment group (29 points) exceeded the minimum clinically important difference of 16 points to be classified as an IBDQ responder.

Figure 11: Proportion of patients classified as IBDQ responders over time



*p<0.05 vs. placebo; P-values from Cochran-Mantel-Haenszel test stratified for prior anti-TNF therapy use; Non-responder imputation used to impute missing data

Figure 12: Mean change in IBDQ scores over time



*p<0.05 vs. placebo; P-values are from ANCOVA with treatment and prior anti-TNF treatment status as factors and baseline value as covariate. Data are LOCF

A summary of the results for the SF-36 HRQoL instrument across the trials is presented in Table 23. A higher score indicates better quality of life. SF-36 scores increased in all treatment groups; however, a statistically significantly greater improvement in the Physical Component Summary score was observed in the adalimumab treatment group compared with placebo at week 8 in the induction study M06-826 and week 52 in the maintenance study M06-827.

Table 23: Change from baseline in SF36 scores across the randomised clinical trials

	ADA Mean (SD)	PBO Mean (SD)	P-value
Change in physical component summary from baseline to week 8			
M06-826	6.53 (7.284)	3.78 (7.174)	< 0.001
M06-827	4.3 (8.11)	3.0 (7.56)	0.081
Change in mental component summary from baseline to week 8			
M06-826	7.62 (12.165)	5.79 (11.406)	0.145
M06-827	3.7 (10.46)	3.6 (11.47)	0.234
Change in physical component summary from baseline to week 52			
M06-827	4.4 (9.34)	2.4 (8.06)	0.011
Change in mental component summary from baseline to week 52			
M06-827	3.4 (10.83)	3.3 (12.75)	0.206

Source: CSR M06-826; CSR M06-827

The long-term effect on HRQoL outcomes from study M10-223 is presented in Table 24. Patient quality of life was maintained through to week 108. The results are consistent with the maintenance effect observed in the Partial Mayo and Full Mayo Scores and Sub-scores. These patients generally had good quality of life at baseline, which reflects the efficacy of adalimumab in the preceding Study M06-826 and Study M06-827, as most of the patients were taking OL adalimumab (either EOW or EW) at the time of enrolment into this extension study. Significantly for IBDQ, which reflects the UC-specific health-related quality of life, the average baseline value in these patients was above 170, the point considered to correspond to remission[6]. Scores fluctuated slightly over time; however, generally the mean scores were maintained over time, with similar values at baseline and week 108.

The improvement of patients' quality of life was also assessed using the SF-36. The average scores for the physical component summary and mental component summary of quality of life were near 50 from Baseline to Week 108 which is defined as the average score of the general population.

Table 24: Long-term maintenance of HRQoL outcomes in the open-label extension study M10-223

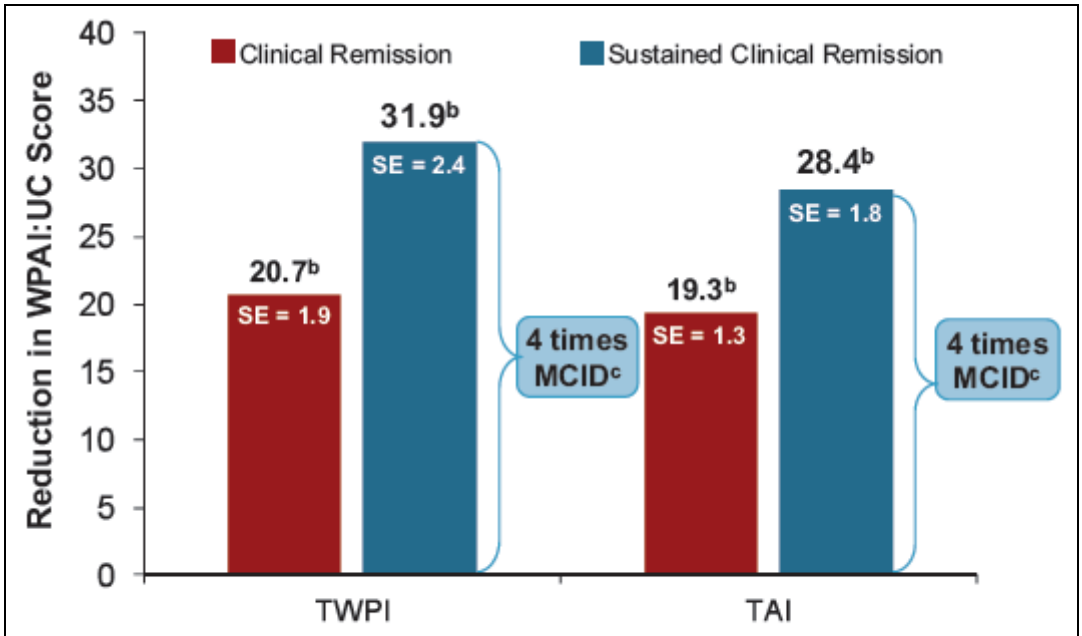
Outcome	Time point; Mean (SD)			
	BL	Week 12	Week 48	Week 108
IBDQ	176.7 (34.14)	178.2 (34.60)	177.2 (34.94)	176.3 (37.15)
SF-36 Physical	49.3 (8.05)	NA	49.6 (8.24)	49.4 (8.13)
SF-36 Mental	47.2 (10.14)	NA	46.1 (10.77)	46.0 (11.00)

Source: CSR M10-223 ITT-1 LOCF Abbreviations: NA = not applicable; SF-36 not assessed at week 12.

2.5 Work Productivity and Activity Impairment

An analysis has investigated the associations between time in sustained clinical remission and quality of life, work productivity, and activity impairment in patients with moderately to severely active UC.[50] Patients were included from the M06-827 RCT of adalimumab or placebo for the treatment of UC. At each study visit, achievement of clinical remission was defined as having a total Mayo Score no greater than 2 and no individual sub-score greater than 1. Outcomes included scores from the Inflammatory Bowel Disease Questionnaire (IBDQ), the Short Form 36 Health Survey (SF-36), and the Work Productivity and Activity Impairment Questionnaire (WPAI). Sustained remission was associated with significant improvements in WPAI scores (Figure 13). Achievement of clinical remission at any time was associated with decreases in total work productivity impairment (TWPI) and total activity impairment (TAI) scores of 20.7 and 19.3, respectively, compared with not being in remission. Achievement of clinical remission and sustained remission for 6 months was associated with decreases in TWPI and TAI scores of 31.9 and 28.4, respectively, compared with not being in remission .TWPI and TAI score reductions can be interpreted as the percentage improvements in work productivity or productivity for non-work activities for those achieving clinical remission or sustained clinical remission. Changes in WPAI scores were interpreted based on a minimum clinically important difference of 7 points in the WPAI. Patients achieving sustained clinical remission can be considered to have had a 31.9% improvement in their work productivity and 28.4% improvement in their productivity for daily activities for those not working.

Figure 13: WPAI: UC Score Reductions Associated With Clinical Remission and Sustained Clinical Remission



Sustained clinical remission was defined as maintaining clinical remission for 6 months.
[b]*P* <.05.
[c]MCID = 7 for WPAI:UC.

Overall results show that patients with sustained remission experienced significantly greater improvements in UC-related quality of life, greater improvements in mental and physical components of quality of life, and greater reductions in work productivity impairment and impairment of non-work activities.

2.6 M10-447: RCT of ADA for moderately to severely active UC in Japan

This section provides a summary of the Japanese study, M10-447[32], which has been excluded from the meta-analyses. Section 2.11 highlights issues regarding the difficulties in comparing studies across countries.

Study design

M10-447 was a 52 week, phase II/III, randomised, double-blind, placebo-controlled study evaluating the efficacy, safety, and pharmacokinetics of adalimumab for induction and maintenance therapy in Japanese patients with moderately to severely active UC. The objective of this study was to show the directional similarity of study results compared with Western studies. The study was conducted at 65 centres in Japan between February 2009 and May 2011.

Study population

Japanese patients ≥15 years of age with biopsy-confirmed, moderately to severely active UC defined by Mayo Score of 6-12 points and an endoscopy sub-score of ≥2 despite concurrent treatment with stable doses of oral corticosteroids (prednisolone equivalent of ≥20 mg/day for ≥2 weeks or 5 to<20 mg/day for ≥40 days before baseline) and/or immunomodulators (azathioprine ≥50 mg/day or 6-mercaptopurine [6-MP] ≥30 mg/day for at least 90 days). If patients were receiving both oral corticosteroids and immunomodulators at baseline, only one of the drugs needed to meet the above criteria. Patients who were previously treated with corticosteroids or immunomodulators during the past five years and who, in the judgment of the investigator, had failed to respond or who could not tolerate their treatment were also eligible for enrolment. Patients who had received prior treatment with anti-TNF therapies or other biologic agents were not eligible. Key exclusion criteria included the following: planned bowel surgery; discontinuation of oral corticosteroids within two weeks before baseline; receipt of corticosteroid injection, ciclosporin, tacrolimus, or mycophenolate mofetil within four weeks before baseline; receipt of therapeutic enema or suppository, other than required for endoscopy, within two weeks before screening endoscopy; receipt of cytapheresis within 56 days of baseline; receipt of total parenteral nutrition during the screening period; receipt of any investigational agent within four weeks or five half-lives before baseline; or non-stable doses or recent (within four

weeks) discontinuation of oral aminosalicylates or UC-related antibiotics (e.g. ciprofloxacin, metronidazole). Other reasons for exclusion included the following: current diagnosis of fulminant colitis or toxic megacolon; disease limited to the rectum (ulcerative proctitis); current diagnosis of indeterminate colitis or CD; positive C difficile toxin stool assay result; recent history of infection requiring antimicrobial therapy; evidence of tuberculosis infection by chest X-ray or purified protein derivative skin test; administration of a live vaccine within 90 days before baseline; history of listeria or histoplasmosis, active tuberculosis, human immunodeficiency virus, immunodeficiency syndrome, central nervous system demyelinating disease, or malignancy (except successfully treated, nonmetastatic, cutaneous squamous cell or basal cell carcinoma, or localised carcinoma in situ of the cervix); evidence of colonic dysplasia; history of poorly controlled medical conditions or known hypersensitivity to excipients of adalimumab.

Patients were randomly assigned in a 1:1:1 ratio to subcutaneous injections of adalimumab (160 mg at week 0, 80 mg at week 2, and then 40 mg EOW beginning at week 4 [160/80 arm], or 80 mg at week 0, 40 mg at week 2, and then 40 mg EOW beginning at week 4 [80/40 arm]), or placebo. The study drug was added to ongoing background therapy for UC (no therapies were washed out). Changes in doses of UC-related concomitant medications other than corticosteroids were not permitted during the study. After the initial 8-week induction period, patients who responded to treatment according to the judgment of the investigator were allowed to taper their corticosteroid dose. Patients with an inadequate response to the study drug (partial Mayo Score greater than or equal to that of the baseline score on two consecutive visits at least 14 days apart for patients with a baseline partial Mayo Score of 3–7, or Partial Mayo Score ≥7 on two consecutive visits at least 14 days apart for patients with a baseline Partial Mayo Score of 8 or 9) or with a flare (Partial Mayo Score increase of ≥3 compared with the score at the last evaluation before the disease flare on two consecutive visits at least 14 days apart) at or after week 8 were entered into the 'rescue arm.' Treatment in the 'rescue arm' consisted of 4 weeks of blinded adalimumab (either 160 mg initially and 80 mg 2 weeks later for patients in the placebo arm, or 40 mg initially and 2 weeks later for patients in either adalimumab arm) followed by open-label adalimumab 40 mg EOW, with a possibility to escalate to 80 mg EOW in case of inadequate response or disease flare. It should be noted that 80mg EOW is not a licensed dose in the UK.

Full Mayo Scores and IBDQ, scores were determined at weeks 8, 32, and 52. The Mayo sub-scores for stool frequency and rectal bleeding were calculated based on entries from patient diaries using the worst diary entry from the three days before each study visit for each sub-score.

Partial Mayo Score was evaluated EOW during the first 8 weeks and monthly thereafter. Efficacy endpoints analysed included response per full Mayo Score, remission and mucosal healing at weeks 8, 32, and 52. Other efficacy analyses at weeks 8, 32, and 52 included RBS, PGA, and stool frequency indicative of mild disease (score ≤1) and IBDQ response (≥16-point increase from baseline in IBDQ score).

Other analyses included comparison of remission rates at week 8 using full Mayo Scores calculated with different calculation methods for the rectal bleeding and stool frequency sub-scores (worst vs. mean diary entries and five vs. three days of diary entries), in order to explore the influence of sub-score calculation methodology on efficacy rates.

Results

A total of 274 patients were randomised. Of these 274 patients, 273 (96 in the placebo arm, 87 in the 80/40 arm, and 90 in the 160/80 arm) constituted the Final Analysis Set. Table 25 shows the patient demographics and baseline characteristics.

Table 25: Patient demographics and baseline characteristics (FAS)

Characteristic	Placebo ($N = 96$)	ADA 80/40 mg ($N = 87$)	ADA 160/80 mg ($N = 90$)
Male, *n* (%)	70 (72.9)	50 (57.5)	61 (67.8)
Age, mean ± SD (years)	41.3 ± 13.6	44.4 ± 15.0	42.5 ± 14.6
Weight, mean ± SD (kg)	60.8 ± 14.1	58.7 ± 11.1	60.1 ± 12.3
Tobacco, nonsmoker, *n* (%)	55 (57.3)	53 (60.9)	50 (55.6)
Alcohol, nondrinker, *n* (%)	36 (37.5)	45 (51.7)	43 (47.8)
Duration of UC (years)			
Mean ± SD	7.8 ± 6.6	8.3 ± 7.7	7.8 ± 7.1
Range	0.6–26.6	0.8–37.8	0.4–32.5
Site of UC, *n* (%)			
Pancolitis	59 (61.5)	54 (62.1)	63 (70.0)
Descending colon	35 (36.5)	32 (36.8)	27 (30.0)
Other[a]	2 (2.1)	1 (1.1)	0
Mayo score, mean ± SD	8.5 ± 1.6	8.5 ± 1.4	8.6 ± 1.4
Partial Mayo score, mean ± SD	6.1 ± 1.3	6.0 ± 1.3	6.2 ± 1.4
IBDQ score, mean ± SD[b]	148.2 ± 28.9	144.9 ± 28.7	146.0 ± 31.7
C-reactive protein, median (range) (mg/dL)	0.34 (0.05–8.72)	0.31 (0.05–10.77)	0.22 (0.05–6.28)
Baseline UC medication, *n* (%)			
5-ASAs	89 (92.7)	84 (96.6)	83 (92.2)
Immunomodulators (AZA, 6-MP)	52 (54.2)	38 (43.7)	41 (45.6)
Systemic corticosteroids	58 (60.4)	63 (72.4)	57 (63.3)

Baseline is the last measurement time point before the first dose of study medication in the induction period

ADA adalimumab, *5-ASA* 5-aminosalicylic acid, *AZA* azathioprine, *FAS* full analysis set, *IBDQ* Inflammatory Bowel Disease Questionnaire, *6-MP* 6-mercaptopurine, *SD* standard deviation, *UC* ulcerative colitis

[a] Two patients (distal colitis and appendix/ascending colon/rectal colon/transverse colon) in the placebo arm and one patient (rectal to sigmoidal colon) in the 80/40 mg arm

[b] Placebo, $n = 96$; 80/40 arm, $n = 85$; 160/80 arm, $n = 88$

Image taken from Suzuki *et al*[32]

Figure 14: CONSORT flow diagram of patients in study M10-447

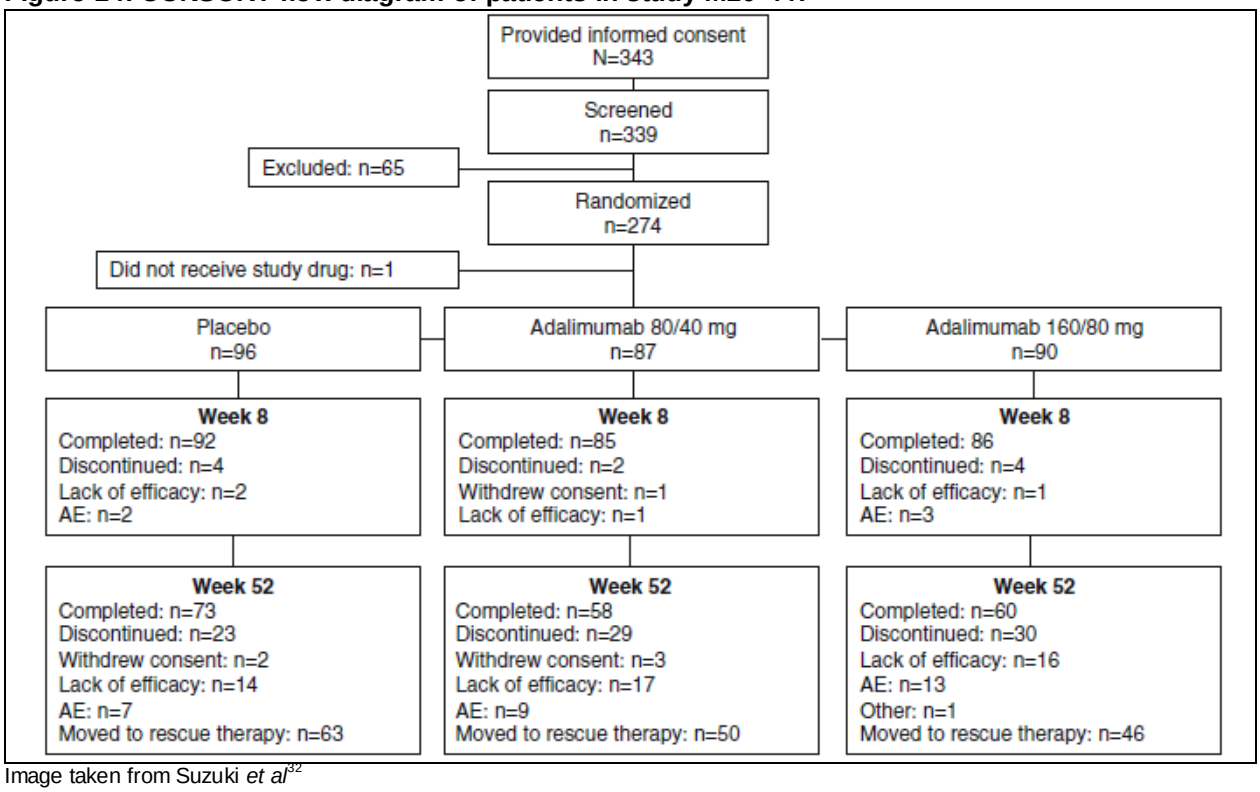


Image taken from Suzuki *et al*[32]

Efficacy for induction therapy

Adalimumab 160/80 mg treatment was associated with the highest rates of clinical response at each time point (P = 0.044 at week 8 vs. placebo). Remission rates were similar between placebo and both adalimumab treatment arms, but adalimumab 160/80 mg was associated with the highest rate of mucosal healing (P = 0.045 for 160/80 mg vs. placebo). The proportions of patients with improvement in each Mayo sub-score (reduction by ≥1) and IBDQ response were greater in the adalimumab arms compared with placebo (Table 26).

Table 26: Efficacy endpoints for induction therapy at week 8 (FAS, NRI)

Endpoint, n (%)	Week 8		
	Placebo (n=96)	ADA 80/40mg (n=87)	ADA 160/80mg (n=90)
Full Mayo Score Response	34(35)	37(43)	45(50)*
Full Mayo Score Remission	11 (11)	12(14)	9(10)
Mucosal healing	29 (30)	34 (39)	40 (44)*
Rectal bleeding sub-score<=1	65 (67.7)	70 (80.5)*	64 (71.1)
PGA sub-score <=1	43 (44.8)	41 (47.1)	55 (61.1)*
Stool frequency sub-score<=1	31 (32.3)	30 (34.5)	36 (40.0)
IBDQ response^	38 (39.6)	42 (48.3)	38 (42.2)
Steroid-free	ND	ND	ND
Steroid-free remission	ND	ND	ND

ADA=adalimumab; EOW=every other week; FAS=full analysis set, IBDQ=Inflammatory Bowel Disease Questionnaire; ND=not determined; NRI=non-responder imputation; PGA=physician's global assessment; UC=ulcerative colitis; ^Response was defined as an increase in IBDQ score of ≥16 points from baseline; *P ≤ 0.05.

Efficacy for maintenance therapy

Maintenance therapy with adalimumab 40 mg EOW was associated with higher rates of response, remission, and mucosal healing at weeks 32 and 52 compared with placebo. Rates of remission for the adalimumab treated patients were greater than placebo at both weeks 32 and 52 (P=0.038 and P=0.001, respectively, Table 27). The proportion of adalimumab-treated patients with remission increased over time, with the highest rate (23.2 %) observed at week 52 despite the use of a non-responder imputation analysis. Nearly one-third (32.5 %) of adalimumab-treated patients taking steroids at baseline were steroid-free at week 52 compared with 20.7 % of patients taking placebo.

Patients exhibiting response to adalimumab induction therapy at week 8 were more likely to achieve efficacy at week 52 compared with the overall adalimumab-treated population. Among the 82 patients who achieved response per full Mayo Score at week 8, 61 % maintained response at week 52; 46 % were in remission, and 57 % had mucosal healing. Similar responses were observed when partial Mayo Scores were used as the measure of response. Rates of remission at week 8 for all three arms and the treatment effect sizes (adalimumab rate minus placebo rate) were affected by the method used to assign values at the study visit for Mayo Score Sub-scores for stool frequency and rectal bleeding. The lowest rates of remission and the smallest effect sizes were observed when Sub-scores were based on the worst daily patient diary entries during a 5-day or a 3-day period. Remission rates and effect sizes were greater when the Mayo Scores were based on the average of these two Sub-scores from 3 or 5 days of diary entries, with the mean of the 5-day method resulting in the highest overall remission rates and the largest effect sizes. Overall, 12 of 240 (5.0 %) patients who received adalimumab during the study developed anti-adalimumab antibodies.

Table 27: Efficacy endpoints for maintenance therapy at week 32 and 52

Endpoint, n (%)	Week 32		Week 52	
	Placebo (n=96)	ADA 40mg EOW (n=177)	Placebo (n=96)	ADA 40mg EOW (n=177)
Full Mayo Score Response	20(21)	64(36)*	17(18)	55(31)*
Full Mayo Score Remission	8(8)	32(18)*	7(7)	41(23)[i]
Mucosal healing	21(22)	51(29)	15(16)	51(29)*
Rectal bleeding sub-score<=1	27 (28.1)	74 (41.8)	22 (22.9)	59 (33.3)
PGA sub-score <=1	27 (28.1)	66 (37.3)	19 (19.8)	57 (32.2)*
Stool frequency sub-score<=1	20 (20.8)	57 (32.2)*	13 (13.5)	51 (28.8)*
IBDQ response^	21 (21.9)	55 (31.1)	12 (12.5)	45 (25.4)[i]
Steroid-free**	12 (20.7)	35 (29.2)	12 (20.7)	39 (32.5)
Steroid-free remission**	5 (8.6)	12 (10.0)	4 (6.9)	17 (14.2)

ADA=adalimumab; EOW=every other week; FAS=full analysis set, IBDQ=Inflammatory Bowel Disease Questionnaire; ND=not determined; NRI=non-responder imputation; PGA=physician's global assessment; UC=ulcerative colitis; ^Response was defined as an increase in IBDQ score of C16 points from baseline; **Percentages calculated based on the number of patients taking steroids at baseline (placebo, N = 58; ADA 40 mg EOW, N = 120); *P ≤ 0.05; [i] P ≤ 0.01.

Discussion

Adalimumab 160/80 mg induction treatment in patients who were unresponsive to corticosteroids and/or immunomodulatory therapy significantly improved the rate of response compared with placebo at week 8, with a rate of response similar to that observed in the pivotal phase III ULTRA 2 M06-827) trial involving Western patients. With the exception of week 8 remission, the results in this study were generally consistent with those observed in the Western studies. In this study, a high rate of remission was noted in the placebo arm among patients taking steroids at baseline. These findings are consistent with the known short-term effects of steroids to reduce symptoms. It is possible that, unlike in the Western studies, the patients in the Japanese study who were taking steroids at baseline may not have been truly steroid-resistant. This was not the case at week 52, which is also consistent with the known lack of long-term efficacy noted with steroid therapy. It should also be noted that baseline IBDQ scores were noticeably higher in this study compared to the Western RCTs. As noted by Cooney *et al* caution should be taken when comparing studies across populations in UC, as available data indicate that responses may not be consistent across populations[42]. This issue is discussed in more detail in section 2.11.

Safety

The overall safety profile of adalimumab was similar to that observed in other clinical trials, including trials in patients with UC and no new safety signals were observed. Most AEs were non-serious, mild, or moderate in severity, and were considered ‘‘not related” or ‘‘probably not related’’ to the study drug by the investigator. During the induction period, the overall rate of AEs was similar in the placebo arm vs. the 80/40 and 160/80 arms for adalimumab.

Serious AEs and worsening or flare of UC were most common in the placebo arm, and infections and injection site reactions were most common in the adalimumab 160/80 arm. There were three serious infections during the induction period, all of which occurred in the adalimumab 160/80 arm. Exposure-adjusted rates of AEs occurring during 52 weeks of double-blind treatment for patients receiving placebo, patients receiving adalimumab, and patients with response to adalimumab at week 8 per full Mayo Score are shown in Table 28.

Table 28: Adverse Events reported

AE, *n* (%)	Week 8, *n* (%)			Week 52, E (E/100 PY)		
	Placebo (*N* = 96)	ADA 80/40 mg (*N* = 87)	ADA 160/80 mg (*N* = 90)	Placebo (*N* = 96) PY = 44.8	ADA 40 mg EOW (*N* = 177) PY = 98.2	ADA week 8 responders per full Mayo score (*N* = 82) PY = 68.7
Any AE	45 (46.9)	49 (56.3)	40 (44.4)	273 (609.4)	538 (547.9)	343 (499.3)
At least possibly drug-related	10 (10.4)	14 (16.1)	12 (13.3)	34 (75.9)	91 (92.7)	64 (93.2)
Serious	7 (7.3)	2 (2.3)	4 (4.4)	14 (31.3)	33 (33.6)	20 (29.1)
Leading to early discontinuation	4 (4.2)	0	6 (6.7)	6 (13.4)	22 (22.4)	11 (16.0)
AE of interest						
Infection	15 (15.6)	11 (12.6)	17 (18.9)	70 (156.3)	134 (136.5)	90 (131.0)
Serious infection	0	0	3 (3.3)	2 (4.5)	8 (8.1)	6 (8.7)
Malignancy[a]	0	0	1 (1.1)	0	2 (2.0)	1 (1.5)
Injection site reaction	2 (2.1)	5 (5.7)	7 (7.8)	4 (8.9)	20 (20.4)	9 (13.1)
Opportunistic infection (excluding tuberculosis)[b]	0	0	1 (1.1)	0	2 (2.0)	2 (2.9)
Tuberculosis	0	0	1 (1.1)	0	1 (1.0)	0
Hepatic event	1 (1.0)	0	1 (1.1)	3 (6.7)	5 (5.1)	3 (4.4)
Allergic reaction	0	1 (1.1)	0	2 (4.5)	6 (6.1)	5 (7.3)
Hematologic event	1 (1.0)	3 (3.4)	1 (1.1)	4 (8.9)	6 (6.1)	4 (5.8)
UC worsening/flare	8 (8.3)	2 (2.3)	2 (2.2)	15 (33.5)	18 (18.3)	7 (10.2)

ADA adalimumab, *AE* adverse event, *E* event, *EOW* every other week, *PY* patient-year, *UC* ulcerative colitis

[a] One pancreatic carcinoma and one parathyroid tumor, which was determined to be benign but was conservatively classified as a malignancy

[b] One *Mycobacterium avium* complex infection and one cytomegalovirus infection

Image taken from Suzuki *et al*[32]

All injection site reactions were mild, and most were managed without study drug interruption or discontinuation. Patients receiving placebo were more likely to experience worsening or flare of UC.

Compared with the overall adalimumab population, patients with response at week 8 were less likely to experience an AE, serious AE, injection site reaction, or flare/ worsening of UC. During the entire trial, two malignancies were reported, both of which were considered to be unrelated to the study drug by the investigator. One case of tuberculosis was reported on day 73 (44 days after the last dose of the study drug) in a 65-year-old patient in the adalimumab 160/80 arm receiving prednisone 20 mg/day; this patient had presented with a negative purified protein derivative test (erythema [10 mm but no induration) and chest X-ray at baseline. The patient was hospitalised on day 81 and died on day 91. There were no cases of lymphoma, melanoma, congestive heart failure, demyelination, or lupus-like syndrome. Similar to data observed in other clinical studies, the presence of immunogenicity did not have a clinically significant influence on the safety of adalimumab.

2.7 Non-RCT clinical studies

- EQ-5D utility scores demonstrate a clear relationship with disease severity as categorised by the IBDQ, with post-surgery patients reporting significantly poorer QoL than non-surgery patients (p=0.016) or controls (p =0.03). Those with the most severe disease report values comparable to colorectal cancer.
- Patients who had undergone surgery reported lower (worse) scores on the IBDQ for bowel symptoms (p<0.01); systemic system (p<0.05); social function (p<0.01) and emotional health (p<0.01) than UC patients who had not undergone surgery.

In addition to the evidence derived from RCTs discussed in the previous sections; the following is a summary of published non-RCT evidence relevant to this submission which AbbVie is aware of.

2.7.1 Impact of Surgery on QoL in UC

Below is a summary of the study conducted by Swinburn *et al*[51]; a detailed report is available as Appendix 3.

Surgery is perceived as curative for ulcerative colitis but may not restore full health. Health-related QoL in ulcerative colitis is often measured using disease-specific instruments (*e.g*. the Inflammatory Bowel Disease Questionnaire, IBDQ) and less commonly using generic instruments (e.g. EuroQol EQ-5D). The generic approach measures QoL on a common “utility” scale ranging from 0 (dead) to 1 (full health). This allows for more useful comparison of impaired QoL relative to a health population or to individuals with other diseases. To examine the impact of surgery on patients’ QoL, this study captured data on both disease-specific and generic QoL on patients post-colectomy where published data are limited, as well as patients without colectomy. Utility scores of patients across the full spectrum of disease severity in UC were also evaluated.

Methods: Two hundred and thirty UC patients (including 30 post-surgery patients) were recruited along with 100 age and gender matched controls. Participants completed an online survey which comprised the Simple Clinical Colitis Activity Index (SCCAI), EuroQol EQ-5D and the IBD-Q. Basic socio-demographic and clinical data were also collected.

Results: EQ-5D utility scores demonstrate a clear relationship with disease severity as categorised by the IBDQ (ANOVA F (2,239) =5.544, p=0.004) with post-surgery patients reporting poorer QoL than non-surgery patients (p=0.016) or controls (p =0.03). Those with the most severe disease report values comparable to colorectal cancer[52].

There was a significant difference on all IBDQ domains and the overall score of the IBDQ between patients who had undergone surgery and those who had not. In all cases, patients who had undergone surgery reported lower (worse) scores for bowel symptoms (t228=3.15, p<0.01); systemic system (t228=2.11, p<0.05); social function (t228=4.75, p<0.01) and emotional health (t228=2.73, p<0.01).

On the bowel symptoms domain, and the overall IBDQ, the control group scored significantly different from both patient groups. Control group scores were consistently higher indicating that both patient groups had significantly worse HRQL than the population at large. On the domains of systemic systems, emotional health and social function, the control group differed significantly from the surgery but not the non-surgery UC group.

There was a significant difference on the overall score of the SCCAI between patients who had undergone surgery, and those who had not. In all cases, patients who had undergone surgery reported higher scores on the scale (t226=-3.81, p<0.01), which indicates greater symptom severity. On the individual items, there was a statistical difference between the surgery and non-surgery group on three items; bowel frequency daytime (t228=-2.69, p<0.01); bowel frequency night time (t228=-5.71, p<0.01) and urgency of defecation (t228=-3.88, p<0.01). On all three domains patients who have received surgery reported greater levels than those who have not received surgery. It should be noted however that the SCCAI has not been validated for use in post-surgery patients. However, the results suggest there are ongoing symptoms for patients after surgery.

Conclusion: Utilities among post-surgical patients was significantly poorer than both age and gender matched population controls and patients in remission or with mildly active colitis, suggesting the identification of effective new drug therapies for severe disease remains the goal for optimising long term QoL. Further assessment of the impact of surgery on QoL would be beneficial given the sample size of post-surgery patients.

2.7.2 Disease severity, QoL, and health care resource use in the UK

Below is a summary of the study conducted by Vaizey and colleagues[53] presented at the ECCO conference.

Methods: This cross-sectional, observational study used a patient questionnaire including demographic, disease characteristics and the EQ-5D-5L & IBDQ. Clinical assessment of the patient's disease severity was measured using the partial Mayo Score (pMayo) and was grouped into remission, mild and moderate/severe for analysis (0–2, 3–4, 5+). UC-related health care resource utilisation was collected using the patient questionnaire and a chart review for UC-related hospitalisations (over 1 year) and all other UC health care resource use (over 3 months). Unit costs were derived from government sources. The Kruskal–Wallis test was used to compare QoL scores between disease severities.

Results: 173 were included in the study. The median pMayo Score was 2.00, with 58% of patients' diseases severity in remission, 18% with mild and 24% with moderate/severe activity. Remission patients had significantly higher EQ-5D-5L (0.86 vs. 0.77 vs. 0.66, p < 0.0001) scores when compared to mild and moderate/severe UC patients. The disease-specific IBDQ was found to be positively correlated with the EQ-5D-5L (0.56, p < 0.0001). Patients reported that general practitioners were the most utilised health care provider, where 69% of patients made at least one visit and more than 15% had 5+ visits in the previous year. 88% of patients saw a gastroenterologist in the previous 3 months. 62% of patients had UC-related investigations, with a mean of 1.75±2.4 investigations per patient. Over the past year, 43% of patients were hospitalised and 8% visited the emergency department without being admitted. The total 3 month cost per patient for UC-related health care was £1,211.06. Prescription medication use accounted for the greatest proportion of the total costs (28%) with other outpatient UC-related investigations and hospitalisations for more than one day accounting for approximately 20% each.

Conclusion: Overall, UC disease severity has a significant impact on a patient's QoL, work productivity and daily activities. UC-related prescription medication, investigations, and hospitalisations account for the greatest proportion of the total UC-related health care costs.

2.7.3 Treatment of UC with ADA or IFX

Below is a summary of the study by Gies and colleagues[54].

To examine the response rates and long-term outcomes of infliximab and adalimumab treatment for out-patients with ulcerative colitis and to study the variables associated with response rates.

Methods: In a prospective study, a single-centre out-patient cohort was treated and followed up according to a structured protocol of clinical care. Response to treatment was assessed using a physician's global assessment that focused on normalisation of bowel frequency, absence of blood with defecation and tapering of corticosteroids to zero.

Results: Fifty-three ulcerative colitis patients were included in the study. Responses to induction therapy were 96.4% (27/28) for infliximab and 80% (20/25) for adalimumab (P = 0.0889). Responses to maintenance therapy were similar: infliximab 77.8% (14/18) and adalimumab 70.0% (14/20) (P =

0.7190). Multivariate analyses of the induction and maintenance responses did not reveal confounding elements. No new safety signals were identified.

Conclusions: This long-term follow-up of a single-centre cohort of ulcerative colitis patients demonstrates that 'real-life' out-patient treatment with infliximab and adalimumab is effective in induction and maintenance of response.

2.7.4 Adalimumab induction and maintenance therapy for infliximab-experienced UC patients

The following is a summary of the study by Taxonera and colleagues[55].

Aim: To evaluate the short- and long-term outcomes of adalimumab in ulcerative colitis patients previously treated with infliximab.

Methods: 30 patients with active ulcerative colitis were treated with adalimumab after failure of other therapies including infliximab. Short-term clinical response and remission were assessed at weeks 4 and 12. The proportion of patients who continued on adalimumab and the proportion of patients who remained colectomy free were assessed over the long term.

Results: Clinical response at weeks 4 and 12 was achieved in 16 (53%) and 18 (60%) patients, respectively, and clinical remission was obtained in 3 (10%) and 8 (27%) patients, respectively. After a mean 48 weeks' follow-up, 15 patients (50%) continued on adalimumab. Six patients (20%) required colectomy. All patients who achieved clinical response at week 12 were colectomy free at long term.

Conclusions: Adalimumab was well tolerated and induced durable clinical response in many patients with otherwise medically refractory ulcerative colitis. Patients achieving clinical response at week 12 avoided colectomy over the long term

2.7.5 Adalimumab in active UC: a “real-life” observational study

The following provides a summary of the observational study by Armuzzi and colleagues[56].

Aims: Although controlled trials have shown that adalimumab is significantly better than placebo, the absolute clinical benefit reported is modest. The authors report data on the effectiveness of adalimumab in a cohort of ulcerative colitis patients treated in 22 Italian centres.

Methods: All patients with active disease treated with adalimumab were retrospectively reviewed. Co-primary endpoints were clinical remission at weeks 4, 12, 24 and 54. Secondary endpoints were sustained clinical remission, steroid discontinuation, endoscopic remission and need for colectomy.

Results: Eighty-eight patients were included. Most patients had received previous infliximab treatment. Clinical remission rates were 17%, 28.4%, 36.4% and 43.2% at 4, 12, 24 and 54 weeks respectively. Twenty-two patients required colectomy. Clinical remission and low C-reactive protein at week 12 predicted clinical remission at week 54 (OR 4.17, 95% CI 2.36-19.44; OR 2.63, 95% CI 2.32-14.94, respectively). Previous immunosuppressant use was associated with a lower probability of clinical remission at week 54 (OR 0.67, 95% CI 0.08-0.66) and with a higher rate of colectomy (HR 9.7, 95% CI 1.46-9.07).

Conclusion: In this large "real-life" study adalimumab appears effective in patients with otherwise medically refractory ulcerative colitis. Patients achieving early remission can expect a better long-term outcome.

2.8 Audit data

2.8.1 UK Inflammatory Bowel Disease (IBD) Audit

Results from a recent national clinical audit of biological therapies in IBD have been published. The purpose of the audit was to measure the efficacy, safety and appropriate use of the biological therapies infliximab and adalimumab in patients with IBD in the UK and to capture the views of patients on their quality of life at intervals during their treatment.

This section presents the first full national report of the biological therapy element of the UK IBD audit and all analyses within the report include only those patients that were newly started on biological therapies between 12 September 2011 and 28 February 2013.

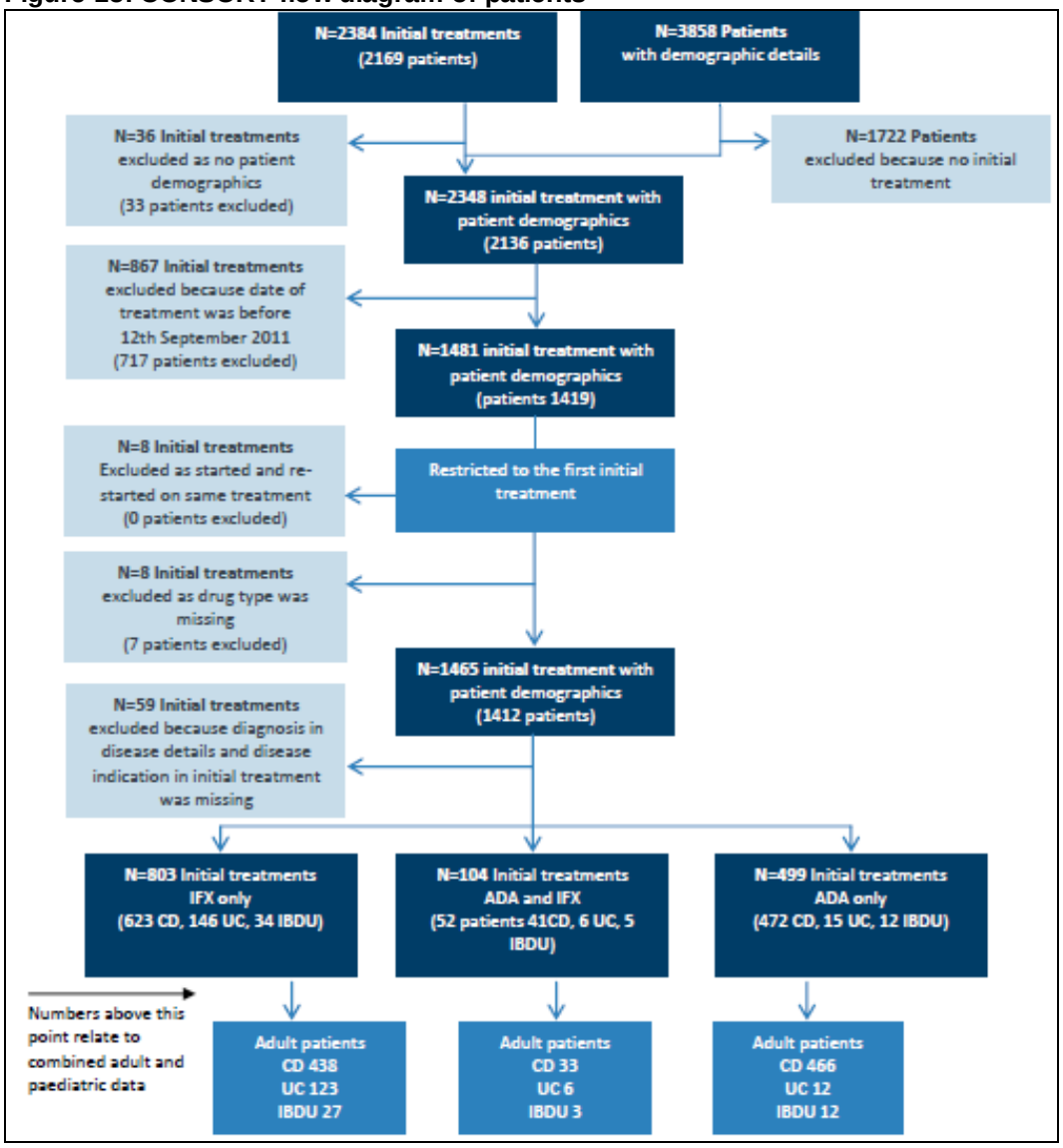
Methods

The UK IBD audit was a prospective audit with data collection taking place in 'real time' during the clinical appointment with the patient. Data entry took place in the form of 'submissions' to a web-based data collection tool. A submission referred to data entered in any of the following categories: patient demographics, IBD disease details, initial anti-TNFα treatment, follow up anti-TNFα treatment and IBD related surgery.

Patients

The published report includes those patients that were newly started on biological therapies between 12 September 2011 and 28 February 2013.On 28 February 2013 there were 3858 individual adult and paediatric patient demographic submissions entered onto the web tool. The study design is outlined in Figure 15 as a CONSORT diagram.

Figure 15: CONSORT flow diagram of patients



Results
Amongst the key findings, results from the UK IBD audit showed:

- Biological therapies are effective treatments for patients with IBD with 62% of adult patients entering clinical remission with corresponding improvements in patient-reported quality of life scores.
- A low proportion of IBD patients completed the quality of life questionnaires at baseline and follow-up treatment (17% (203/1162) and 16% (45/289) for the EQ-5D respectively).
- Recorded adverse events are uncommon. Acute treatment reactions and infections are the commonest events recorded among 6.3% and 5.3% of all patients, respectively. Malignancy is seen in <1% of patients.

Conclusion
The data presented in this report suggest that the biological therapies are safe and effective treatments for IBD that are used to good effect throughout the participating adult sites in the UK. Objective assessment of response to therapy is an important part of using biologic medicines and the collection of disease activity scores and quality of life data is central to this. Individual services should assess the delivery of these drugs to ensure that patients are not waiting unduly for these therapies.
It must be noted that there were relatively few UC patients studied in the UK IBD Audit which likely reflects the absence of NICE-recommended anti-TNF therapy options for subacute UC patients.

2.9 Studies unpublished at the time of writing

AbbVie also wishes to highlight the following on-going studies that are receiving funding from AbbVie.

2.9.1 M14-033

M14-033 (NCT02065622) is A Double-Blind, Randomised, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Patients With Moderately to Severely Active UC. It is estimated to complete in March 2018.

2.9.2 M13-045 InspirAda

INSPIRADA (M13-045) (NCT01550965) is an Open-Label Multicenter Study to Evaluate the Impact of Adalimumab on Quality of Life, Health Care Utilization and Costs of UC Subjects in the Usual Clinical Practice Setting. It is estimated to complete in January 2015.

2.9.3 P11-282 LEGACY

LEGACY (P11-282) (NCT01848561) is a Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Adalimumab in Patients with Moderately to Severely Active UC. It is estimated to complete in April 2027.

2.9.4 Non-interventional study in Japan

Special Investigation in Patients with UC to clarify the following information regarding the use of adalimumab 40mg Syringe 0.8mL for Subcutaneous Injection in patients with ulcerative colitis:

- Unknown adverse reactions (in particular, clinically significant)
- Onset status of adverse reactions in clinical practice
- Factors likely to affect the safety and effectiveness

This study plans to enroll 600 Japanese patients with moderate to severe active ulcerative colitis (only when ineffectively treated with the existing medications) who use adalimumab.

2.10 Evidence for the safety of adalimumab in patients with UC

- The adverse event profile of ADA in M06-826 and M06-827 studies suggests a favourable benefit risk profile in moderately to severely active UC patients and is consistent with the known profile established in other indications.

- In study M06-826, rates of adverse events were similar in the ADA 160/80/40 and PBO groups during the double blind safety period (50.2% vs. 48.4%) and open label period (69.6% vs. 73.5%). Similar results were observed in M06-827.
- The only adverse event which was reported at a statistically significantly different rate between the ADA160/80/40 and PBO groups in M06-826 was influenza like illness. During Double Bind administration, injection site reactions were more common in the ADA than the PBO group in M06-827 (39.7 vs. 14.2 events/100 PYs).
- Two patients on adalimumab had a treatment-emergent malignancy during DB administration; one squamous cell carcinoma (SCC) and one gastric cancer; neither of which was considered to be related to the study drug.
- The safety data from M06-826 and M06-827 demonstrates there were few differences between PBO and ADA treatment either in the Induction Set or in the Maintenance Set in terms of the frequency, severity, and relationship to study drug for common adverse events, serious adverse events, and discontinuations due to adverse events.

A summary of the adverse events reported in the included randomised trials is presented in Table 29. The incidence of adverse events in patients treated with ADA or PBO was similar (M06-826: 50.2% vs. 48.4%; M06-827: 82.9% vs. 83.8%). The majority of AEs were mild or moderate in nature and there were no deaths. The adverse event profile supports a favourable benefit risk profile for ADA when used in the treatment of moderate to severe UC (subacute).

Table 29: Summary of treatment-emergent adverse events across the randomised trials

Trial ID Adverse events	ADA n (%)	Placebo n (%)
M06-826		
Number of subjects	*223*	*223*
Any AE	112 (50.2)	108 (48.4)
Any AE at least possibly drug related	43 (19.3)	48 (21.5)
Any severe AE	19 (8.5)	17 (7.6)
Any serious AE	9 (4.0)	17 (7.6)
Any AE leading to discontinuation	12 (5.4)	12 (5.4)
Any at least possibly drug related SAE	1 (0.4)	4 (1.8)
Deaths	0	0
M06-827		
Number of subjects	*257*	*260*
Any AE	213 (82.9)	218 (83.8)
Any AE at least possibly drug related	101 (39.3)	86 (33.1)
Any severe AE	41 (16.0)	37 (14.2)
Any serious AE	31 (12.1)	32 (12.3)
Any AE leading to discontinuation of study drug	23 (8.9)	34 (13.1)
Deaths	0	0

Source: CSR M06-826; CSR M06-827; Data expressed as n (%); SAE=serious adverse event; AE=adverse event

Frequently reported (≥5% in any treatment arm) treatment-emergent AEs, or events with a significant difference in either treatment arm in the clinical studies are presented in Table 30. The most frequently reported AE across both studies was colitis ulcerative (M06-826: ADA 5.8% vs. PBO 9.4%; M06-827: ADA 22.6% vs. PBO 29.2%). Other frequently reported AEs in study M06-827 were nasopharyngitis, headache, nausea, arthralgia, abdominal pain, fatigue, anaemia, pyrexia, and upper respiratory tract infection. The incidence of three AEs were significantly different between patients treated with adalimumab and those treated with placebo including; iron deficiency anaemia, gastroenteritis, and nasopharyngitis. In all cases, the incidence rate was higher in patients treated with adalimumab. The majority of AEs were mild to moderate in severity and considered not related or probably not related to study drug.

Table 30: Summary of AEs reported by ≥5% of subjects or events with a significant difference in either treatment arm across the randomised trials

Trial ID MedDRA System Organ Class and Preferred Term	ADA n (%)	PBO n (%)
M06-826		
Number of subjects	*223*	*223*
Any AE	213 (82.9)	218 (83.8)
Gastrointestinal disorders		
Colitis ulcerative	13 (5.8)	21 (9.4)
M06-827		
Number of subjects	*257*	*260*
Any AE	213 (82.9)	218 (83.8)
Blood and Lymphatic System Disorders		
Anaemia	10 (3.9)	15 (5.8)
Iron deficiency anaemia	7 (2.7)*	1 (0.4)
Gastrointestinal Disorders		
Colitis ulcerative	58 (22.6)	76 (29.2)
Abdominal pain	20 (7.8)	16 (6.2)
Nausea	15 (5.8)	22 (8.5)
General Disorders and Administration Site Conditions		
Fatigue	16 (6.2)	15 (5.8)
Pyrexia	11 (4.3)	14 (5.4)
Infections and Infestations		
Gastroenteritis	9 (3.5)*	2 (0.8)
Nasopharyngitis	45 (17.5)*	27 (10.4)
Pharyngitis	9 (3.5)	3 (1.2)
URTI	11 (4.3)	14 (5.4)
Muscoloskeletal and connective tissue disorders		
Arthralgia	20 (7.8)	16 (6.2)
Nervous System Disorders		
Headache	22 (8.6)	37 (14.2)
Respiratory, Thoracic & Mediastinal Disorders		
Oropharyngeal pain	15 (5.8)	7 (2.7)

Source: CSR M06-826; CSR M06-827; *statistically significant difference compared with placebo

Pre-defined adverse events of special interest were specifically examined in the randomised studies and are summarised in Table 31.

Table 31: Summary of adverse events of special interest for M06-826 and M06-827

AE of special interest n (%)	ADA n (%)	PBO n (%)
M06-826		
Infectious AE	32 (14.3)	35 (15.7)
Serious infectious AE	0	3 (1.3)
Opportunistic infection (excluding TB)	0	1 (0.4)
Malignant AE	0	2 (0.9)
Injection site reaction related	13 (5.8)	7 (3.1)
Congestive heart failure related	0	0
Demyelinating disease	0	0
Hepatic related	5 (2.2)	1 (0.4)
Allergic reaction related	1 (0.9)	1 (0.4)
Lupus-like syndrome	0	0
Haematologic related	2 (0.9)	1 (0.4)
Deaths	0	0
M06-827		
Infectious AE	116 (45.1)	103 (39.6)
Serious infectious AE	4 (1.6)	5 (1.9)
Opportunistic infection (excluding TB)	5 (1.9)	3 (1.2)
Malignant AE	2 (0.8)	0
Lymphomas	0	0
Injection site reaction related	31 (12.1)*	10 (3.8)
Congestive heart failure related	1 (0.4)a	0
Demyelinating disease	0	0
Hepatic related	10 (3.9)	7 (2.7)
Allergic reaction related	4 (1.6)	1 (0.4)
Lupus-like syndrome	1 (0.4)b	0
Haematologic related	5 (1.9)*	0
Deaths	0	0

Source: CSR M06-826; CSR M06-827; *Statistically significant difference compared with placebo; a non-serious, mild, right ventricular overload considered by the Investigator to be not related to study drug; b systemic lupus erythematous rash was not serious, moderate in severity, and considered probably related, remained unresolved.

In conclusion, the safety profile observed in the clinical studies was consistent with previous clinical trials for adalimumab, and no new safety signals were observed. The majority of TEAEs were mild to moderate in intensity and were not considered by the Investigator to be related to study drug. Serious AEs, AEs leading to discontinuation, and AEs of special interest occurred infrequently, and did not statistically significantly differ between treatment groups, with the exception of injection site reaction and haematology-related TEAEs.

2.10.1 Long-term safety during open-label treatment

An overview of adverse events occurring in the long-term M10-223 study is provided in Table 32. These data have been recently presented as a poster presentation at the 2014 ECCO congress.

Table 32: Overview of treatment emergent adverse event rates (exposure as of 15 April 2013)

Adverse Event	ADA 40 mg EOW/EW N = 1010; Patient Years = 2338 Events (Events/ 100 Patient Years)
Any AE	8057 (344.6
Any serious AE	414 (17.7)
Any AE leading to discontinuation of study drug	249 (10.7)
Serious Infection	79 (3.4)
Opportunistic infection (excluding TB)	6 (0.3)
Active tuberculosis	1 (<0.1)
Injection site reaction	246 (10.5)
Any malignancy (including lymphoma)	23 (1.0)*
Lymphoma	3 (0.1)
Congestive heart failure	4 (0.2)
Demyelinating disease	3 (0.1)
Hepatic event	12 (0.5)
UC worsening/flare	588 (25.2)
AE leading to death	2 (0.1)**

Source: Poster P571, presented at ECCO 2014; *One malignant event was reported twice in the same patient; **Two additional non-treatment-emergent deaths were also recorded but not reflected in this table

As of 15 April 2013, a total of 1010 patients had received at least one dose of adalimumab in M06-826, M06-827, and M10-223, representing 2338 patient-years (PYs) of exposure. Serious AEs were reported with an incident rate of 17.7 events per 100 PYs with adverse events leading to discontinuation occurring at a rate of 10.7 events per 100PYs. Three events of B-cell lymphoma occurred during M10-223; all three patients had a history of smoking and either prior or concomitant azathioprine use

Overall exposure-adjusted adverse event rates during the entire treatment period were similar to or lower than those observed during the double-blind treatment phases.

In conclusion, the AE profile in this long term extension study supports a favourable benefit risk profile for ADA in moderate to severe UC and there no new safety risk or trends have been identified.

2.10.2 Cochrane overview of adverse effects of biologics

This section presents summary results for the 2011 Cochrane review examining the potential adverse effects of tumour necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), interleukin (IL)-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) therapy in patients with any disease condition except human immunodeficiency disease (HIV/AIDS).

In February 2011, Singh *et al.*[57] published a network meta-analysis and Cochrane review of adverse effects of biologics across multiple indications, including RA and other inflammatory arthritis. Since serious risks such as tuberculosis (TB) reactivation, serious infections, and lymphomas may be common to the biologics but occur in small numbers across the various indications, the authors aimed to combine the results from all the biologics used in many conditions to obtain the risk estimates.

The biologics investigated were the anti-TNFs (etanercept, adalimumab, infliximab, golimumab, and certolizumab), the interleukin (IL)-1 antagonist (anakinra), the IL-6 antagonist (tocilizumab), the anti-CD28 (abatacept), and the anti-B cell therapy (rituximab). Randomised controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extension (OLE) studies that studied one of the nine biologics for use in any indication (with the exception of HIV/AIDS) and that reported pre-specified adverse outcomes were considered for inclusion. The authors searched The Cochrane Library, MEDLINE, and EMBASE (to January 2010). Identifying search results and data extraction were performed independently and in duplicate. For the network meta-analysis, Singh *et al.* performed mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayesian framework.[57]

The authors included 163 RCTs with 50,010 participants and 46 extension studies with 11,954 participants. The median duration of RCTs was six months and 13 months for OLEs. Data were limited for tuberculosis (TB) reactivation, lymphoma, and congestive heart failure. Adjusted for dose, biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio (OR) 1.19, 95% CI 1.09 to 1.30; number needed to treat to harm (NNTH) = 30, 95% CI 21 to 60) and withdrawals due to adverse events (OR 1.32, 95% CI 1.06 to 1.64; NNTH = 37, 95% CI 19 to 190) and an increased risk of TB reactivation (OR 4.68, 95% CI 1.18 to 18.60; NNTH = 681, 95% CI 143 to 14706) compared to control. [57]

The rate of serious adverse events, serious infections, lymphoma, and congestive heart failure were not statistically significantly different between biologics and control treatment Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to control (OR 2.04, 95% CI 1.43 to 2.91; NNTH = 12, 95% CI 8 to 28).

Indirect comparisons revealed that adalimumab and golimumab were significantly less likely than infliximab to result in withdrawals due to adverse events.

For SAEs: Certolizumab pegol was statistically significantly more likely to be associated with SAEs compared to adalimumab (OR 1.63, 95%CI 1.01 to 2.62). Abatacept was statistically significantly less likely to be associated with SAEs compared to certolizumab (OR 0.56, 95% CI 0.33 to 0.94). In sensitivity analyses conducted in unadjusted models, neither difference was significant. Golimumab

was statistically significantly less likely to be associated with SAEs compared to adalimumab (OR 1.18, 95% CI 1.10 to 3.14). There were no other statistically significant differences between the biologics in both the unadjusted model and dose-adjusted model.
For withdrawals due to AE: In sensitivity analyses only in unadjusted model, infliximab was more likely to be associated with withdrawals due to AEs compared with abatacept (OR 1.92, 95% CI 1.01 to 3.71), adalimumab (OR 2.00, 95% CI 1.17 to 3.49), and etanercept (OR 1.72, 95% CI 1.02 to 2.91). Rituximab was also more likely to be associated with withdrawals due to AEs than adalimumab (OR 2.17, 95% CI 1.04 to 4.74)
Serious infections: Certolizumab was associated with higher odds of serious infections than abatacept, adalimumab, etanercept, golimumab and rituximab. The odds ratios were roughly 0.25 times or lower for each of the five biologics compared with certolizumab in the indirect comparisons. In sensitivity analyses: Anakinra was associated with a statistically significantly higher odds of serious infections compared with rituximab. [57]

The authors concluded that overall, in the short term, biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results. There is a need for more research regarding the long-term safety of biologics and the comparative safety of different biologics. National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics.

2.10.3 Data from extensive safety databases evaluating adalimumab for multiple indications

Finally, the 2010 global safety update for adalimumab is also presented here for completeness.

The safety profile of adalimumab has been studied in 71 global clinical trials up to 6 November 2010, including 23,458 patients representing 36,730.5 patients years of treatment. For this analysis, published by Burmester and colleagues in 2012, data were derived from the 71 clinical trials, which included randomised controlled trials, open-label trials, and long-term extension studies conducted in Europe, North America, South America, Asia, Australia, New Zealand, and South Africa. The trials spanned multiple indications; 36 trials in RA, three in juvenile idiopathic arthritis, four in AS, four in PsA, 13 in psoriasis, and 11 in Crohn's disease but none were included for ulcerative colitis at this time. [58] Safety data from post-marketing surveillance for adalimumab was not included in the analysis to avoid any limitations which may be introduced with voluntary reporting.

The incidence rates of serious AEs reported during adalimumab treatment for inflammatory diseases are presented in Table 33, separated by indication. Serious infectious events were the most frequently reported serious adverse events across all six therapeutic indications; the greatest rates were seen in patients with RA or CD. Furthermore, the risk of serious infection rates was generally stable across time for all indications[58].

Across all indications, the rate of active TB was 0.2/100 PYs including cases from the older RA clinical trials, which were conducted before the implementation of tuberculin test screening. No serious opportunistic infections have been reported with adalimumab in AS, PsA or psoriasis clinical trials. Twenty serious opportunistic infections, excluding TB and oral candidiasis, have been reported during adalimumab clinical trials (<0.1 events/100 PYs), 14 cases in patients with RA, four cases in patients with CD and two cases in JIA. The most common opportunistic infections were oesophageal *candidiasis* (n=3), and aspergillosis, Candida sepsis, *coccidioidomycosis*, cytomegalovirus infection, herpes zoster and nocardiosis (n=2 each)[58].

Rates of malignancies across all indications were 0.7 events/100 PYs for malignancies, excluding lymphoma and non-melanoma skin cancer (NMSC), 0.1/100 PY for lymphoma, and 0.2/100 PYs for NMSC. Compared with age- and sex-matched populations, the observed number of malignancies (all malignancies including lymphoma but excluding NMSC) in each disease population was similar to the expected number in the reference population. However, the number of lymphomas observed in the RA studies was significantly greater than expected compared with a US-based age- and sex-matched population, likely because RA itself is normally associated with an SIR of 2 irrespective of treatment, thus this increase is expected vs. a matched population that does not necessarily have RA. A greater proportion of patients with RA, psoriasis, and Crohn's disease demonstrated

standardised incidence rates of NMSC of >1, indicating a higher number of observed NMSC cases than expected in the general population[58]. Lastly; for subjects treated with adalimumab in the RA, AS, and psoriasis clinical studies, the observed number of deaths was lower than expected in an age- and sex-match population[58].

Table 33: Incidence rates of serious AEs of relevance to adalimumab treatment in patients being treated for a range of inflammatory diseases (rates are reported as E/100 PY)

	AS	RA	Juvenile idiopathic arthritis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	**1684**	14 109	212	837	3010	3606
Exposure, PYs	**1985.6**	23 942.6	604.9	997.5 5	061.8	4138.0
Serious infections	**1.4**	4.6	2.0	2.8	1.7	6.7
NMSC	**0.3**	0.2	0	0.1	0.1	<0.1
CHF	**0.1**	0.2	0	0	<0.1	0
Active tuberculosis	**0**	0.3	0	0.2	0.1	<0.1
Opportunistic infections	**0**	<0.1	0	0	0	<0.1
Demyelinating disorder	**<0.1**	<0.1	0	0	0	0.1
Lupus-like syndrome	**0.1**	<0.1	0	0	0	<0.1
New onset/worsening of psoriasis	**<0.1**	<0.1	0	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	**0.2**	0.9	0	0.2	0.6	0.5
Lymphoma	**<0.1**	0.1	0	0.2	<0.1	<0.1
Melanoma	**<0.1**	<0.1	0	0	0.2	0
Any AE leading to death	**<0.1**	0.8	0	0.3	0.2	0.1

Source: Burmester 2012[58]
AE: Adverse event, AS: Ankylosing spondylitis, CHF: Congestive heart failure, NMSC: non-melanoma skin cancer, PY: Patient year, RA: Rheumatoid arthritis

The risks of AEs associated with adalimumab and other anti-TNF agents have been extensively studied and rates are consistent with increased exposure; the results of this analysis are consistent with previous safety analyses. The increased risk of serious infections and NMSC are a well-known AE associated with anti-TNF therapy, and were no higher here for adalimumab than expected for this class of treatments. The overall rates of malignancy were similar to rates expected in the reference population, with event rates stable over time, suggesting no increased risk with prolonged exposure.[58]

In summary, the analyses reported here provide additional support for the long-term safety profile of adalimumab. Important differences in events rates have been demonstrated across indications, however, the AE rates were stable over time and no new safety signals were identified.

2.11 Clinical interpretation of the evidence

- Caution should be observed in comparing results across trials due to study design differences, placebo response variation and difference in choice and scoring of endpoints.
- Challenges exist in comparing Mayo Scores across trials since no common method exists for determining the full Mayo Score or the individual sub-scores.
- Severe patients excluded from the M06-826 and M06-827 studies with unstable severe disease may actually be those for whom the use of anti-TNF therapy is considered in the UK

2.11.1 Limitations of the Mayo scoring system

The Mayo Score is the most commonly used measure in randomised clinical trials, but trials vary in whether remission or response is defined as the primary endpoint. It is also not feasible to use the full Mayo Score including endoscopy for repeated measurements so the partial Mayo Score is often used in follow up. However, D'Haens *et al* note that there has been '*considerable heterogeneity and confusion regarding the optimal instruments (activity indices) and end points for assessing the efficacy of medical therapies for UC*' and that "an 'optimal' scoring index for UC is still to be developed"[47]. Joyce *et al* note that it has never been established that any of the disease activity indices actually measures all of the important components of ulcerative colitis[59]. Most current indices were developed without patient input and items were not tested for their responsiveness to change.

The lack of a patient-centred index raises the issue of whether or not the available indices capture all of the symptoms that are important to a patient; i.e. the ability to lead a 'normal' life[60]. Indeed one study reported that a Mayo Score cut off of 4.5 shows the highest sensitivity to detect patient defined remission, rather than the more stringent definition often used in clinical studies of 2 or less. The Mayo Score also does not take into account major important symptoms for patients such as urgency, tenesmus, and incontinence[60]. These symptoms undoubtedly affect a patient's quality of life and it is therefore essential that HRQOL tools such as the IBDQ are used as they reflect the disease and health state of a UC patient which clinical indices may not. Anti-TNF therapy also improves symptoms of fatigue and extra-intestinal manifestations of IBD which are not components of the Mayo Score further emphasising that consideration of clinical activity scores alone are not sufficient to elucidate the benefits of anti-TNF therapy in the treatment of UC.

Therefore the Mayo Score may not capture the full benefits of treatment with anti-TNF therapy from the patient perspective. Turner *et al* note that the requirement for physician global assessment limits the use of the Partial Mayo Score in retrospective clinical research and by non-physician research personnel[61]. When focusing on specific items, the authors found that the PGS subjective item of the Mayo Score (and the partial Mayo Score) contributed to the reduced reliability found in their study. In addition, the inter-observer reliability of the endoscopic component of Mayo Score has also been shown to be low [42,62].

2.11.2 Limitations affecting comparability across trials

It should be noted that the Partial Mayo Score is not commonly recorded for use in UK clinical practice so it is difficult to compare trial results with observational study results from the UK. Full or Partial Mayo Scores can be calculated with different methods for the rectal bleeding and stool frequency sub-scores (worst vs. mean diary entries and 5 vs. 3 days of diary entries). This sub-score calculation methodology can have an impact on efficacy rates. Currently, there is not a standard method for the determination of these sub-scores in terms of days of diary entries used or the use of mean or worst rank approaches, and different studies have used different approaches. For example, the adalimumab M06-826 and M06-827 studies used the worst entry of 3 days of diary entries, whereas the golimumab and infliximab UC development programme used the average of 3 days of diary entries.

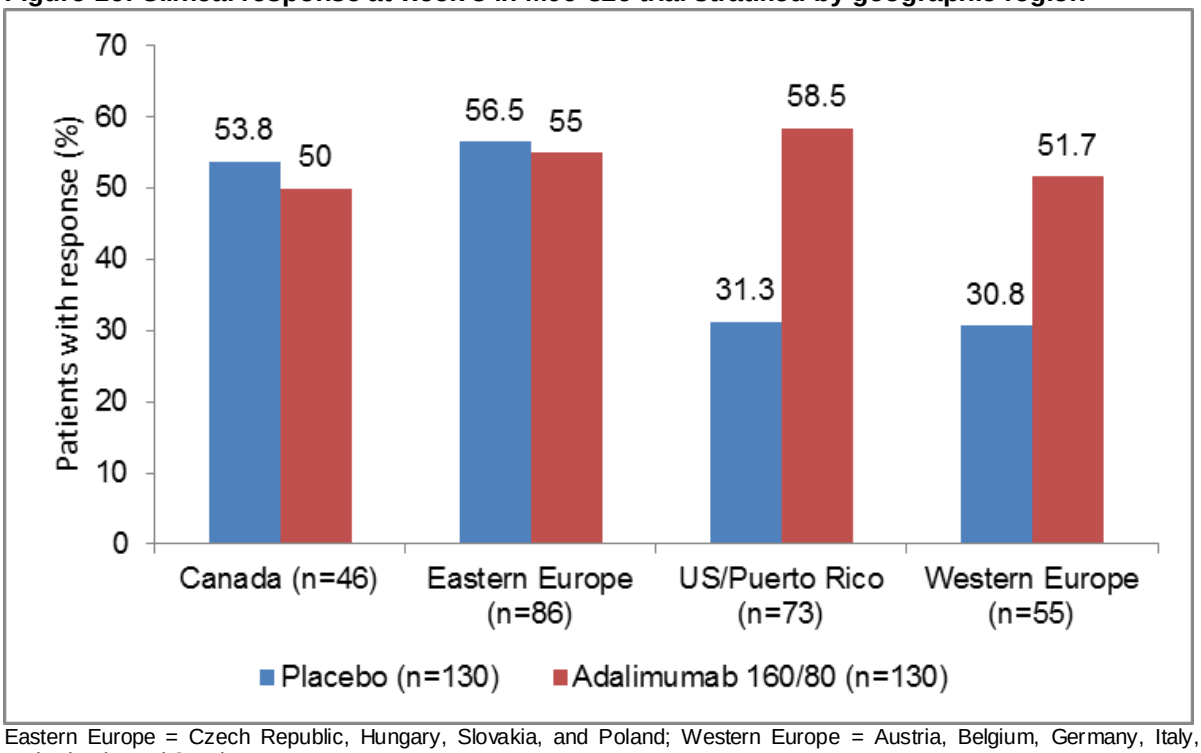
The Mayo Score and the Partial Mayo Score have been shown to be able to distinguish between responders and non-responders fairly well[41]. However, the scores are not without their limitations and the subjective nature of 3 out of the 4 sub scores could lead to variation. The stool frequency sub score is not an absolute score and is calculated relative to the 'normal' frequency for that individual as determined by the patient, and could therefore introduce variation. Indeed data from a sub-analysis of the M06-827 trial, showed that in patients with a mucosal healing sub score of 0 or 1 (the definition of mucosal healing) at week 52, only 33.9% of patients reported a stool frequency sub score of 0 ('normal') with 5.4% reporting a sub score of 3, which equates to >4 stools a day more than 'normal'[63]. The rectal bleeding sub score is calculated using the most severe bleeding of the day[36], and the physician's global assessment may vary in interpretation and could be influenced by the recording of the patient reported stool frequency and rectal bleeding sub scores[41].

The limitations of the Mayo Score are also apparent in the variation of placebo results across trials as highlighted by Su *et al*[64]. They conducted a meta-analysis of the placebo rates of remission and response in clinical trials where the Mayo Score was grouped with the Sutherland Index. This combined group (called the UCDAI here) showed placebo remission rates of 0-21% when remission was defined as a UCDAI score of 0, and 4-33% when remission was defined as a score of less than 3. Similar variation was seen when looking at the placebo response rates, with rates of 9-56% where response was defined as a decrease of 3 or more on the UCDAI score, and 47-67% where response was defined as a decrease of 2 or more points. Factors that could affect the rates of placebo response and remission were identified as study duration, number of study visits, disease duration, disease severity and inclusion of endoscopy in the scoring.

2.11.3 Issue of comparability and geographic variation

The conclusions presented by Reinisch *et al*[30] state that adalimumab, in the 160/80mg loading protocol, was effective for the induction of clinical remission in the 8 week M06-026 trial. Clinical response at week 8 was assessed in a secondary analysis and the results, having been stratified by geographic region, showed consistency in the adalimumab response rates. The placebo response rates however were not consistent across the four regions assessed; Figure 16, which is a reproduction from the paper, demonstrates this.

Figure 16: Clinical response at week 8 in M06-826 trial stratified by geographic region



Eastern Europe = Czech Republic, Hungary, Slovakia, and Poland; Western Europe = Austria, Belgium, Germany, Italy, Netherlands, and Sweden

The reason for this variation in placebo response across the regions remains unclear. The authors offer the explanation that the placebo effect may have been enhanced by high expectations of success among both the clinicians and the patients involved in the trial. However, such differences could be the result of differing interpretations of the Mayo scoring system and the limitations discussed in the previous sections. These data highlight that it may be difficult to compare the Mayo Score across trials particularly where the trials are multinational.

Geographic variations of this nature could very well be the cause of the discrepancies noted in the Japanese RCT discussed in section 2.6.

The issue of geographic variation was investigated in a meta-analysis[65] encompassing 110 English language RCTs carried out between 1955 and 2005 in which factors significantly modifying placebo response were explored using regression. In this meta-analysis the pooled placebo remission rate was 23% (95%CI: 18.4-28%) and the pooled placebo improvement rate was 32.1% (95%CI: 28.1-36.3%). Multivariate analysis showed that the country where the study was performed (P = 0.025 for placebo remission and P = 0.0083 for placebo response rates) significantly influenced the placebo remission and response rates.

2.11.4 Variation in colectomy rates in trials over time

It should be noted that the colectomy rates observed in the ULTRA studies of adalimumab was lower than those previously observed for the infliximab ACT studies (see Table 34). The overall colectomy rate was generally lower than that observed in the ACT trials (9% on infliximab and 16% on placebo), despite higher Mayo Scores in the ULTRA studies and the inclusion of anti-TNF experienced patients in ULTRA 2 (M06-827). This finding was likely due to multiple factors, including the availability of adalimumab rescue therapy for all patients in the ULTRA trials; however, this reasoning does not

explain why the colectomy rate observed in the ULTRA trials was lower than that of the infliximab group in the ACT trials (9%). Knowledge that patients were being treated with open-label adalimumab therapy could have influenced physician decision making in the ULTRA studies. Other reasons could include differences in alternative commercial treatment options to colectomy available at the time the ULTRA and ACT trials were conducted (e.g. increased use of conventional immunosuppressive therapy during the ULTRA trials) or other changes in clinical practice in the time since the ACT studies were conducted.

2.11.5 Generalisability of the patient population in RCTs

It should be noted that a number of the inclusion and exclusion criteria for the ULTRA studies of adalimumab may have led to a lower severity of patients being included in these studies in comparison with the severity of patients expected in UK clinical practice. Firstly, it should be noted that patients expected to require surgery or not receiving stable doses of corticosteroids were excluded from the ULTRA studies. However these difficult to treat patients may closely fit the profile of patients for whom anti-TNF therapy would be considered in the UK.

2.11.6 Limitations of using cross-sectional utilities to assess QoL in UC

Given the relapsing nature and unpredictability of UC and difficulties in classifying the severity of patients by clinician or patient defined outcome measures there would be value in assessing utility longitudinally as well as in cross sectional studies with consistent well-defined measures of disease severity. A moderate to severe UC patient experiencing an acute flare may have a significantly lower utility than a moderate to severe UC patient who is in a period of more stable disease. An instrument with a short recall period, such as the EQ-5D, completed by a patient when they are experiencing a more stable disease state would likely provide artificially high utilities and may not capture the true impact of the condition on a patient's quality of life. The Swinburn *et al*. (2012) study showed that, of the 200 pre-surgery UC patients that completed the EQ-5D questionnaires, 153 (76.5%) had reported that their disease had been inactive over the past week (see Appendix 3). These data may suggest that patients reported a better quality of life compared with if the mean utility score was calculated based on a series of questionnaires administered longitudinally over a period of time. Further research in cross-sectional versus longitudinal quality of life assessment in UC patients may help substantiate this hypothesis. A key consideration will be whether the mapped measures are assessing disease and symptom severity using the same recall period.

In addition, results from the UK IBD audit suggest that only 17% (203/1162) of patients completed an EQ-5D questionnaire at biologic treatment initiation. It is not known whether the high non completion rate was systematically biased with patients who had not completed the questionnaire being in a more severe condition than those who completed it. If this were the case, there would be some bias introduced in data collection as patients in acute flares whom you would expect to have lower utilities, may be excluded from the analysis.

2.12 Network Meta-analysis

- No formal network meta-analysis was conducted as part of this submission
- Only results from adalimumab vs. placebo studies have been included due to differences in trial design, placebo responses and endpoint scoring making network meta-analysis inappropriate

No formal network meta-analysis comparing; adalimumab, infliximab, and golimumab in moderate to severe UC (subacute) was conducted as part of this evidence submission. In general, in the absence of head to head RCT data, as is the case in the present evaluation, the use of network meta-analysis techniques are useful and widely accepted as a method of synthesising comparative data estimates. That said; the reliability of such estimates is dependent upon similarity between the trial design, setting and the endpoints being compared.

Of most relevance, the calculation of the Mayo Score in classifying patients' clinical severity was conducted differently in the adalimumab trials M06-826, M06-827 compared with the trials involving infliximab and golimumab (see section 2.9.1). This difference in Mayo Score estimation method may result in data for the endpoints of remission and response which are not directly comparable between

the adalimumab trials and the trials involving infliximab and golimumab. A network meta-analysis utilising the proportion of patients achieving remission or response from each trial would inherently assume that these endpoints have been defined in exactly the same manner across trials. The method of calculation of Mayo Score in the adalimumab trials, i.e. the worst entry of 3 days of diary entries, will produce numerically worse Mayo Scores at baseline and over time than taking the average Mayo Score over a 3 day period. Furthermore, even if the calculations had used equivalent methods across studies there are concerns about pooling studies using the Mayo Score across different countries with different levels of scoring experience as outlined in section 2.11. Placebo responses have been shown to differ markedly depending on the severity of the trial population, study design and country or region in which the trial was conducted. Due to the challenges in comparison of the clinical activity indices it may be more instructive to compare the change in IBDQ observed across studies when similar populations are studied.

AbbVie are aware of three recently published network meta analyses which have compared the efficacy of adalimumab, infliximab and golimumab for the treatment of moderate to severe UC[66,67,68]. However, there are other important and relevant differences in clinical trial design between the RCT's studying adalimumab, golimumab and infliximab in moderately to severely active UC (subacute) which would make evidence synthesis via network meta-analysis unreliable in producing estimates of comparative efficacy. Table 34 outline some of the key differences. Consequently, AbbVie have not provided a network meta-analysis of adalimumab, infliximab and golimumab.

Table 34: Differences in RCT design studying adalimumab, infliximab and golimumab in moderate to severe UC

	M06-826 (ULTRA 1)	M06-827 (ULTRA 2)	ACT 1	ACT 2	PURSUIT
Parallel group design	✓	✓	✓	✓	Adaptive design with Phase 2 dose ranging to Wk-6, followed by confirmatory Phase 3 component
Primary endpoint	Remission at wk 8	Remission at wk 8 Remission at wk 52	Response at wk 8	Response at wk 8	Response at wk 6 (induction) Response at wk 54 in Wk-6 responders (maintenance)
Study Duration	8 Weeks	52 Weeks	54 Weeks	30 Weeks	54 Weeks
Requirement for steroid and/or IMM failure	✓	✓	✓	Need only have failed 5ASA as a minimum	Need only have failed 5ASA as a minimum
Inclusion of anti-TNF experienced patients	x	✓ ~40%	x	x	Unclear*
Steroid Tapering	Optional	Optional	Mandatory	Mandatory	Mandatory
Mayo scoring methodology	Worst-rank	Worst-rank	Average	Average	Average
Open Label escape allowance	x	✓	x	x	✓
Timing of primary endpoint efficacy assessments	Trough	Trough	2 wks post-infusion	2 wks post-infusion	2 wks post-injection
Long-term data	Up to 4yrs ULTRA 3	Up to 4yrs ULTRA 3	Up to 3 years	Up to 3 years	Up to 2 years

*The wording used in the PURSUIT induction publication (Sandborn *et al*[69]) contains the following wording regarding study entry and previous biologics use "Earlier use of the following medications also precluded study participation: biologic anti-TNF agent(s) natalizumab or other agents targeting the a-4 integrin, B-cell-depleting agents (rituximab), or Tcell-depleting agents (alemtuzumab, visilizumab) within 12 months of the first study-agent injection (or continued B- or Tcell depletion >12 months after completing therapy with lymphocyte-depleting agents);" Therefore some patients may have had previous exposure of anti-TNF greater than 12 months before receiving study drug

Section 3: Cost-effectiveness

Full details of the economic evaluation are presented in appendix 1. An overview of the economic model is provided in this section.

3.1 Overview of cost utility model for adalimumab

- **There is currently a high unmet need for patients in England and Wales with moderately to severely active UC (subacute) who have failed on standard of care with no recommended biologic options in this patient population**
- **The cost-effectiveness of adalimumab + standard of care (SOC) vs. SOC alone was evaluated in moderate to severe UC patients using a Markov model over a 10-year treatment time horizon**
- **Base case results showed that adding adalimumab to SOC gave an ICER vs. SOC alone of £34,417/QALY (in 2013 GBP pounds)**
- **The ICER for adalimumab +SOC versus SOC alone remained robust in the majority of deterministic sensitivity analyses undertaken**

In the base case, the model evaluates the cost effectiveness of adalimumab plus standard of care (SOC) vs. SOC alone in patients with moderately to severely active UC (subacute).

The analysis was based on two trial datasets; an induction and maintenance RCT Phase III study M06-827 (ULTRA 2) which studied adalimumab+SOC versus SOC alone in moderately to severely active UC patients (sub-acute) who had failed conventional therapies and, an open-label extension study M10-223 (ULTRA 3). In the RCT M06-827, patients were randomised to either adalimumab 160/80mg at week 0 and 2 followed by 40mg every other week (n=258) or placebo (n=260) for 52 weeks double-blind treatment. Remission by Mayo Score was assessed at weeks 8 and 52. Forty percent of patients in the study M06-827 had prior experience with infliximab. In the open-label extension study M10-223, patients were included from M06-827 and followed for up to 4 years. Only interim results were available from M06-827 at the time of this analysis.

A Markov model was developed using Microsoft Excel to simulate the treatment path of hypothetical cohorts of moderately to severely active UC patients receiving two different treatments (adalimumab with SOC or SOC alone) and to estimate the associated costs and quality-adjusted life years (QALYs). The model consists of a series of health states, which can be divided into pre-surgery, surgery, and post-surgery health states (Figure 17). The three pre-surgery health states were defined using the Mayo Scoring system, or partial Mayo Scores if full Mayo Scores are not available and included; remission, mild, and moderate-to-severe disease states. Only patients in the moderate-to-severe health state, from either arm, were allowed to transition to surgery using published rates of colectomy. Following surgery, four additional health states were defined; post-surgery remission, short-term transient complications, long-term chronic complications or death related to surgery. Patients in the adalimumab +SOC arm, and SOC alone arm enter the model in the pre-surgery moderate-to-severe state consistent with the inclusion criteria for disease severity from M06-827.

A Markov cycle was defined as a 2-week cycle, during which a stable disease state was assumed. At the end of each cycle, patients in each of the disease states would either remain in the same health state or transit to a different health state in the next cycle based on the transitional probabilities calculated from M06-827 and M10-223 trial data. A half cycle correction was applied to costs and QALYs so that the transitions between health states can occur continuously through each Markov cycle, instead of at the beginning or end of a cycle.

The model consists of two components. The first 8 weeks, or induction period, assessed the impact of therapy on the Mayo Score from the M06-827 RCT. However, because UC is a lifelong condition, it is important to assess the impact of therapy beyond the duration of the RCT period (up to 10 years) which required the extrapolation of long-term disease prognosis beyond the time of switch to open label therapy. Thus, response is assessed at week 8 in line with recommendations made within the SmPC. Patients who were in remission or mild disease state at this time point would continue on adalimumab combined with SOC and patients in the moderate-to-severe disease state were assumed to be non-responders to adalimumab and would discontinue adalimumab and remain on

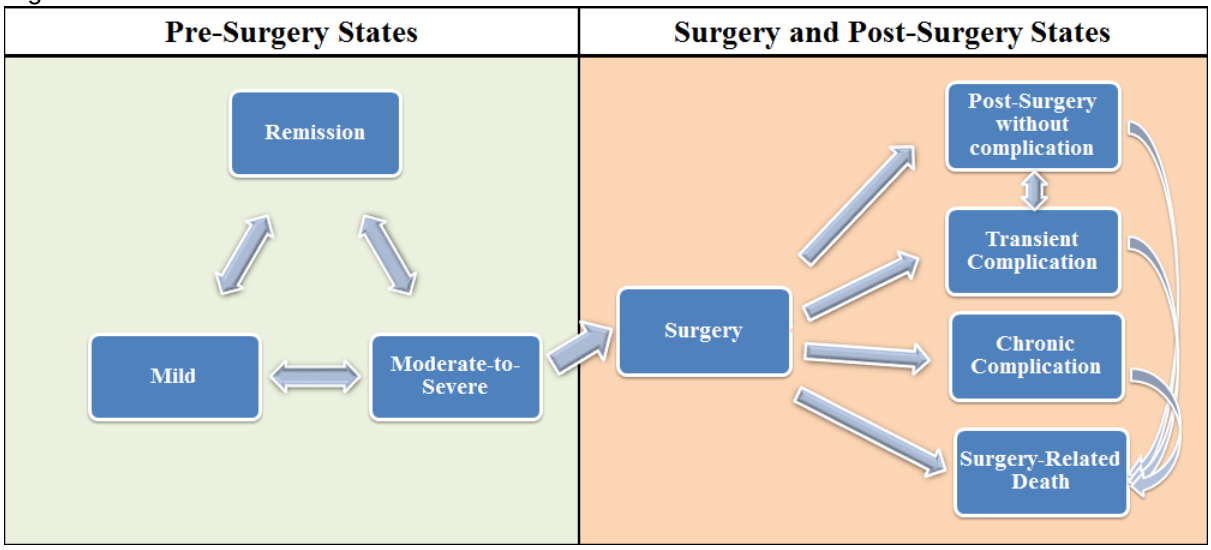
SOC alone. Thereafter, transition probabilities between pre-surgery health states were calculated using trial data from M06-827 for weeks 8-104 and then M10-223 for weeks 104 to 520 (10 years). Discontinuations due to adverse events (AEs) or reasons other than therapeutic failures were also considered based on trial data.

The model was developed from the perspective of the UK National Health Service. Only direct health care costs were considered. Drug costs and medical costs, including costs related to disease states, hospitalisation, surgery, surgery-related complications, and terminal care cost before death, were included based on published data which was inflated to 2013 Pounds Sterling. Utilities were assigned to Markov health states using directly collected EQ-5D data from a UK population. Discounting was applied at 3.5% for both costs and outcomes in the base case. Parameter uncertainty was addressed using a series of deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA).

In the base-case analysis (10 year time horizon), a patient treated with adalimumab and SOC was estimated to gain 0.74 additional quality-adjusted life years (QALYs), at an additional cost of £25,446 relative to SOC alone. The base case incremental cost-effectiveness ratio (ICER) of adalimumab+SOC vs. SOC alone in moderate to severe UC patients was £34,417 per QALY (in 2013 GBP pounds). Deterministic Sensitivity Analyses (DSA) varying key model inputs produced incremental costs per QALY gained in the range of £29,437 to £38,073.

There is currently a high unmet need for patients in England and Wales with moderately to severely active UC (subacute) who have failed on standard of care, with no NICE recommended biologic options in this patient population. This economic evaluation demonstrated that when compared to SOC alone, the addition of ADA to SOC therapy has a reasonable cost-effectiveness ratio.

Figure 17: Overview of model structure



Section 4: Implications for the NHS

4.1 Budget impact model

- AbbVie estimate there are 16,088 adult patients who would experience 2 or more exacerbations per year and would require maintenance treatment with oral azathioprine or oral mercaptopurine for UC in England and Wales with 662 new adult patients of a similar severity presenting per year.
- There are limited data to suggest how many of these patients may be eligible and treated with adalimumab
- Based on weight distribution data for UC patients in England, adalimumab treatment is likely to be associated with a significantly lower budget impact than infliximab or golimumab treatment based on licensed dosing and current drug list prices
- Adalimumab dosing is independent of patient weight
- Adalimumab can be self-administered outside of a hospital setting thereby reducing the burden on outpatient and community nursing services when compared to drugs which are administered intravenously in specialist settings
- Adalimumab is delivered to a patient's home by a homecare delivery provider at no extra cost to the NHS

No formal budget impact has been calculated for the use of adalimumab in moderate to severe subacute UC patients in England and Wales as AbbVie believe there is considerable uncertainty in the likely number of UC patients who may be eligible and receive adalimumab for their condition in clinical practice.

Epidemiology estimates suggest that there are 240 per 100,000 people with UC in England and Wales with around 10 per 100,000 people developing UC per year.[70] Of these patients, it is estimated 36 per 100,000 people would experience 2 or more exacerbations per year and would require maintenance treatment with oral azathioprine (5%) or oral mercaptopurine (95%).[71] Of these, 79% are assumed to be adults. Assuming a population of 56,567,800 people in England and Wales[72], AbbVie consider there would be 107,253 adult patients with UC, of which 16,088 would experience 2 or more exacerbations per year and would require maintenance treatment with oral azathioprine or oral mercaptopurine in England and Wales with 662 new adult patients of a similar severity presenting per year. There are limited data to inform how many of these UC patients would be eligible and treated with adalimumab and therefore any estimates would be subject to a high degree of uncertainty.

AbbVie consider the weight distribution of UC patients in England and Wales to be an important consideration in the likely budget impact which results from using, either; adalimumab, golimumab or infliximab in eligible patients. Table 35 and Table 36 shows the weight-distribution of UC patients based on data extracted from the General Practice Research Database (GPRD)[73] and the estimated mean annual drug acquisition cost per patient based on 1st year and maintenance dosing regimens listed in the respective SmPCs and current drug list prices (MIMS January 2014[29]). Costs are based on no vial sharing. Please note drug acquisition costs presented below exclude VAT and an administration cost has been applied in the calculation of infliximab costs. AbbVie consider infliximab treatment costs would be subject to VAT as it is likely to be given in a hospital setting and therefore the results presented below for infliximab may underrepresent the actual costs incurred in clinical practice.

Table 35: Weight distribution results for UC patients (n=15,345) from the General Practice Research Database (GPRD) and 1st year drug acquisition costs

Patient weight	% distribution	Adalimumab 1st year dosing schedule		Golimumab 1st year dosing schedule		Infliximab 1st year dosing schedule	
		mg per dose	No. of doses per year	mg per dose	No. of doses per year	mg per dose	No. of doses per year
<=40kg	0.00%	40mg	30	50mg	18	200mg	8
41-60kg	18.85%	40mg	30	50mg	18	300mg	8
61-80kg	47.52%	40mg	30	50mg	18	400mg	8
81-100kg	26.53%	40mg	30	100mg	15	500mg	8
101-120kg	6.22%	40mg	30	100mg	15	600mg	8
>120kg	0.87%	40mg	30	100mg	15	700mg	8
Estimated mean annual drug acquisition cost per patient based on 1st year dose		£10,564		£16,813**		£17,126*	

*Infliximab cost excludes VAT; Administration cost of £367 for each infusion obtained from Payment by Results (PbR) mandatory tariff 2013/14. Healthcare Resource Groups (HRG) code FZ37F; **Golimumab cost for 100mg dose is based on the current list price cost of 2x50mg pre-filled syringe[29]

Table 36: Weight distribution results for UC patients (n= 15,345) from the General Practice Research Database (GPRD)[73] and subsequent years drug acquisition costs

Patient weight	% distribution	Adalimumab maintenance dosing schedule		Golimumab maintenance dosing schedule		Infliximab maintenance dosing schedule	
		mg per dose	No. of doses per year	mg per dose	No. of doses per year	mg per dose	No. of doses per year
<=40kg	0.00%	40mg	26	50mg	13	200mg	6.5
41-60kg	18.85%	40mg	26	50mg	13	300mg	6.5
61-80kg	47.52%	40mg	26	50mg	13	400mg	6.5
81-100kg	26.53%	40mg	26	100mg	13	500mg	6.5
101-120kg	6.22%	40mg	26	100mg	13	600mg	6.5
>120kg	0.87%	40mg	26	100mg	13	700mg	6.5
Estimated mean annual drug acquisition cost per patient based on maintenance dose		£9,156		£13,254**		£13,915*	

*Infliximab cost excludes VAT; Administration cost of £367 for each infusion obtained from Payment by Results (PbR) mandatory tariff 2013/14. Healthcare Resource Groups (HRG) code FZ37F; **Golimumab cost for 100mg dose is based on the current list price cost of 2x50mg pre-filled syringe[29]

Adalimumab is supplied in a pre-filled, pen or syringe, which can be self-administered at home, as a subcutaneous injection; which is associated with lower NHS services when compared to drugs which are administered intravenously in specialist settings. Adalimumab is delivered to the patient's home using a homecare delivery service provided by the manufacturer at no additional cost to the NHS. In addition to this direct medical cost saving to the NHS; AbbVie consider that existing infusion clinics may struggle to meet the capacity demands of an incremental patient load resulting from more widespread management of UC with anti-TNF therapy. While this opportunity cost is difficult to formally quantify, AbbVie consider the extra resource may benefit patients with other conditions receiving appropriate and timely care in IV clinics.

The dosing for adalimumab in ulcerative colitis is independent of patient weight as detailed in the posology section of its SmPC. This allows for greater certainty in the budget impact calculation for a local health economy irrespective of geographical weight-distribution differences which may exist throughout England and Wales.

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