

**NIHR Innovation Observatory
Evidence Briefing: July 2018****Ustekinumab for moderately to severely active
ulcerative colitis**

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LAY SUMMARY

Ulcerative colitis (UC) a type of inflammatory bowel disease (IBD) which is a long term condition that causes inflammation and ulcers in the bowel and rectum which can bleed and produce pus. UC is thought to be caused when the immune system mistakes harmless bacteria inside the bowel as a threat and attacks the tissues of the colon, causing inflammation. The main symptoms of UC include recurring diarrhoea (which may contain blood, mucus or pus), abdominal pain and feeling the need to empty your bowels more frequently. The symptoms of UC often follow a pattern of periods of very mild or no symptoms (remission) followed by periods of increased symptoms (relapse or active disease).

Ustekinumab is a drug which is given as an injection and works by blocking the molecules that are involved in the inflammation which occurs in UC. Ustekinumab is already licenced for use in people with Crohn's disease, which is another type of IBD. If ustekinumab is licenced this would provide another treatment option for people with moderate to severe active UC.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Ulcerative colitis (moderately to severely active) – substitute therapy

TECHNOLOGY

DESCRIPTION

Ustekinumab (Stelara; CNTO-1275) is a fully human IgG1 κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12R β 1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12R β 1 cell surface receptors, therefore ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway.

However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis and Crohn's disease. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis and Crohn's disease through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases. In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase.¹

In the phase III study of moderately to severely active ulcerative colitis (UNIFI; NCT02407236), participants received a single dose of ustekinumab 130 mg as IV infusion or weight-range-based ustekinumab doses approximating 6mg/kg IV at week 0. Participants with clinical response at week 8 received subcutaneous maintenance injections of 90 mg of ustekinumab (either every 8 weeks or every 12 weeks) or placebo, for 44 weeks.²

Ustekinumab is currently licenced in the EU for the treatment of:¹

- Moderate to severe plaque psoriasis that has not responded to other systemic treatments or photochemotherapy, or when these treatments cannot be used because of intolerance or contra-indications (specialist use only) – 12 years and older
- Active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (specialist use only)
- Moderate to severe active Crohn's disease in patients who have had an inadequate response with, lost response to, are intolerant to, or have contra-indications to either conventional therapy or a tumour necrosis factor alpha inhibitor (specialist use only)

The most common side effects of ustekinumab (affecting between than one in ten people and one and one hundred people) include upper respiratory tract infection, nasopharyngitis, dizziness,

headache, oropharyngeal pain, diarrhoea, nausea, vomiting, pruritus, back pain, myalgia, arthralgia, fatigue, injection site erythema and injection site pain.¹

INNOVATION and/or ADVANTAGES

Novel approaches for the treatment of inflammatory bowel disease (IBD) including Crohn's Disease and ulcerative colitis (UC), include the development of drugs that inhibit downstream signalling in the inflammatory pathways which are involved in the pathogenesis of IBD. Ustekinumab targets IL-12 and IL23, which are pro-inflammatory cytokines thought to be involved in the pathogenesis of IBD.³

Ustekinumab has been licenced for the treatment of adults with moderate to severe Crohn's disease who have had inadequate response to, lost response to or are intolerant to conventional therapies or a TNF α inhibitor. Ustekinumab is not currently licenced for use in UC.¹

If ustekinumab is licenced for use in moderate to severely active UC, this could provide an additional or alternative treatment option for patients.

DEVELOPER

Janssen-Cilag Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Ustekinumab was designated a US orphan drug status for the treatment of paediatric ulcerative colitis in February 2017.⁴

PATIENT GROUP

BACKGROUND

Ulcerative Colitis (UC) is one of the two main forms of inflammatory bowel disease (IBD), the other being Crohn's disease. UC causes inflammation and ulceration of the inner lining of the rectum and colon.⁵ The ulcers which develop in UC can bleed and produce pus.⁶ UC can be divided into the following four subtypes according to the exact location affected: proctitis (affecting only the rectum), proctosigmoiditis (affecting the rectum and sigmoid colon), left-sided colitis (starting in the rectum and continuing into the left side of the large bowel) and extensive colitis (affecting most or all of the large bowel).⁷ UC is a chronic condition which follows a relapsing – remitting disease pattern. Most people develop UC between 15 to 25 years old or between 55 and 65 years old, although it can occur at any age.⁷

It is believed that UC is caused by a combination of many different factors including genetic susceptibility and an abnormal reaction of the digestive system to bacteria in the intestine, along with an unknown 'trigger' which can include viruses, bacteria, diet, stress or other environmental factors (e.g. oral contraceptive use and not smoking).^{5, 11}

During a relapse (or active disease), the main symptom of UC is diarrhoea (which may have blood or mucus in it). Other symptoms include lower abdominal pain/cramps, extreme fatigue, need to go to the toilet but not passing anything, weight loss, feeling unwell, loss of appetite and high temperature.^{5,}

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There are a variety of complications associated with UC which can be both intestinal and extra intestinal. Intestinal complications can include strictures (narrowing of the bowel), perforations (holes in the bowel), fistulas (abnormal channels/passageways connecting internal organs or to the outside of the body), toxic megacolon (most severe form of colitis) and colorectal cancer (risk of developing colorectal cancer in people with UC is 2%, 8% and 18% after 10, 20 and 30 years of having the disease, respectively). Extra intestinal complications can include anaemia, pauci-articular arthritis, erythema nodosum, aphthous ulcers, episcleritis, metabolic bone disease, axial arthritis, polyarticular arthritis, pyoderma gangrenosum, uveitis, hepatobiliary conditions and venous thromboembolism.¹¹

Living with UC can have emotional and practical impacts including: the need to see the GP or IBD hospital team regularly, impact on work and relationships due to ill health (especially during periods of active illness), need to maintain a healthy diet as certain foods may make symptoms worse (e.g. raw vegetables and spicy/high fibre food) and issues during pregnancy (as pregnancy during active disease may increase the risk of premature birth or low birth weight).⁵

CLINICAL NEED and BURDEN OF DISEASE

UC is the most common form of IBD with an incidence rate of 10 per 100,000 people in the UK and a prevalence rate of 240 per 100,000 people (the equivalent to approximately 146,000 people in the UK with UC).¹¹

An estimated 50% of people with UC will have at least one relapse per year, with 80% of these classed as mild to moderate and 20% classed as severe. Approximately 25% of people with UC will have one or more episodes of acute severe colitis in their lifetime, with 29% requiring a colectomy (operation to remove all or part of the colon).⁸

The mortality rate in those with UC is slightly higher than in the general population in the first 2 years of diagnosis.¹¹ Mortality rate in those with acute severe colitis is up to 2%.⁸

Prognosis of UC depends on many factors including initial response to treatment, with people who respond completely having a more favourable disease course than non-responders. A Norwegian cohort study of 519 people with ulcerative colitis showed that:¹¹

- After 10 years, the cumulative colectomy rate was 9.8%, predominantly as a result of uncontrolled disease.
- Initially, 83% of people had relapsing disease, but after 5 years half were relapse-free.
- Of people with proctitis or left-sided colitis, around 20% progressed to extensive colitis over 10 years.

According to the Hospital Episode Statistics for 2016-17, there were 69,753 admissions, 79,869 finished consultant episodes and 76,274 bed days due to UC (ICD 10: K51).⁹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Tofacitinib for moderately to severely active ulcerative colitis (ID1218). Expected publication date to be confirmed.

- NICE technology appraisal guidance. Vedolizumab for treating moderately to severely active ulcerative colitis (TA342). June 2015.
- NICE technology appraisal guidance. Infliximab, adalimumab and golimumab for treating moderately and severely active ulcerative colitis after the failure of conventional therapy (TA329). February 2015.
- NICE technology appraisal guidance. Infliximab for acute exacerbations of ulcerative colitis (TA163). December 2008.
- NICE guideline in development. Ulcerative colitis (update) (CG166). Expected publication date 18 April 2019.
- NICE clinical guideline. Ulcerative colitis: management (CG166). June 2013.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult). A08/S/c.

OTHER GUIDANCE

- European Crohn's and Colitis Organisation. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. 2017.¹⁰
- NICE Clinical Knowledge Summary. Ulcerative Colitis. 2015.¹¹
- European Crohn's and Colitis Organisation. European evidence based consensus on surgery for ulcerative colitis. 2015.¹²

CURRENT TREATMENT OPTIONS

Treatment of UC, in relation to severity of the condition and response to treatment, are as follows:

Initial treatment of acute mild to moderate UC

Acute treatment of UC, with the aim of inducing remission, generally consists of aminosalicylate with or without a corticosteroid. According to guidance outlined by NICE, treatment of acute mild-to-moderate UC should be as follows:¹³

- First line:
 - Oral aminosalicylate (balsalazide sodium, mesalazine, olsalazine sodium, sulfasalazine) alone or in combination with:
 - rectal aminosalicylate (mesalazine and sulfasalazine)
 - oral beclomethasone dispropionate
- Second line (for those who cannot tolerate, have a contraindication to or refuse aminosalicylate):
 - Oral prednisolone
 - Rectal corticosteroid (budesonide, hydrocortisone or prednisolone) monotherapy

Treatment of mild to moderate UC following initial treatment failure

NICE recommend for patients who do not respond within 4 weeks to initial treatment with an aminosalicylate, additional oral prednisolone should be given. If there is no response to this after 2-4 weeks of treatment, oral tacrolimus (unlicensed for this indication) can be added to induce remission. Budesonide multimatrix (a corticosteroid that is taken orally but exerts its action topically in the colon) is licensed for inducing remission in mild-to-moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient and can be considered as an additional therapeutic option.¹³

Moderate to severe disease may require treatment with a monoclonal antibody (due to inadequate response to conventional treatment or if conventional treatment is not tolerated or contra-indicated). Adalimumab, golimumab, infliximab and vedolizumab can be used to treat moderate-to-severe active ulcerative colitis following an inadequate response to conventional treatment options, or if conventional treatment options are not tolerated or contra-indicated. Infliximab can be used to treat acute exacerbations of severely active ulcerative colitis if ciclosporin is contra-indicated or clinically inappropriate.¹³

Treatment of acute severe UC

First line treatment for acute severe UC is regarded as a medical emergency. Intravenous corticosteroids (e.g. hydrocortisone or methylprednisolone) should be given at first presentation or exacerbation of active, severe UC to induce remission while the need for surgery is assessed. If the use of intravenous corticosteroids are contra-indicated, declined or cannot be tolerated, intravenous ciclosporin (unlicensed for this indication) or surgery should be considered.¹³

Second line treatment for acute severe UC is a combination of intravenous ciclosporin in combination with intravenous corticosteroids or surgery for patients who have little or no improvement within 72 hours of treatment with intravenous corticosteroids or for those whose symptoms worsen despite treatment. Infliximab is commonly used in practice in place of ciclosporin.¹³

Surgical options for severe UC which does not respond to medication include colectomy (permanent removal of the colon). During this surgery, an ileostomy (where the small intestine is diverted out of a whole made in abdomen where a bag is placed to collect waste material) or an ileo-anal pouch (where part of the small intestine is used to create an internal pouch connected to the anus so stools can be passed normally) is also created.¹⁴

EFFICACY and SAFETY	
Trial	NCT02407236 , EudraCT-2014-005606-38, IRAS-163080; ustekinumab vs placebo; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ²
Location	15 EU countries (including UK), USA, Canada, Australia, Israel, Japan, Korea, New Zealand, Russian Federation
Design	Randomised, double blind, placebo-controlled
Participants	n=972; aged 18 years or older; clinical diagnosis of ulcerative colitis; moderate to severely active; failed or failure to respond to/tolerate biological therapy

	(e.g. one or more TNF antagonists or vedolizumab) or naive to biological therapy or inadequate response/failure on oral corticosteroids or immunomodulators
Schedule	<p>This clinical trial consists of 2 studies: the induction study and the maintenance study:</p> <p><u>Induction study</u> Participants are originally randomised to the following treatment arms:</p> <ul style="list-style-type: none"> - <u>Placebo</u>: participants receive single dose of placebo as intravenous (IV) infusion at week 0. Participants with clinical response at week 8 will be eligible to enter the maintenance study, but are not randomized - Participants without clinical response to placebo at week 8 will receive a single IV infusion of ustekinumab approximating 6mg/kg along with matching subcutaneous (SC) placebo (to maintain the blind). Participants in clinical response at week 16 will be eligible to enter maintenance study and will be randomized - <u>Ustekinumab 130mg</u>: participants receive single dose of ustekinumab 130 mg as IV infusion at week 0. Participants with clinical response at week 8 will be eligible to enter the Maintenance study and are randomized - <u>Ustekinumab 6mg/kg</u>: participants receive ustekinumab approximating 6 mg/kg of body weight, as IV infusion at Week 0. Participants with clinical response at week 8 will be eligible to enter the maintenance study and will be randomized <p><u>Maintenance Study:</u> Participants are originally randomised to the following treatment arms:</p> <ul style="list-style-type: none"> - <u>Placebo comparator</u>: Participants in clinical response (at week 8 or Week 16) to induction treatment with single IV infusion of ustekinumab will be randomized to receive placebo subcutaneously, beginning week 0 of maintenance study through week 44 - <u>Ustekinumab 90mg every 12 weeks</u>: Participants in clinical response (at week 8 or week 16) to Induction treatment with single IV infusion of ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 12 weeks, beginning week 0 of maintenance study through week 44 - <u>Ustekinumab 90mg SC every 8 weeks</u>: Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning week 0 of maintenance study through Week 44 - <u>Placebo responder</u>: Participants in clinical response to Induction treatment with IV Placebo will receive placebo subcutaneously, beginning week 0 of maintenance study through week 44. Participants are not randomized - <u>Delayed Responder-Ustekinumab 90mg every 8 weeks</u>: Participants without clinical response to induction treatment ustekinumab (130 mg or 6 mg/kg [IV]) at week 8 but in clinical response at Week 16 after receiving Induction ustekinumab at week 8 (delayed responders) will receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning

	week 0 of maintenance study through week 44. Participants are not randomized
Follow-up	Induction study – 8 weeks active treatment Maintenance study – 44 weeks active treatment (with a long term extension for eligible participants for an additional 3 years)
Primary Outcomes	<p>1. Induction Study - number of participants with clinical remission [time frame: week 8] Clinical remission is defined as Mayo score (tool designed to measure disease activity in ulcerative colitis consisting of a score ranging from 0-12 with 4 subscores graded 0-3 with higher scores indicating more severe disease activity) less than or equal to (\leq) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States</p> <p>2. Maintenance Study - number of Participants with Clinical Remission Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44]</p>
Secondary Outcomes	<p>1. Induction Study - number of Participants with Clinical Response [Time Frame: Week 8] Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to (\geq) 30 percent (%) and \geq3 points, with either a decrease from induction baseline in the rectal bleeding subscore \geq1 or rectal bleeding subscore = 0 or 1</p> <p>2. Induction Study - number of Participants With Endoscopic Healing [Time Frame: Week 8] Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1</p> <p>3. Induction Study - mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score [Time Frame: Week 8] The IBDQ is a 32-item questionnaire for participants with Inflammatory Bowel Disease (IBD) that will be used to evaluate the disease-specific health-related quality of life across 4 dimensional scores: bowel, systemic, social, and emotional. The total score ranges from 32 to 224 with higher scores indicating better quality of life</p> <p>4. Maintenance Study - number of Participants with Clinical Response Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Through Week 44] Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to (\geq) 30 percent (%) and \geq3 points, with either a decrease from Induction baseline in the rectal bleeding subscore \geq1 or rectal bleeding subscore = 0 or 1</p> <p>5. Maintenance Study - number of Participants with Endoscopic Healing Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44] Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1</p>

	<p>6. Maintenance Study - number of Participants with Clinical Remission Among those who Achieved Clinical Remission at Maintenance Study Baseline [Time Frame: Through Week 44]</p> <p>The global definition of Clinical remission is defined as Mayo score less than or equal to (\leq) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States (US). For the US Clinical remission is defined as absolute stool number \leq3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis</p> <p>7. Maintenance Study - number of Participants with Clinical Remission and not Receiving Concomitant Corticosteroids Among those Receiving Concomitant Corticosteroids at Maintenance Baseline [Time Frame: Week 44]</p> <p>The global definition of Clinical remission is defined as Mayo score less than or equal to (\leq) 2 points, with no individual subscore greater than ($>$) 1, for countries outside the United States (US). For the US Clinical remission is defined as absolute stool number \leq3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis</p>
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as November 2021

ESTIMATED COST and IMPACT

COST

Ustekinumab is already marketed in the UK in the following formulations; 45mg solution for injection in pre-filled syringe, 90mg solution for injection in pre-filled syringe, 45mg solution for injection (vial) and 130mg/26ml (5mg/1ml) concentrate for solution for infusion (vial) each cost £2,147.¹⁵ A confidential pricing arrangement has been agreed with the Commercial Medicines Unit.^a

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
 Reduced symptoms or disability
- Other
 No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

^a Company confidential information

- Increased use of existing services Decreased use of existing services
- Re-organisation of existing services Need for new services
- Other None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs Reduced drug treatment costs
- Other increase in costs Other reduction in costs
- Other None identified

OTHER ISSUES

- Clinical uncertainty or other research question identified None identified

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