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Newcastle University

Health Technology Briefing
October 2024

Ustekinumab for treating moderately to severely active ulcerative colitis in children aged 2 to 17 years

Company/Developer	Janssen-Cilag Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30813	NICE ID: Not Available	UKPS ID: 666883

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Ustekinumab is currently in clinical development for the treatment of moderately to severely active ulcerative colitis (UC) in paediatric patients. UC, a type of inflammatory bowel disease, is a long-term condition where the colon and rectum become inflamed and small ulcers can develop on the colon's lining, which may bleed and produce pus. Symptoms of UC include recurring diarrhoea, which may contain blood, mucus or pus, stomach pain, a frequent need to empty the bowels, fatigue, loss of appetite and weight loss. The exact cause of UC is unknown, although it is thought to be the result of a problem with the immune system. There is a high unmet need for new safe and effective treatment options in UC in paediatric populations, especially new therapies that can provide improved long-term efficacy.

Ustekinumab is a biologic, a human-made protein designed to recognise and attach to a specific target in the body. It attaches to two messenger molecules in the immune system, both of which are involved in inflammation processes that are important in UC. By blocking their activity, ustekinumab reduces the activity of the immune system and the symptoms of the disease. Ustekinumab is given intravenously (into the vein) and subcutaneously (under the skin). If licensed, ustekinumab will offer an additional treatment option for moderately to severely active UC among paediatric patients.

Proposed Indication

Treatment of moderately to severely active ulcerative colitis (UC) in paediatric patients.[1]

Technology

Description

Ustekinumab (Stelara) is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. This prevents p40 from binding to receptors on the surface of immune cells, inhibiting the bioactivity of IL-22 and IL-23. IL-12 and IL-23 are heterodimeric cytokines and both cytokines participate in immune functions; IL-12 stimulates natural killer cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype and 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 UC. By binding to the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in UC through interruption of the Th1 and Th17 cytokine pathways.[2]

Ustekinumab is currently in clinical development for the treatment of moderately to severely active UC in paediatric patients.[1] In the phase III clinical trial (UNIFI Jr, NCT04630028), all participants receive a single intravenous (IV) administration of ustekinumab at induction week 0 based on body surface area (BSA) or weight-tiered induction dose. During the maintenance period, participants receive subcutaneous (SC) administration of ustekinumab every 8 or 12 weeks based on BSA or weight-tiered induction dose.[1]

Key Innovation

There is an unmet need for new safe and effective treatment options in UC in paediatric populations, especially new therapies that can provide improved long-term efficacy (i.e. sustained remission).[3] There remains problems with immunomodulatory therapies – remission rates are as low as 20–30%, a considerable proportion of patients develop secondary loss of response and some patients still require corticosteroids.[4] The rate of steroid dependency is reported to be much higher in children than in adults (45% vs 8%, respectively).[5] Novel approaches for the treatment of IBD 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.[6] A systematic review evaluating the efficacy and safety of ustekinumab for paediatric IBD found that for UC/IBD unspecified, the pooled corticosteroid-free clinical remission rates were 24% at 26 weeks and 46% at 1 year, and endoscopic remission was found in 63.6% of UC.[7]

If licensed, ustekinumab will offer an additional treatment option for moderately to severely active ulcerative colitis among paediatric patients.

Regulatory & Development Status

Ustekinumab currently has Marketing Authorisation in the EU/UK for the following indications:[2]

- the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies
- the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies

- the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or psoralen and ultraviolet A
- the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies
- alone or in combination with MTX for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug therapy has been inadequate

Ustekinumab is also in phase III clinical development for juvenile psoriatic arthritis and Crohn's disease in paediatric patients.[8]

Patient Group

Disease Area and Clinical Need

UC is the most common type of IBD.[9] It is a long-term condition where the colon and rectum become inflamed and small ulcers can develop on the colon's lining, which can bleed and produce pus. Some people may go for weeks or months with very mild symptoms, or none, known as remission, followed by periods where the symptoms are particularly troublesome, known as flare-ups or relapses. Symptoms of UC include recurring diarrhoea, which may contain blood, mucus or pus, stomach pain, needing to frequently empty bowels, fatigue, loss of appetite and weight loss.[9,10] The exact cause of UC is unknown, although it is thought to be the result of a problem with the immune system. Many experts believe UC is the result of an autoimmune condition whereby the immune system mistakes "helpful" bacteria in the colon, which aid digestion, for a harmful infection. This causes the immune system to attack healthy tissue and leads to the colon and rectum becoming inflamed.[11] It is also believed that genes are a factor in the development of UC, and certain environmental factors such as viral and bacterial infection, air pollution, medication and diet may be triggers.[11,12]

UC affects males and females at approximately equal rates. The incidence of paediatric-onset UC, which represents about 15–20% of all UC cases, ranges from 1–4 per 100,000 per year in most North American and European regions.[13] In England, 2022-23, when considering all patients and not specifically paediatrics, there were 139,419 finished consultant episodes (FCEs) and 127,198 admissions for UC (ICD-10 code K51) which resulted in 83,684 FCE bed days and 115,015 day cases.[14] When adjusted to represent the incidence of paediatric-onset UC (approximately 15-20% of all UC cases), these figures become 20,913-27,884 FCEs and 19,080-25,440 admissions for UC which resulted in 12,553-16,737 FCE bed days and 17,252-23,003 day cases.

Recommended Treatment Options

Treatment is focused on treating active disease to manage symptoms and to induce and maintain remission. The National Institute for Health and Care Excellence (NICE) recommends the following:[15]

- topical or oral aminosalicylates for acute mild-to-moderate UC
- topical or oral corticosteroid for children whom aminosalicylates are unsuitable in mild-to-moderate UC
- intravenous corticosteroids (e.g. hydrocortisone or methylprednisolone) in acute severe UC
- if intravenous corticosteroids show little or no improvement within 72 hours, children over 6 years can be provided with infliximab

If the disease does not adequately respond to oral corticosteroids (beclometasone, budesonide, hydrocortisone, or prednisolone) then an immunosuppressant (such as mercaptopurine or azathioprine) may be considered.[16]

Clinical Trial Information

Trial	**UNIFI Jr, NCT04630028, EudraCT 2019-004224-38;** A Phase 3 Study of the Efficacy, Safety and Pharmacokinetics of Ustekinumab as Open-label Intravenous Induction Treatment Followed by Randomized Double-blind Subcutaneous Ustekinumab Maintenance in Pediatric Participants With Moderately to Severely Active Ulcerative Colitis **Phase III** – Active, not recruiting **Locations:** Four EU countries, UK, USA, Israel, Japan and the Russian Federation **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, double masked
Population	Actual N=113; subjects with moderately to severely active UC; aged 2 to 17 years.
Intervention(s)	Ustekinumab dose based on BSA and body weight administered SC and IV
Comparator(s)	Matched placebo administered SC
Outcome(s)	Primary outcomes: • Global: number of participants with clinical remission at induction week 8 (I-8) visit • Number of participants with adverse events (AEs) as a measure of safety and tolerability • Number of participants with serious adverse events (SAEs) as a measure of safety and tolerability • Number of participants with AEs leading to discontinuation of study intervention • Number of participants with AEs of special interest (AESI) as a measure of safety and tolerability • Number of participants with laboratory abnormalities • Reactions temporally associated with an IV infusion and SC injection-site reactions • Serum concentration of ustekinumab • US specific: clinical remission at maintenance period 44 for participants who are in clinical response at induction period 8 See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ustekinumab is already marketed in the UK. The NHS indicative price is:[17]

- For 45mg/0.5ml solution for injection pre-filled pens £2,147.00
- For 45mg/0.5ml solution for injection pre-filled syringes £2,147.00
- For 45mg/0.5ml solution for injection vials £2,147.00
- For 90mg/1ml solution for injection pre-filled pens £2,147.00
- For 90mg/1ml solution for injection pre-filled syringes £2,147.00
- For 130mg/26ml concentrate for solution for infusion vials £2,147.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Etrasimod for treating moderately to severely active ulcerative colitis in people aged 16 and over (TA956). March 2024.
- NICE technology appraisal. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). February 2015.
- NICE guideline. Ulcerative colitis: management (NG130). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Gastroenterology, Hepatology and Nutrition. E03/S/c.
- NHS England 2013/14. Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult). A08/S/c.

Other Guidance

- NHS University Hospitals of Leicester. Management of acute severe ulcerative colitis in children. 2021.[18]
- European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline. 2018.[19]
- Tun GS, Harris A, Lobo AJ. Ulcerative colitis: management in adults, children and young people – concise guidance. 2017.[20]
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Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.