Health Technology Briefing
November 2023

Ustekinumab for the treatment of moderately to severely active Crohn's disease in children

Company/Developer	Janssen-Cilag Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30946	NICE ID: Not available	UKPS ID: 666881

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Ustekinumab is in clinical development for the treatment of moderately to severely active Crohn's disease in children. Crohn's disease is an autoimmune disease, where the immune system attacks the body, and in Crohn's disease this causes ulcers and inflammation in the gut wall. Symptoms include diarrhoea, stomach aches and cramps, blood in the faeces, fatigue and weight loss. The condition has periods of good health, known as remission, and times when it is active, known as flare-ups or relapses. Current treatment options can have considerable toxicity, low efficacy and poor remission rates.

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 Crohn's disease. 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 licenced, ustekinumab will provide an additional treatment option for children with moderately to severely active Crohn's disease.

Proposed Indication

Treatment of paediatric patients with moderately to severely active Crohn's disease.[1]

Technology

Description

Ustekinumab (Stelara)[2] 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. Abnormal regulation of IL-12 and IL-23 has been associated with immune mediated diseases, including Crohn's disease (CD).[3] Inhibiting IL-12 and IL-23 activation downregulates the immune system, which reduces inflammation and alters the body's immune response.[4]

Ustekinumab is currently in clinical development for the treatment of moderately to severely active CD in paediatrics. In the phase III clinical trial (UNITI Jr, NCT04673357), patients are given ustekinumab administered intravenously in the induction period based on body surface area (BSA) (milligram per meter square [mg/m^2]) or weight-tiered induction dose (milligram per kilogram [mg/kg]) and subcutaneously in the maintenance period every 8 weeks (q8w) or every 12 weeks (q12w) based on BSA (mg/m^2) or weight-tiered induction dose (mg/kg).[1] In the long term extension phase III trial (UNITED, NCT05092269), patients who enrol from blinded primary studies with both q8w and q12w dosing groups just prior to the end of the primary study will be assigned to the q8w dosing regimen. Participants enrolling in the long-term extension from an unblinded primary study will remain on the final dosing regimen that they were receiving in the primary study.[2]

Key Innovation

Conventional therapies for CD include corticosteroids, thiopurines and methotrexate, but these agents often have clinical remission rates of less than 50% and have considerable toxicity.[5,6] In addition, patients with refractory or more severe disease may not benefit sufficiently from conventional therapies and often need treatment with biologics. Currently, several biologics are available for the treatment of moderately to severely active CD.[7] Despite the increasing number of available biologics, their efficacy is limited because some patients may have an inadequate response or lose response over time. This results in discontinuation of therapy or suboptimal treatment, which is associated with higher rates of surgery, hospitalisation, and/or prolonged corticosteroid use as well as impaired quality of life.[8] Therefore, a need remains for novel biologic therapies that target new pathways, which could offer greater efficacy and durable long-term disease control for patients with CD.[5] Pivotal clinical trials have largely demonstrated the efficacy and safety of ustekinumab for CD patients who were refractory to other biologic treatments.[9-11]

If licenced, ustekinumab will provide an additional treatment option for children with moderately to severely active CD.

Regulatory & Development Status

Ustekinumab currently has Marketing Authorisation in the EU/UK for the following indications:[12]

- 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 ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.
- 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 PUVA (psoralen and ultraviolet A).
- The treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, 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 (DMARD) therapy has been inadequate.

Ustekinumab is also in phase II/III clinical development for several indications, some of which are:[13]

- Juvenile psoriatic arthritis
- Type 1 diabetes mellitus

Patient Group

Disease Area and Clinical Need

CD is a lifelong condition where parts of the digestive system becomes inflamed.[14,15] CD is an autoimmune disease, where the immune system attacks the gut wall, causing ulcers and inflammation.[15] Although the exact cause is unknown, several factors could play a role, including genes, immune system problems, smoking, a previous stomach illness or an abnormal balance of gut bacteria.[14] Without treatment, symptoms of CD can be constant or may come and go every few weeks or months. Presence of symptoms (active CD) is called a flare-up or relapse, and the periods between flare-ups are called remission. The main symptoms of Crohn's disease are diarrhoea, stomach aches and cramps, blood in the stool, fatigue and weight loss.[15,16]

At least 1 in 323 people in the UK live with CD[15]. The prevalence of CD has increased over the past 18 years at a rate of 3.5% per annum and is predicted to reach a prevalence of 487.2 per 100,000 by 2025. CD is also associated with an increased risk of all-cause mortality.[17] In England, in 2022-23, there were 158,613 finished consultant episodes (FCE) and 148,896 admissions for CD (ICD-10: K50) which resulted in 84,234 FCE bed days and 135,009 day cases.[18]

Recommended Treatment Options

NICE recommends the following pharmacological treatment options for moderate to severe active CD:

- Remsima (infliximab biosimilar) for managing Crohn's disease and ulcerative colitis.[19]

There are no treatment options recommended by NICE specifically for children with CD.

Other therapies include:[20]

- Aminosalicylates, such as sulfasalazine, mesalazine
- Steroids, such as prednisolone, methylprednisolone, intravenous hydrocortisone
- Add-on treatment, such as azathioprine, mercaptopurine and methotrexate

- Antibiotics, such as metronidazole and ciprofloxacin
- Loperamide hydrochloride and colestyramine.

Clinical Trial Information

Trial	**UNITI Jr,** NCT04673357, EudraCT 2019-004225-24; 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 Crohn's Disease **Phase III:** Recruiting **Location:** Four EU countries, UK, USA, Israel, Japan and Russia **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, double-blinded
Population	N = 102 (estimated); all sexes; children aged 2-17 years old; diagnosed with moderately to severely active Crohn's disease or fistulizing Crohn's disease with active colitis, ileitis, or ileocolitis.
Intervention(s)	Ustekinumab administered intravenously in the induction period and subcutaneously in the maintenance period.
Comparator(s)	Matched placebo administered subcutaneously in the maintenance period.
Outcome(s)	Primary outcome measures: • Number of participants with clinical remission at induction week 8 [time frame: week 8] • Number of participants with adverse events [time frame: up to week 74] • Number of participants with serious adverse events [time frame: up to week 74] • Number of participants with adverse events leading to discontinuation of study intervention [time frame: up to week 74] • Number of participants with adverse events of interest [time frame: up to week 74] • Number of participants with abnormalities in clinical laboratory parameters [time frame: up to week 52] • Number of participants with reactions temporally associated with intravenous infusion [time frame: up to week 8] • Number of participants with subcutaneous injection-site reactions [time frame: up to week 44] • Serum ustekinumab concentrations [time frame: up to week 52] • Number of participants with clinical remission at maintenance week 44 See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**UNITED**, NCT05092269, EudraCT-2016-001647-39; A Phase 3, Multicenter, Open-label, Basket, Long-term Extension Study of Ustekinumab in Pediatric Clinical Study Participants (2 to <18 Years of Age) **Phase III:** Recruiting **Location:** Five EU countries, USA, Japan and Argentina **Primary completion date:** September 2027
Trial Design	Single group assignment, open label
Population	N = 151 (estimated); all sexes; children aged 2-17 years old; completed the dosing planned in the primary paediatric ustekinumab study (including NCT04673357)
Intervention(s)	Ustekinumab administered subcutaneously
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Number of participants with adverse events [time frame: up to 6 years and 4 months] • Number of participants with serious adverse events [time frame: up to 6 years and 4 months] • Number of participants with adverse events leading to discontinuation of study intervention [time frame: up to 6 years and 4 months] • Number of participants with adverse events of interest [time frame: up to 6 years and 4 months] • Number of participants with abnormalities in clinical laboratory parameters [time frame: up to 6 years and 4 months] • Number of participants with injection site reactions [time frame: up to 6 years and 4 months] • Number of participants with adverse events of worsening of the disease [time frame: up to 6 years and 4 months] • Number of participants with concomitant therapy due to loss of response [time frame: up to 6 years and 4 months]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ustekinumab is already marketed in the UK. The NHS indicative price is:[21]

- 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 syringes £2,147.00
- For 130mg/26ml concentrate for solution for infusion vials £2,147.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Guselkumab for treating moderately to severely active Crohn's disease (GID-TA11245). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Mirikizumab for treating moderately to severely active Crohn's disease (GID-TA11267). Expected date of issue to be confirmed.
- NICE technology appraisal. Risankizumab for previously treated moderately to severely active Crohn's disease (TA888). Published: 17 May 2023.
- NICE clinical guideline. Crohn's disease: management (NG129). May 2019
- NICE interventional procedures guidance. Extracorporeal photopheresis for Crohn's disease (IPG288). February 2009.
- NICE diagnostic guidance. PredictSURE IBD and IBDX to guide treatment of Crohn's Disease (DG45). February 2022.
- NICE evidence summary. Remsima (infliximab biosimilar) for subcutaneous injection for managing Crohn's disease and ulcerative colitis (ES35). February 2021.

NHS England (Policy/Commissioning) Guidance

No relevant guidance found.

Other Guidance

- Macaluso FS, Papi C, Orlando A, Festa S, Pugliese D, Bonovas S, et al. Use of biologics for the management of Crohn's disease: IG-IBD clinical guidelines based on the GRADE methodology. 2023.[22]
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. June 2021.[23]
- ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. 2019.[24]

Additional Information

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