Ustekinumab (Stelara) for plaque psoriasis in adolescents

SUMMARY

Ustekinumab (Stelara) is a human monoclonal antibody that targets the p40 subunit of interleukin-23 (IL-23), preventing binding to receptors on T-cells and natural-killer cells. Ustekinumab is intended for use in the treatment of moderate to severe plaque psoriasis in adolescents aged 12 to 18 years. It is administered by subcutaneous (SC) injection at 22.5mg, 45mg or 90mg at weeks 0 and 4, followed by maintenance dosing every 12 weeks.

Psoriasis is a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. It is characterised by scaly skin lesions, which can be in the form of patches, papules, or plaques. Chronic plaque psoriasis is typified by itchy, well demarcated circular-to-oval bright red/pink elevated lesions (plaques) with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp. Plaque psoriasis may manifest differently in children—plaques may not be as thick, and lesions may be less scaly. Psoriasis may also often appear in the flexural areas in children and the disease more commonly affects the face in children compared with adults. The impact of psoriasis on quality of life may be particularly severe in adolescents who may be severely affected psychosocially, underlying the need for prompt, effective treatment, and long-term disease control. Plaque psoriasis is the most common type of psoriasis, representing 90% of cases.

The prevalence of psoriasis in those aged between 10 and 19 years is around 1.4% which suggests that around 40,000 children and adolescents in this age group are affected by psoriasis in the UK. The estimated prevalence of people with severe psoriasis currently eligible for biological therapy in England is 1.1% of those with psoriasis; equivalent to around 717 adolescents in England and Wales. In 2011-12, for all age groups there were 13,546 hospital admissions due to psoriasis in England, equating to 14,094 finished consultant episodes and 23,195 bed days. There were a total of 356 finished consultant episodes for patients aged up to 14 years in 2011-12.

Ustekinumab is currently in a phase III clinical trial evaluating its safety and efficacy compared with placebo.
TARGET GROUP

- Plaque psoriasis: moderate to severe; patients aged 12 to 18 years.

TECHNOLOGY

DESCRIPTION

Ustekinumab (Stelara, CNTO-1275) is a human monoclonal antibody that targets the p40 subunit of interleukin-23 (IL-23), preventing binding to receptors on T-cells and natural-killer cells. Ustekinumab is intended for use in the treatment of moderate to severe plaque psoriasis in adolescents aged 12 to 18 years. It is administered by subcutaneous (SC) injection at 22.5mg, 45mg or 90mg at weeks 0 and 4, followed by maintenance dosing every 12 weeks.

Ustekinumab is licensed in the EU for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond, have a contraindication, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen plus ultraviolet light treatment (PUVA). Recognised adverse effects include: upper respiratory tract infection, nasopharyngitis, cellulitis, hypersensitivity reactions, depression, pharyngolaryngeal pain, nasal congestion, diarrhoea, pruritus, back pain, myalgia, arthralgia, fatigue and injection site erythema.

Ustekinumab is currently also in phase III development for Crohn's disease and psoriatic arthritis. It is in phase II development for rheumatoid arthritis.

INNOVATION and/or ADVANTAGES

If licensed, ustekinumab will offer an additional treatment option for the treatment of plaque psoriasis in this age group.

DEVELOPER

Janssen.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Psoriasis is defined as a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. It is characterised by scaly skin lesions, which can be in the form of patches, papules, or plaques. The skin lesions of psoriasis are characterised by:

- Hyperproliferation of the epidermis.
- Dilation and proliferation of blood vessels in the dermis.
- Accumulation of inflammatory cells, particularly neutrophils and T-lymphocytes.
Chronic plaque psoriasis is typified by itchy, well demarcated circular-to-oval bright red/pink elevated lesions (plaques) with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp. Plaque psoriasis may manifest differently in children—plaques may not be as thick, and the lesions may be less scaly. Psoriasis may also often appear in the flexural areas in children and the disease more commonly affects the face in children compared with adults.

NHS or GOVERNMENT PRIORITY AREA

None identified.

CLINICAL NEED and BURDEN OF DISEASE

Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. The estimated UK prevalence of psoriasis is 1.63%; 1.1% of people with psoriasis have severe disease. It has a bimodal onset, with the first peak occurring in persons aged 16 to 22 years, and the second in persons aged 57 to 60 years. However, the prevalence of psoriasis in those aged between 10 and 19 years is around 1.4% which suggests that around 40,000 children and adolescents in this age group are affected by psoriasis in the UK. The estimated prevalence of people with severe psoriasis currently eligible for biological therapy in England is 1.1% of those with psoriasis; equivalent to around 717 adolescents in England and Wales. Females typically develop plaque psoriasis earlier than males, and patients with a positive family history for psoriasis also tend to have an earlier age of onset. Acute flares or relapses of plaque psoriasis may evolve into more severe disease, such as pustular or erythrodermic psoriasis. Up to 10-20% of patients with plaque psoriasis also experience psoriatic arthritis.

The significant reduction in quality of life and psychosocial disability suffered by people with psoriasis underlies the need for prompt, effective treatment, and long-term disease control. Psoriasis in children has a marked effect on quality of life. Children can suffer greatly from the psychosocial consequences of psoriasis and clinical experience shows that the impact of psoriasis on quality of life may be particularly severe in adolescents who may be severely affected psychosocially.

In 2011-12, for all age groups there were 13,546 hospital admissions due to psoriasis in England, equating to 14,094 finished consultant episodes and 23,195 bed days. There were a total of 356 finished consultant episodes for patients aged up to 14 years in 2011-12.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


**Other Guidance**


• SIGN. Diagnosis and management of psoriasis and psoriatic arthritis in adults. 2010.

• British Association of Dermatologists and Primary Care Dermatology Society. Clinical guideline: Recommendations for the initial management of psoriasis. 2009.


**EXISTING COMPARATORS and TREATMENTS**

First-line therapies:
• Emollients, salicyclic acid, topical steroids, vitamin D analogues (for children 6 years and above), coal tar and dithranol.

Phototherapy:
• UVB or a psoralen/UVA combination (PUVA)
  The use of phototherapy and photochemotherapy is limited in children by concerns over carcinogenicity and premature aging. PUVA is contraindicated in young children, but may be used in adolescents if absolutely necessary.

Systemic treatment (licensed for severe disease resistant to other therapies in patients aged 16 years and above):
• Acitretin, ciclosporin, methotrexate.

Biological therapies:
• Etanercept (licensed for use in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies).
• Adalimumab, infliximab and ustekinumab (not licensed in children and adolescents).
  There is currently very little data regarding the use of biological therapies in children and adolescents. Information currently available is mainly from anti-TNF therapies, predominantly etanercept. Anti-TNF therapies carry a black box warning in the USA due to an increased risk of malignancy in the paediatric population.

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* Expert clinical opinion.
EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>CADMUS, NCT01090427; ustekinumab vs placebo; phase III.</th>
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<tr>
<td>Sponsor</td>
<td>Centocor Inc.</td>
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<tr>
<td>Status</td>
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<tr>
<td>Source of information</td>
<td>Trial registry25, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (inc UK), Canada, Russia and Ukraine.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=110 (planned); aged 12 to 18 years; plaque psoriasis with or without psoriatic arthritis and without non-plaque forms of psoriasis ≥6 months; candidates for phototherapy or systemic treatment of psoriasis; no prior use of interleukin-12 or interleukin-23 reducing therapeutic agents; not received conventional systemic therapies or phototherapy ≥ 4 weeks or biologic therapies ≥3 months.</td>
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| Schedule | Randomised to 1 of 4 arms: 
Arm 1: ustekinumab (low dose) 0.375mg/kg for <60kg or a fixed dose of 22.5mg or 45mg based on weight, all given SC at weeks 0 and 4, with maintenance dosing every 12 weeks to week 40. Patients will receive a single dose of placebo SC at week 12. 
Arm 2: ustekinumab (high dose) 0.75mg/kg for <60kg or a fixed dose of 45mg or 90mg based on weight, all given SC at weeks 0 and 4, with maintenance dosing every 12 weeks to week 40. Patients will receive a single dose of placebo SC at week 12. 
Arm 3a: placebo SC at week 0 and 4 and then ustekinumab low dose (as for arm 1 above) at weeks 12, 16, with maintenance dosing every 12 weeks to week 40. 
Arm 3b: placebo SC at week 0 and 4 and then ustekinumab high dose (as for arm 2 above) at weeks 12, 16, with maintenance dosing every 12 weeks to week 40. |
| Follow-up | Active treatment to week 40. |
| Primary outcome/s | Physician’s Global Assessment (PGA)\(^b\) score of cleared or minimal disease at week 12. |
| Secondary outcome/s | Psoriasis Area Severity Index (PASI)\(^c\) 90 response at week 12; PASI 75 response at week 12; Children’s Dermatology Life Quality Index (CDLQI)\(^d\) at week 12. |
| Expected reporting date | Estimated study completion date December 2014. |

ESTIMATED COST and IMPACT

COST

Ustekinumab is already marketed in the UK for the treatment of moderate to severe plaque psoriasis in adults. A 45mg/0.5mL prefilled syringe costs £2,147.00 and treatment with 45mg at weeks 0 and 4, followed by maintenance dosing every 12 weeks to week 40 would cost...

\(^b\) PGA (Physicians Global Assessment) is a measure of patients' psoriasis overall relative to baseline. It considers involvement of body-surface area, induration, scaling and erythema. It is scored as 1 (clear), 2 (excellent), 3 (good), 4 (fair), 5 (poor), or 6 (worse).

\(^c\) PASI (Psoriasis area-and-severity index score) is a measure of overall psoriasis severity and coverage which combines assessments of the extent of body-surface involvement in four anatomical regions (head, trunk, arms, and legs), and the severity of desquamation, erythema, and plaque induration. It can be measured as a percentage improvement, where a PASI 75 is a 75% improvement in PASI score.

\(^d\) CDLQI (Children’s Dermatology Life Quality Index) is a 10-item questionnaire completed by the patient, and measures the effect of psoriasis on quality of life.
A patient access scheme is available where the manufacturer provides the 90mg dose (two 45mg prefilled syringes) for adults with plaque psoriasis who weigh more than 100kg at the same total cost as for a single 45mg prefilled syringe.

**IMPACT - SPECULATIVE**

### Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: *expert opinion suggests that treatment with ustekinumab may be particularly appealing to younger people due to decreased frequency of injection compared to current biological therapies. If effective and licensed, ustekinumab has the potential to become the first line biological therapy in this patient group.*
- No impact identified

### Impact on Services
- Increased use of existing services
- Decreased use of existing services: *expert opinion suggests that ustekinumab would require a decreased injection frequency compared to current biological therapies for this patient group.*
- Re-organisation of existing services
- Need for new services
- Other: None identified

### Impact on Costs
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: *more patients eligible for treatment with biological agents.*
- Other reduction in costs:
- None identified

### Other Issues
- Clinical uncertainty or other research question identified: *expert opinion suggests that the relationship between psoriasis and psoriatic arthritis in a younger population remains unclear. The potential for ustekinumab use in this clinical pathway is still unknown.*
- None identified

### REFERENCES


*Expert clinical opinion.*