NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Apremilast for treating moderate to severe plaque psoriasis in children and young people

Company/Developer	Amgen Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26977	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Apremilast is being investigated for the treatment of moderate to severe plaque psoriasis in children and adolescents (aged 6 to 17 years old). Psoriasis is a skin disease that causes a rash with itchy, scaly patches, most commonly on the knees, elbows, trunk, and scalp. Plaque psoriasis is the most common, and is characterised by epidermal thickening and scaling, usually affecting external surfaces and the scalp. The plaques can be itchy or sore, or both. In severe cases, the skin around your joints may crack and bleed. Common psoriasis triggers include injuries such as cuts, abrasions or sunburn, obesity, smoking and excessive alcohol. Psoriasis poses a significant economic burden because lifelong care is often required. In addition to physical pain, psoriasis causes social and psychological burden: social exclusion, discrimination, and stigma can be devastating for patients, who suffer from burdensome depression. Long-term use of currently available therapies is often compromised by side effects, loss of effectiveness over time, and administration by injection.

Apremilast is a small molecule medicinal product, orally administered, that inhibits the activity of an enzyme known as phosphodiesterase type-4 (PDE4). PDE4 controls the inflammation process in the skin for people with psoriasis, or the joints in people with psoriatic arthritis. Reducing or controlling the inflammation in the skin or joints can lead to improvement of symptoms in people with psoriasis and/or psoriatic arthritis. If licensed, apremilast will offer an effective and safe treatment option for young people with moderate to severe plaque psoriasis.

Proposed Indication

Treatment of paediatric subjects (aged 6 to 17 years old) with moderate to severe plaque psoriasis.[1,2]

Technology

Description

Apremilast (Otezla, CC-10004), an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17, and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.[3]

Apremilast is currently in a phase III long term extension study for treatment of paediatric subjects with moderate to severe plaque psoriasis. In the clinical trial (NCT04175613) subjects with a weight between 20 kg to < 50 kg will receive apremilast 20 mg twice daily (BID) and subjects with weight ≥ 50 kg at Visit 1 will receive apremilast 30 mg BID. Subjects that begin the study receiving apremilast 20 mg BID and later record a body weight ≥ 50 kg, will be switched to apremilast 30 mg BID.[1]

Key Innovation

Psoriasis is a common chronic systemic inflammatory skin disease that affects people of all ages worldwide. Because of the chronic nature of psoriatic disease, long-term treatment is often required. Patients' dissatisfaction with the current treatments often lead to reduced compliance with therapy and, consequently, worsening of the disease. This may be due to a deterioration in health status due to tolerability issues, safety concerns (e.g., concerns over infection or malignancy with biological agents) and lack or loss of effectiveness, but also for psychological reasons, such as the administration modality (e.g., the burden imposed by subcutaneous or intravenous routes of administration). A therapeutic alternative for patients with psoriasis who fail to respond to, or have contraindications to, other systemic therapies is apremilast.[4]

In psoriasis, preliminary findings (NCT02576678) provide the first evidence of the potential efficacy of apremilast in paediatric patients with plaque psoriasis, and safety was generally consistent with the known safety profile of apremilast in adult patients with psoriasis. Improvement in Psoriasis Area Severity Index (PASI) score was observed in patients treated with apremilast 20 mg twice daily and apremilast 30 mg twice daily as early as week 2 .[5] If licensed, apremilast will provide an effective and safe treatment for paediatric patients with moderate to severe plaque psoriasis.

Regulatory & Development Status

Apremilast has marketing authorisation in the UK/EU for treatment of active psoriatic arthritis and moderate to severe plaque psoriasis in adults.[6]
Apremilast alone or in combination is currently in phase II/III clinical development for the treatment of various indications including:[7]

- Behçet's disease
- Juvenile psoriatic arthritis
- Psoriasis

Patient Group

Disease Area and Clinical Need

Psoriasis is a chronic, immune-mediated inflammatory skin disease. It ranges in severity from a few scattered red, scaly plaques to involvement of almost the entire body surface. It may progressively worsen with age, or wax and wane in its severity; the degree of severity depends on inheritance and environmental factors.[8] Moderate to severe describes how much of your body is covered in red, scaly psoriasis patches. Moderate psoriasis covers 3% to 10% of your body, while severe psoriasis covers more than 10% of your body or is on sensitive areas like your face, palms, soles, or skin folds.[9,10] Plaque psoriasis is the most common form of psoriasis. Its symptoms are dry skin lesions, known as plaques, covered in scales.[11]. Psoriasis can occur at any age and be different depending on your age and can change over time. In babies and infants, psoriasis can affect the nappy area. Older children have psoriasis on the face more commonly than adults. In children psoriasis may be itchier than in grown-ups and can sometimes be confused with eczema. Sometimes injury to the skin or certain infections can cause psoriasis to start or make the psoriasis reappear. Up to half of children or young people with psoriasis will have more psoriasis after infectious illnesses (including colds, throat and ear infections).[12] While the scope of a psoriasis outbreak may be relatively small, its impact on a child's self-esteem may be large. And it may contribute to feelings of depression, isolation or anxiety.[13] Psoriasis is not contagious, so it cannot spread from person to person.[14] There's no cure for psoriasis, but a range of treatments can improve symptoms and the appearance of skin patches.[15]

Psoriasis affects about 1 in every 50 people. It can develop at any age – from a baby to an old person.[12] Approximately one-third of those who get psoriasis are under 20 years old when the disease first surfaces. Every year, roughly 20,000 children under 10 are diagnosed with psoriasis.[16] In the UK, the prevalence was found to increase from 0.55% in children between 0-9 years of age to 1.37% in children between 10-19 years.[17,18] In England (2021/22) there were 870 total hospital admissions for primary diagnosis of plaque psoriasis (also known as Psoriasis vulgaris, ICD-10 code L40.0) for all ages, of which 19 were for ages 5-17 which makes up 2.18% of the total admitted population. This percentage of the population resulted in 21 finished consultant episodes (FCE) with 15-day cases and 35 FCE bed days.[19]

Recommended Treatment Options

Systemic treatments for children and young people with plaque psoriasis include ciclosporin, methotrexate and phototherapy.[20]

The National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options for children and young people with moderate to severe plaque psoriasis, where it has not responded to systemic treatment, or these options are contraindicated or not tolerated: [15,21]

- Secukinumab
- Adalimumab
- Etanercept
- Ustekinumab

Clinical Trial Information

Trial	NCT04175613; 2019-003497-13; A Phase 3b, Multi Centre, Open-label, Long-term Extension Study of Apremilast (CC-10004) in Paediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis. **Phase III - Active**, not recruiting.

	Location(s): 5 EU countries, USA, Canada, Israel, and Russia **Primary completion date:** December 2022
Trial Design	Single group assignment, open label.
Population	N=140 (estimated); paediatric patients (6 to 17 years of age) with moderate to severe plaque psoriasis.
Intervention(s)	• Subjects with a weight between 20 kg to < 50 kg will receive apremilast 20 mg BID and subjects with weight ≥ 50 kg at Visit 1 will receive apremilast 30 mg BID. Subjects that begin the study receiving apremilast 20 mg BID and later record a body weight ≥ 50 kg, will be switched to apremilast 30 mg BID.
Comparator(s)	No comparator.
Outcome(s)	Primary outcome measure: Adverse Events (AEs) [Time frame: Up to approximately 4 years] See trial records for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03701763; 2018-002918-12. A Phase 3, Multi-centre, Randomised, Double-blind, Placebo-controlled Study to Assess the efficacy and safety of Apremilast (CC-10004) in Paediatric subjects from 6 through 17 years with moderate to severe plaque psoriasis. **Phase III –** Completed **Location(s):** 6 EU countries, USA, Canada, Israel, and Russia **Study completion date:** March 2023
Trial Design	Randomised, parallel assignment, quadruple masking.
Population	N=230 (actual); paediatric patients (aged 6 to 17 years) with moderate to severe plaque psoriasis.
Intervention(s)	• Apremilast 20mg BID. • Apremilast 30mg BID
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome measure: Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline [Time Frame: Up to week 16] See trial records for full list of other outcomes.
Results (efficacy)	The primary endpoint of the static Physician's Global Assessment (sPGA) response (defined as an sPGA score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) at week 16 was met with a 33.1% sPGA response for Otezla versus 11.5% for placebo (95% CI: 11.2%,

	32.1%; P<0.0001). The major secondary endpoint was also met: a greater proportion of patients achieving a 75% or more reduction in the Psoriasis Area and Severity Index (PASI 75) score, with 45.4% for Otezla versus 16.1% for placebo (95% CI: 17.8%, 40.9%; P<0.0001).[22]
Results (safety)	The adverse events were consistent with the known safety profile of Otezla. The most commonly reported (in at least 5% of patients) adverse events were diarrhoea (20.2%), nausea (19.6%), abdominal pain (19.6%), vomiting (17.8%), headache (10.4%), pyrexia (6.7%), nasopharyngitis (6.1%) and upper abdominal pain (5.5%).[22]

Estimated Cost

Apremilast is already marketed in the UK; the NHS indicative price for apremilast 30mg tablets x 56 is listed as £550.00.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Secukinumab for treating moderate to severe plaque psoriasis in children and young people. (TA734). October 2021
- NICE technology appraisal. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people. (TA455). July 2017
- NICE clinical guideline. Psoriasis: assessment and management (CG153). September 2017.
- NICE interventional procedures guidance. Grenz rays' therapy for inflammatory skin conditions (IPG236). November 2007.
- NICE quality standards. Psoriasis (QS40). August 2013.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All ages). A12/S/a.

Other Guidance

- Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. 2020.[24]
- British Association of Dermatologists. Guidelines for biologic therapy for psoriasis. April 2017.[25]
- European S3-Guideline on the systemic treatment of psoriasis vulgaris – Update Apremilast and Secukinumab – EDF in cooperation with EADV and IPC. 2017.[26]

Additional Information

Amgen Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical

companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. *A Long-term Extension Study of Apremilast (CC-10004) in Pediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis*. *Trial ID: NCT04175613*. 2019. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04175613 [Accessed 07 July 2023].

2 Clinicaltrials.gov. *Efficacy and Safety Study of Apremilast (CC-10004) in Pediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis*. *Trial ID: NCT03701763*. 2018. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03701763 [Accessed 07 July 2023].

3 Electronic Medicines Compendium. *Otezla 30 mg Film-Coated Tablets*. 2021. Available from: https://www.medicines.org.uk/emc/product/3648/smpc [Accessed 07 July 2023].

4 Malara G, Politi C, Trifirò C, Verduci C, D'Arrigo G, Testa A, et al. Effectiveness of Apremilast in Real Life in Patients with Psoriasis: A Longitudinal Study. *Acta Dermato-Venereologica*. 2021;101(9):adv00545. Available from: https://doi.org/10.2340/00015555-3846.

5 Paller AS, Hong Y, Becker EM, de Lucas R, Paris M, Zhang W, et al. Pharmacokinetics and safety of apremilast in pediatric patients with moderate to severe plaque psoriasis: Results from a phase 2 open-label study. *Journal of the American Academy of Dermatology*. 2020;82(2):389-97. Available from: https://doi.org/https://doi.org/10.1016/j.jaad.2019.08.019.

6 European Medical Agency. *Otezla-apremilast*. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/otezla [Accessed 08 July 2023].

7 Clinicaltrials.gov. *Apremilast, Amgen | Recruiting, Not yet recruiting, Active, not recruiting Studies | Child | Phase 2, 3*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/results?term=Apremilast%2C+Amgen&recrs=b&recrs=a&recrs=d&age_v=&age=0&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 07 August 2023].

8 Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *Journal of Investigative Dermatology*. 2013;133(2):377-85. Available from: https://doi.org/https://doi.org/10.1038/jid.2012.339.

9 WebMD Editorial Contributors. *Treating Moderate to Severe Psoriasis*. 2023. Available from: https://www.webmd.com/skin-problems-and-treatments/psoriasis/severe-psoriasis [Accessed 21 July 2023].

10 Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *Journal of Investigative Dermatology*. 2012;132(3 Pt 1):556-62. Available from: https://doi.org/10.1038/jid.2011.365.

11 NHS. *Symptoms-Psoriasis*. Available from: https://www.nhs.uk/conditions/psoriasis/symptoms/ [Accessed 08 July 2023].

12 Dermatologists BAo. *Psoriasis in children and young people*. Available from: https://www.bad.org.uk/pils/psoriasis-in-children-and-young-people/ [Accessed 21 July 2023].

13 Healthline. *Understanding Psoriasis in Children: Symptoms, Treatments, and More*. 2022. Available from: https://www.healthline.com/health/psoriasis/psoriasis-in-children [Accessed 21 July 2023].

14 NHS. *Causes-Psoriasis*. Available from: https://www.nhs.uk/conditions/psoriasis/causes/ [Accessed 09 July 2023].
15 National Health Service (NHS). *Treatment-Psoriasis*. Available from: https://www.nhs.uk/conditions/psoriasis/treatment/ [Accessed 08 July 2023].
16 National Psoriasis Foundation. *Children with Psoriasis*. Available from: https://www.psoriasis.org/children-with-psoriasis/ [Accessed 23 July 2023].
17 Branisteanu DE, Georgescu S, Serban IL, Pinzariu AC, Boda D, Maranduca MA, et al. Management of psoriasis in children (Review). *Experimental and Therapeutic Medicine*. 2021;22(6):1429. Available from: https://doi.org/10.3892/etm.2021.10864.
18 Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Archives of Dermatology*. 2005;141(12):1537-41. Available from: https://doi.org/10.1001/archderm.141.12.1537.
19 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 14 August 2023.].
20 National Institute for Health and Care Excellence NICE. *Psoriasis*. Available from: https://bnfc.nice.org.uk/treatment-summaries/psoriasis/ [Accessed 23 July 2023].
21 National Institute for Health and Care Excellence NICE. *Psoriasis Products A list of all our products on psoriasis*. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/skin-conditions/psoriasis/products?ProductType=Guidance&Status=Published [Accessed 08 July 2023].
22 AMGEN. *AMGEN ANNOUNCES POSITIVE NEW DATA AT EADV 2022 FOR OTEZLA® (APREMILAST)*. 2022. Available from: https://www.amgen.com/newsroom/press-releases/2022/09/amgen-announces-positive-new-data-at-eadv-2022-for-otezla-apremilast [Accessed 08 August 2023].
23 National Institute for Health and Care Excellence NICE. *Apremilast Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/apremilast/medicinal-forms/ [Accessed 08 July 2023].
24 Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DM, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *Journal of the American Academy of Dermatology*. 2020. Available from: https://doi.org/10.1016/j.jaad.2020.02.044.
25 British Association of Dermatologists. *British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update*. Available from: https://www.bad.org.uk/guidelines-and-standards/clinical-guidelines/ [Accessed 08 July 2023].
26 Nast A, Spuls PI, van der Kraaij G, Gisondi P, Paul C, Ormerod AD, et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology*. 2017;31(12):1951-63. Available from: https://doi.org/10.1111/jdv.14454.

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