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HEALTH TECHNOLOGY BRIEFING
MAY 2019

Guselkumab for active psoriatic arthritis

NIHRIO ID	10982	**NICE ID**	10075
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	648739

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Guselkumab is in clinical development for the treatment of adults with active psoriatic arthritis. Psoriatic arthritis is a type of chronic inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of the skin or nails. Although the exact cause of the disease still remains unknown, it is thought to occur as a result of the immune system mistakenly attacking healthy tissues around the joint and bones. Psoriatic arthritis can get progressively worse and may lead to the joints becoming permanently damaged or deformed.

Guselkumab is a type of biologic medicine that has been designed to suppress immune response associated with psoriasis. It works by specifically targeting a chemical messenger (known as a cytokine) in the body called interleukin-23 (IL-23). The IL-23 are produced by leucocytes (mainly by lymphocytes T, macrophages and eosinophils) in response to mechanical stress, and has an important role in the pathogenesis of psoriasis and psoriatic arthritis. Guselkumab is already licensed in the EU/UK for the treatment of moderate to severe plaque psoriasis and may offer an additional treatment option for patients with active psoriatic arthritis.

PROPOSED INDICATION

Patients with active psoriatic arthritis.[1]

TECHNOLOGY

DESCRIPTION

Guselkumab (Tremfya) is a human IgG1λ monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL-23) protein with high specificity and affinity. IL-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalize production of these cytokines.[2]

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In in vitro models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signalling, activation and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway.[2]

Guselkumab is currently in phase III clinical development for the treatment of adults with active psoriatic arthritis. In a phase III clinical trial (NCT03158285), participants with active psoriatic arthritis who are biologically naïve were randomised in three different arms. In group 1, participants will receive subcutaneous (SC) guselkumab 100 mg once every 4 weeks for 100 weeks. In group 2, participants will receive SC guselkumab 100 mg at weeks 0 and 4 then once every 8 weeks with placebo injections between the visits to maintain the blind. In group 3, participants will receive SC placebo from 0 to week 20 and will cross over at week 24 to receive SC guselkumab 100 mg from week 24 to week 100. In all arms assessed the participants will be followed for 100 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Psoriatic arthritis is a common comorbidity of psoriasis with an umet need for novel treatments. Drugs targeting interleukin 23 that do not affect interleukin 12 might enhance efficacy in psoriatic arthritis and psoriasis compared with interleukin 12 and 23 antagonists.[3] Guselkumab is an IL-23 inhibitor that selectively targets the unique p19 subunit of human IL-23 without binding IL-12, allowing the sparing of the interleukin 12–T-helper-1 axis, which is important for defence against intracellular pathogens via interferon γ production.[4]

Guselkumab, significantly improved signs and symptoms of active psoriatic arthritis and was well tolerated during 44 weeks of treatment. The results of this study support further development of guselkumab as a novel and comprehensive treatment in psoriatic arthritis.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Guselkumab is licensed in the EU/UK for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The most commonly reported adverse event (very common) was upper respiratory infection.[2]

Guselkumab is currently in phase II and III clinical development for the treatment of various conditions, including palmoplantar pustulosis, psoriasis, pustular psoriasis, chronic plaque-type psoriasis, and hidradenitis suppurativa, ulcerative colitis, and Crohn's disease.[5]

PATIENT GROUP

DISEASE BACKGROUND

Psoriatic arthritis (PsA) is a type of chronic, immune-mediated inflammatory arthritis that causes irreversible structural damage to the joints over time and may significantly worsen the patient's quality of life.[6] Although the aetiology of PsA remains still to be completely understood, multiple immune system cell types and cytokines have been implicated in PsA disease activity. The synovial fluid of joints affected by PsA shows increased levels of T-cells and cytokines such as TNF, IL-6, IL-12/IL-23, and IL-17. Together, these cytokines drive joint inflammation and other downstream biological effects, such as osteoblast and osteoclast activation, which further contributes to joint damage.[7]

Between 1 and 2 in every 5 people with psoriasis develop PsA. Like psoriasis, PsA is thought to occur as a result of the immune system mistakenly attacking healthy tissue. However, it is not clear why some people with psoriasis develop psoriatic arthritis and others do not.[8] Symptoms of PsA can include a red, scaly rash (psoriasis), swollen, stiff and painful joints, sausage-like swelling of fingers or toes (dactylitis), thickening, discolouration and pitting of the nails, pain and swelling at the back of the heel, and fatigue.[9]

CLINICAL NEED AND BURDEN OF DISEASE

PsA affects in the same measure men and women[10] and tends to affect more adults than young people.[9] It is estimated that around 1 in 5 people with psoriasis develop psoriatic arthritis, although this figure may be higher in people who have severe psoriasis. In around 70% of people, psoriasis precedes psoriatic arthritis. The prevalence of psoriatic arthritis in England in 2016 was estimated to be around 105,010 adults. Men and women are equally likely to develop psoriatic arthritis with the peak onset being between the ages of 30 and 50 years.[11]

In 2017-18 there were 3,920 admissions (of which 3,510 were day cases) for arthropathic psoriasis (ICD-10 code L40.5) in England which resulted in 4,097 finished consultant episodes (FCE) and 2,388 FCE bed days.[12]

The severity of psoriatic arthritis can range from mild to severe and despite improvement on conventional synthetic DMARD medication, up to 47% people will develop joint damage which is visible on radiograph by 2 years. People with psoriatic arthritis also have 60% higher risk of mortality and a 3 year decreased life expectancy compared to the general population.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main aims of treatment will be to relieve the symptoms, slow the progression of disease and improve the quality of life. The main medications used to treat PsA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and biological therapies.[8]

The healthcare management of symptoms related to the disease can be delivered by a multidisciplinary team formed by the general practitioner (GP), rheumatologist, specialist nurse, dermatologist, physiotherapist, occupational therapist, and psychologist.

Moreover, change of habits such as having a balance between rest and regular physical activity, losing weight, not smoking and only drinking a moderate amount of alcohol may help to ease the symptoms.[8]

CURRENT TREATMENT OPTIONS

There are several therapeutic treatment approaches according to different steps of disease and include:[8]

- Nonsteroidal anti-inflammatory drug (NSAIDs) may be used to help relieve pain and reduce inflammation. There are two types of NSAIDs, the traditional NSAIDs, such as ibuprofen and naproxen or diclofenac, and the COX-2 inhibitors (also called coxibs), such as celecoxib or etoricoxib.
- Like NSAIDs, corticosteroids can help reduce pain and swelling.
- DMARDs are medications that work by tackling the underlying causes of the inflammation in your joints. Leflunomide is often the first drug given for psoriatic arthritis, although sulfasalazine or methotrexate may be considered as alternatives.
- Biological treatment may be offered for patients who have not responded to at least two different types of DMARD or are not able to be treated with at least two different types of DMARD. Some of the biological medicines that may be offered include: adalimumab, apremilast, certolizumab, etanercept, golimumab, infliximab, secukinumab, ustekinumab, ixekizumab, and tofacitinib.

PLACE OF TECHNOLOGY

If licensed, guselkumab will offer an additional treatment option for patients with active psoriatic arthritis.

CLINICAL TRIAL INFORMATION

Trial	NCT03158285, EudraCT 2016-001224-63; 18 years and older; guselkumab vs guselkumab and placebo; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry[1,14]
Location	EU countries (not including the UK), US and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=738 (enrolled); ≥ 18 years older; diagnosed with PsA for at least 6 months before the first administration of study agent and meet Classification criteria for Psoriatic Arthritis (CASPAR) at screening; have active PsA in at least 5 joints swollen and tender at screening and at baseline, and serum C-Reactive Protein (CRP) greater than or equal to 0.6 milligrams per deciliter (mg/dL); have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilates, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; have active plaque psoriasis, with at least one psoriatic plaque of >= 2 centimetre (cm) diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis; Have active PsA despite previous DMARD, apremilast, and/or NSAID therapy.
Schedule	Participants were randomised to one of the treatment arms: 1. Subcutaneous (SC) guselkumab 100 mg once every 4 weeks from week 0 through week 100.

	2. SC guselkumab 100 mg at weeks 0 and 4 then every 8 weeks and placebo injections at other visits to maintain the blind. 3. SC placebo once every 4 weeks from week 0 to week 20 and will cross over at week 24 to receive SC guselkumab 100 mg once every 4 weeks from week 24 to week 100.
Follow-up	The study consist of a screening phase (up to 6 weeks), a blinded treatment phase (approximately 100 weeks) including a placebo controlled period from week 0 to week 24 and an active treatment period from week 24 to week 100 and a safety follow-up phase of 12 weeks after the last administration of study agent.
Primary Outcomes	Percentage of participants who achieve an American College of Rheumatology (ACR) 20 response at week 24.
Secondary Outcomes	Time frame at week 16: • Percentage of participants who achieve an ACR 20 response. • Percentage of participants who achieve an ACR 50 response. Time frame at week 24: • Percentage of participants who achieve an ACR 50 response. • Percentage of participants with a psoriasis response of investigator's global assessment (IGA) among the participants with ≥ 3% body surface area (BSA) psoriatic involvement and an IGA score of ≥ 2 (mild) at baseline. • Percentage of participants with resolution of enthesitis among the participants with enthesitis at baseline. • Percentage of participants with resolution of dactylitis among the participants with dactylitis at baseline. • Percentage of participants who achieve an ACR 70 response. Time frame: baseline and week 24: • Change from baseline in health assessment questionnaire-disability index (HAQ-DI) score • Change from baseline in modified van der Heijde-Sharp (vdH-S) score • Change from baseline in enthesitis score (based on Leeds enthesitis index [LEI]) among the participants with enthesitis at baseline • Change from baseline in dactylitis score. • Change from baseline in disease activity score 28 (DAS28) C-reactive protein (CRP). • Change from baseline in 36-item short form health survey (SF-36) physical component summary (PCS). • Change from baseline in SF-36 mental component summary (MCS).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date February 2019.

Trial	NCT03162796, EudraCT 2016-001163-37; 18 years and older; guselkumab vs placebo; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing

Source of Information	Trial registry[15,16]
Location	EU countries (not including the UK), US and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=383 (enrolled); ≥ 18 years older; diagnosed with PsA for at least 6 months before the first administration of study agent and meet Classification criteria for Psoriatic Arthritis (CASPAR) at screening; have active PsA in at least 3 joints swollen and tender at screening and at baseline, and serum C-Reactive Protein (CRP) greater than or equal to 0.3 milligrams per deciliter (mg/dL); have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilates, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; have active PsA despite previous DMARD, apremilast, and/or NSAID therapy; participants may have been previously treated with up to 2 anti-TNF (tumor necrosis factor) alpha agents (approximately 30 percent [%] of the overall study population), and must document the reason for discontinuation.
Schedule	Participants were randomised to one of the treatment arms: 4. Subcutaneous (SC) guselkumab 100 mg once every 4 weeks from week 0 through week 48. 5. SC guselkumab 100 mg at weeks 0 and 4, then every 8 weeks (Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48) to maintain the blind. 1. SC placebo once every 4 weeks from week 0 to week 20 and will cross over at week 24 to receive SC guselkumab 100 mg once every 4 weeks from week 24 to week 48.
Follow-up	The study will consists of 4 phases: a screening phase of up to 6 weeks, a blinded treatment phase of approximately 1 year (that is, 52 weeks), including a placebo controlled period from week 0 to week 24 and double-blind active treatment period from week 24 to week 52, and a safety follow-up phase of 8 weeks after week 52 (week 52 to 60) and will be 12 weeks from the last administration of study agent (at week 48) to the final safety follow-up visit.
Primary Outcomes	Percentage of participants who achieve an American College of Rheumatology (ACR) 20 response at week 24.
Secondary Outcomes	Time frame at week 16: • Percentage of participants who achieve an ACR 20 response. • Percentage of participants who achieve an ACR 50 response. Time frame at week 24: • Percentage of participants who achieve an ACR 50 response. • Percentage of participants with a psoriasis response of investigator's global assessment (IGA) among the participants with ≥ 3% body surface area (BSA) psoriatic involvement and an IGA score of ≥ 2 (mild) at baseline. • Percentage of participants with resolution of enthesitis among the participants with enthesitis at baseline. • Percentage of participants with resolution of dactylitis among the participants with dactylitis at baseline. • Percentage of participants who achieve an ACR 70 response. Time frame: baseline and week 24: • Change from baseline in health assessment questionnaire-disability index (HAQ-DI) score

	• Change from baseline in enthesitis score (based on Leeds enthesitis index [LEI]) among the participants with enthesitis at baseline • Change from baseline in dactylitis score. • Change from baseline in disease activity score 28 (DAS28) C-reactive protein (CRP). • Change from baseline in 36-item short form health survey (SF-36) physical component summary (PCS). • Change from baseline in SF-36 mental component summary (MCS).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date March 2019.

Trial	NCT02319759, EudraCT 2014-003697-17; 18 years and older; guselkumab vs placebo; phase II
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry[3,17]
Location	EU countries (not including the UK), US and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	N=149 (enrolled); ≥ 18 years older; diagnosed with PsA for at least 6 months before the first administration of study agent and meet Classification criteria for Psoriatic Arthritis (CASPAR) at screening; have active PsA in at least 3 joints swollen and tender at screening and at baseline, and serum C-Reactive Protein (CRP) greater than or equal to 0.3 milligrams per deciliter (mg/dL); have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilates, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; have plaque psoriasis with body surface area (BSA) involvement greater than or equal to (>=) 3% at Screening and baseline; Have active PsA despite previous DMARD, oral corticosteroid, and/or NSAID therapy.
Schedule	Participants were randomised to one of the treatment arms: 2. Subcutaneous (SC) guselkumab 100 mg at weeks 0, 4, 12, 20, 28, 36, and 44, and placebo for guselkumab at week 24 to maintain the blind. 3. SC placebo at weeks 0, 4, 12, and 20, and SC guselkumab 100 mg at weeks 24, 28, 36, and 44, and placebo subcutaneous injection will be administered at week 24 to maintain the blind. 4. In both placebo and guselkumab groups, if the participants qualify for early escape, they will switch to receive ustekinumab 45 mg or 90 mg subcutaneous injection at weeks 16, 20, 32, and 44.
Follow-up	The maximal study duration for a participant will not exceed 62 weeks including the screening period.
Primary Outcomes	Percentage of participants who achieve an American College of Rheumatology (ACR) 20 response at week 24.
Secondary Outcomes	Time frame at week 16: • Percentage of participants who achieve an ACR 20 response. Time frame at week 24:

	• Percentage of participants who achieve an ACR 50 response. • Percentage of participants who achieve a Psoriatic Area and Severity Index (PASI) 75 response. Time frame: baseline and week 24: • Change from baseline in the Disability Index of the Health Assessment Questionnaire (HAQ-DI) Score • Percent improvement in enthesitis score (based on Leeds enthesitis index [LEI]) among the participants with enthesitis at baseline • Percent improvement in dactylitis score at week 24 among participants with dactylitis at baseline.
Key Results	Between March 27, 2015, and Jan 17, 2017, we randomly assigned 149 patients to treatment: 100 to guselkumab and 49 to placebo. 17 (35%) of 49 patients in the placebo group and ten (10%) of 100 patients in the guselkumab group were eligible for early escape to ustekinumab at week 16. 29 (59%) of 49 patients in the placebo group crossed over and received guselkumab at week 24. Three (6%) of 49 patients in the placebo group, one (3%) of 29 patients who crossed over from placebo to guselkumab, and six (6%) of 100 patients in the guselkumab group discontinued study treatment before week 44. 58 (58%) of 100 patients in the guselkumab group and nine (18%) of 49 patients in the placebo group achieved an ACR20 response at week 24 (percentage difference 39·7% [95% CI 25·3-54·1]; p<0·0001).
Adverse effects (AEs)	Between week 0 and week 24, 36 (36%) of 100 guselkumab-treated patients and 16 (33%) of 49 placebo-treated patients had at least one adverse event. The most frequent adverse event was infection in both groups (16 [16%] of 100 patients in the guselkumab group vs ten [20%] of 49 patients in the placebo group). The prevalence of adverse events between week 0 and week 56 in guselkumab-treated patients (51 [40%] of 129) indicated no disproportional increase with longer guselkumab exposure. No deaths occurred.
Expected reporting date	Study completion date January 2017.

ESTIMATED COST

Guselkumab is already marketed in the UK for the treatment of moderate-to-severe plaque psoriasis; a pre-filled disposable injection 100 mg per 1 mL, pen or syringe cost £2,250.00.[18]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Psoriatic arthritis (moderate to severe) - leflunomide (ID391). Expected publication: TBC.
- NICE technology appraisal guidance. Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs (TA543). October 2018.
- NICE technology appraisal guidance. Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs (TA537). August 2018.
- NICE technology appraisal guidance. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (TA445). May 2017.

- NICE technology appraisal guidance. Ustekinumab for treating active psoriatic arthritis (TA340). March 2017.
- NICE technology appraisal guidance. Apremilast for treating active psoriatic arthritis (TA433). February 2017.
- NICE technology appraisal guidance. Golimumab for the treatment of psoriatic arthritis (TA220). April 2011.
- NICE technology appraisal guidance. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (TA199). August 2010.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a.

OTHER GUIDANCE

- European League Against Rheumatism (EULAR). European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. December 2015.[19]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of psoriasis and psoriatic arthritis in adults: a national clinical guideline (SIGN 121). October 2010.[20]

ADDITIONAL INFORMATION

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