NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
AUGUST 2019

Upadacitinib for active psoriatic arthritis with inadequate response to biological or non-biological DMARDs

NIHRIO ID	19366	**NICE ID**	9976
Developer/Company	AbbVie	**UKPS ID**	651521

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Upadacitinib is in clinical development for the treatment of adults with active psoriatic arthritis who have an inadequate response to at least one biological or non-biological Disease Modifying Anti-Rheumatic Drug (DMARDs). 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. Around two in every five people with psoriasis will develop psoriatic arthritis. 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.

Upadacitinib acts by selectively blocking the Janus-Associated Kinase 1 (JAK1) enzymes that mediate the pathways involved in the inflammatory process in psoriatic arthritis and other inflammatory diseases. There are emerging body of evidence establishing that JAK-dependent enzymes are major contributors to the progression of immune-mediated diseases such as psoriatic arthritis and that blocking such enzymes can be beneficial. Recent research suggests that selective JAK inhibitors may decrease adverse effects, and thus increase safety and efficacy. Upadacitinib is taken orally and if licensed, it will offer an additional treatment option for patients with active psoriatic arthritis who have an inadequate response to at least one biological or non-biological DMARDs.

PROPOSED INDICATION

Patients with active psoriatic arthritis who have an inadequate response to at least one biological or non-biological Disease Modifying Anti-Rheumatic Drug (DMARDs).[1,2]

TECHNOLOGY

DESCRIPTION

Upadacitinib (ABT-494) is an orally administered janus kinase (JAK) inhibitor, engineered for greater selectivity for JAK1 than for other members of the JAK family.[3] JAKs are proteins that mediate the transduction of intracellular signals involved in the process of inflammatory diseases. The JAK1 pathway has been implicated in the pathogenesis of psoriatic arthritis.[4]

Upadacitinib is currently in clinical development for the treatment of active psoriatic arthritis (PsA) in patients who have an inadequate response to at least one biological or non-biological Disease Modifying Anti-Rheumatic Drug (DMARDs). In the phase III clinical trials (NCT03104400; SELECT-PsA 1,[2,5] NCT03104374; SELECT-PsA 2[1,6]), upadacitinib is administered at different doses and compared to placebo and to adalimumab. Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table section of this briefing.

INNOVATION AND/OR ADVANTAGES

An overwhelming body of evidence has established that JAK-dependent cytokines are major contributors to immunopathology and that blocking such cytokines with biologics can be beneficial in immune-mediated diseases.[7]

There is currently no JAK1-selective inhibitor licensed in the UK for psoriatic arthritis, although tofacitinib, a JAK1/JAK3 selective inhibitor is available.[8] JAK1-selective inhibitors target the broadest cytokine profile among JAKs.[9] JAK inhibitors act on the intracellular signalling apparatus comprising the JAK family network used by inflammatory cytokines and other growth factors.[10]

Recent research has focused on the development of selective JAK inhibitors as inhibition of specific JAK kinase may decrease adverse effects, and thus increase safety and efficacy.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Upadacitinib does not currently have Marketing Authorization in the EU for any indication.

Upadacitinib is currently in development for the treatment of psoriatic arthritis, ulcerative colitis, atopic dermatitis, Crohn's disease, systemic lupus erythematosus (SLE), giant cell arteritis (GCA), rheumatoid arthritis, and axial spondyloarthritis.[11]

PATIENT GROUP

DISEASE BACKGROUND

Psoriatic arthritis (PsA) is a type of chronic, immune-mediated inflammatory arthritis that can cause irreversible structural damage to the joints over time and may significantly worsen the

patient's quality of life.[12] 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.[13]

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.[14]

Symptoms of PsA can include a red, scaly rash (psoriasis), swollen, stiff and painful joints, sausage-like swelling of fingers or toes (dactylitis), inflammation of the connective tissues (enthesitis), thickening, discolouration and pitting of the nails, pain and swelling at the back of the heel, and fatigue, as well as extra-articular manifestations such as uveitis and inflammatory bowel disease (IBD).[15]

CLINICAL NEED AND BURDEN OF DISEASE

PsA affects in the same measure men and women[16] and tends to affect more adults than young people.[15] It is estimated that around 1 in 5 people with psoriasis develop PsA, although this figure may be higher in people who have severe psoriasis. In around 70% of people, psoriasis precedes PsA. The prevalence of PsA in England in 2016 was estimated to be around 105,010 adults. Men and women are equally likely to develop PsA with the peak onset being between the ages of 30 and 50 years.[17]

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.[18]

The severity of PsA can range from mild to severe and despite the improvement on conventional synthetic Disease Modifying Anti-Rheumatic Drug (DMARD) medication, up to 47% of people will develop joint damage which is visible on radiograph by 2 years. People with PsA also have 60% higher risk of mortality and a 3 year decreased life expectancy compared to the general population.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main aims of treatment will be to relieve the symptoms, slow the progression of the disease and improve the quality of life. The main medications used to treat PsA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic (csDMARDs), and biological (bDMARDs).[14]

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.[14]

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.[14]

CURRENT TREATMENT OPTIONS

There are several therapeutic treatment approaches according to different steps of disease and include:[14]

- 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 csDMARD 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 csDMARD or are not able to be treated with at least two different types of csDMARD. Some of the biological medicines that may be offered include TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), IL-17 inhibitors (secukinumab, ixekizumab), PDE4 inhibitors (apremilast), IL-12/23 inhibitors (ustekinumab), and JAK inhibitors (tofacitinib).

PLACE OF TECHNOLOGY

If licensed, upadacitinib will offer an additional treatment option for patients with active psoriatic arthritis who have an inadequate response to at least one biological or non-biological DMARDs.

CLINICAL TRIAL INFORMATION

Trial	SELECT – PsA 1, NCT03104400, M15-572, EudraCT 2016-004130-24; aged ≥18 years old; upadacitinib vs placebo; phase III
Sponsor	AbbVie
Status	Ongoing
Source of Information	Trial registry[2,5]
Location	EU countries (incl the UK), USA, Canada and other countries
Design	Randomised, placebo and active comparator-controlled, double-blind study
Participants	n=1705; aged ≥ 18 years and older; active psoriatic arthritis; inadequate response to previous or current treatment with at least 1 non-biologic DMARD.
Schedule	This study includes 2 periods and patients will be randomised among 5 arms. • Arm 1: upadacitinib 15 mg • Arm 2: upadacitinib 30 mg • Arm 3: active comparator, adalimumab 40 mg • Arm 4: upadacitinib placebo followed by upadacitinib 15 mg • Arm 5: adalimumab placebo followed by upadacitinib 30 mg Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg once daily (QD) and 30 mg QD versus placebo and versus adalimumab every other week in participants with moderately to

	severely active psoriatic arthritis and have an inadequate response to non-biologic DMARDs (csDMARD-IR). Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo for the prevention of structural progression. Period 2 evaluates the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in participants with psoriatic arthritis who have completed period 1.
Follow-up	A follow-up to 24 weeks
Primary Outcomes	Proportion of participants achieving American College of Rheumatology (ACR) 20 response [Time frame: week 12]
Secondary Outcomes	• ACR 70 response [Time frame: week 12] • Change from baseline in Leeds Dactylitis Index (LDI) [Time frame: week 24] • Change from baseline in FACIT-Fatigue Questionnaire [Time frame: week 12] • Change from baseline in Leeds Enthesitis Index (LEI) [Time frame: week 24] • ACR 50 response [Time frame: week 12] • Proportion of participants achieving a static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline [Time frame: week 16] • Change from baseline in Patient's Assessment of Pain NRS (superiority of ABT-494 vs. adalimumab) [Time frame: week 12] • Change from baseline in HAQ-DI [Time frame: week 12] • ACR 20 response rate (superiority of ABT-494 vs. adalimumab) [Time frame: week 12] • ACR 20 response [Time frame: week 2] • Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire [Time frame: week 16] • Change from baseline in modified PsA Sharp/van der Heijde Score (SHS) [Time frame: week 24] • ACR 20 response rate (non-inferiority of ABT-494 vs adalimumab) [Time frame: week 12] • Psoriasis Area Severity Index (PASI) 75 response (for participants with >= 3% BSA psoriasis at baseline) [Time frame: week 16] • Change from baseline in Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2) [Time frame: week 12] • Proportion of participants achieving Minimal Disease Activity (MDA) [Time frame: week 24] • Change from baseline in HAQ-DI (superiority of ABT-494 vs. adalimumab) [Time frame: week 12]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in September 2019.

Trial	SELECT – PsA 2, NCT03104374, M15-554, EudraCT 2016-004152-30; aged ≥18 years old; upadacitinib vs placebo; phase III
Sponsor	AbbVie
Status	Ongoing

Source of Information	Trial registry[1,6]
Location	EU countries (incl the UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, double-blind study
Participants	n=640; aged ≥ 18 years and older; active psoriatic arthritis; inadequate response or intolerance to treatment with at least 1 biologic DMARD.
Schedule	This study includes 2 periods and participants will be randomised among 4 arms. • Arm 1: upadacitinib 15 mg • Arm 2: upadacitinib 30 mg • Arm 3: placebo then upadacitinib 15 mg • Arm 4: placebo then upadacitinib 30 mg Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg once daily (QD) and 30 mg QD versus placebo in participants with moderately to severely active psoriatic arthritis who have an inadequate response to bDMARDs. Period 2 evaluates the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with psoriatic arthritis who have completed period 1.
Follow-up	A follow-up to 24 weeks
Primary Outcomes	Proportion of participants achieving American College of Rheumatology (ACR) 20 response [Time frame: week 12]
Secondary Outcomes	• ACR 50 response [Time frame: week 12] • Proportion of participants achieving a static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline [Time frame: week 16] • Psoriasis Area Severity Index (PASI) 75 response (for participants with >= 3% BSA psoriasis at baseline) [Time frame: week 16] • Proportion of participants achieving Minimal Disease Activity (MDA) [Time frame: week 24] • Change from baseline in HAQ-DI [Time frame: week 12] • ACR 70 response [Time frame: week 12] • ACR 20 response [Time frame: week 2] • Change from baseline in Short-Form (SF)-36 Physical Component Summary (PCS) [Time frame: week 12] • Change from baseline in FACIT-Fatigue Questionnaire [Time frame: week 12] • Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire [Time frame: week 16]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in August 2019.

ESTIMATED COST

The cost of upadacitinib is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.[20]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of psoriasis and psoriatic arthritis in adults: a national clinical guideline (SIGN 121). October 2010.[21]
- British Society for Rheumatology (BSR). The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. October 2013.[22]
- Coates LC. et al, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. May 2016.[23]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *A Study Comparing Upadacitinib (ABT-494) to Placebo in Participants With Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (SELECT - PsA 2). Trial ID: NCT03104374*. Available from: https://clinicaltrials.gov/ct2/show/NCT03104374 [Accessed 07 June 2019].

2 ClinicalTrials.gov. *A Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Participants With Psoriatic Arthritis Who Have an Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (SELECT - PsA 1). Trial ID: NCT03104400*. Available from: https://clinicaltrials.gov/ct2/show/NCT03104400 [Accessed 07 June 2019].

3 Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018 Jun 23;391(10139):2513-24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29908670 10.1016/S0140-6736(18)31116-4.

4 Mease P, Coates LC, Helliwell PS, Stanislavchuk M, Rychlewska-Hanczewska A, Dudek A, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018 Dec 1;392(10162):2367-77. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30360969 10.1016/S0140-6736(18)32483-8.

5 EU Clinical Trial Register. *A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1. Trial ID: 2016-004130-24*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004130-24/GB [Accessed 07 June 2019].

6 EU Clinical Trial Register. *A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. Trial ID: 2016-004152-30*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004152-30/GB [Accessed 07 June 2019].

7 Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov*. 2017 Dec 28;17(1):78. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29282366 10.1038/nrd.2017.267.

8 Electronic Medicines Compendium (eMC). *Pharmacological properties.* Available from: https://www.medicines.org.uk/emc/product/9410/smpc#PHARMACOLOGICAL_PROPS [Accessed 21 August 2019].

9 Virtanen AT; Haikarainen T; Raivola J; Silvennoinen O. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. *BioDrugs*. 2019 Feb;33(1):15-32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30701418 10.1007/s40259-019-00333-w.

10 Braun J. New targets in psoriatic arthritis. *Rheumatology (Oxford)*. 2016 Dec;55(suppl 2):ii30-ii7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27856658 10.1093/rheumatology/kew343.

11 ClinicalTrials.gov. *Upadacitinib - Clinical trial phase II and III.* Available from: https://clinicaltrials.gov/ct2/results?term=upadacitinib%2C+abbvie&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 09 July 2019].

12 Paik J, Deeks ED. Tofacitinib: A Review in Psoriatic Arthritis. *Drugs*. 2019 Mar 20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30895473 10.1007/s40265-019-01091-3.

13 Menter A. Psoriasis and psoriatic arthritis overview. *Am J Manag Care*. 2016 Jun;22(8 Suppl):s216-24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27356193.

14 National Health Service (NHS). *Psoriatic arthritis.* Available from: https://www.nhs.uk/conditions/psoriatic-arthritis/ [Accessed 08 July 2019].

15 Arthritis Research UK. *Psoriatic arthritis.* Available from: https://www.versusarthritis.org/media/1262/psoriatic-arthritis-information-booklet.pdf [Accessed 08 April 2019].

16 Scotti L, Franchi M, Marchesoni A, Corrao G. Prevalence and incidence of psoriatic arthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018 Aug;48(1):28-34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29398124 10.1016/j.semarthrit.2018.01.003.

17 National Institute for Health and Care Excellence (NICE). *Single Technology Appraisal - Tofacitinib for treating active psoriatic arthritis following diseasemodifying anti-rheumatic drugs.* Available from: https://www.nice.org.uk/guidance/ta543/documents/final-scope [Accessed 07 May 2019].

18 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 11 June 2019].

19 National Institute for Health and Care Excellence (NICE). *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.* Available from: https://www.nice.org.uk/guidance/ta199/chapter/2-Clinical-need-and-practice [Accessed 07 May 2019].

20 Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis*. 2016 Mar;75(3):499-510. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26644232 10.1136/annrheumdis-2015-208337.

21 Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of psoriasis and psoriatic arthritis in adults: a national clinical guideline (SIGN 121).* Available from: https://www.sign.ac.uk/assets/sign121.pdf [Accessed 9 April 2019].

22 Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology (Oxford)*. 2013 Oct;52(10):1754-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23887065 10.1093/rheumatology/ket187.

23 Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol*. 2016 May;68(5):1060-71. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26749174 10.1002/art.39573.