National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: November 2017

Upadacitinib for adults with moderate to severe active rheumatoid arthritis after conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) or biologic DMARDs failure

NIHRIO (HSRIC) ID: 10453 NICE ID: 9189

LAY SUMMARY

Rheumatoid arthritis (RA) is a long-term condition that causes pain, swelling and stiffness in the joints. The condition occurs in women more often than men. The symptoms usually affect the hands, feet and wrists. There may be periods where symptoms become worse, known as flare-ups. Some people with RA also experience problems in other parts of the body, or more general symptoms such as tiredness and weight loss. RA is an autoimmune disease (the immune system attacks the cells that line the joints), resulting in the symptoms. Over time, this can damage the joint itself, the cartilage and nearby bone.

There is currently no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. The most common treatment options are steroids to reduce inflammation, medications to reduce pain and swelling, and medications that slow the progression of joint damage from RA. Upadacitinib is currently being developed to be taken orally as a treatment option for those who have active moderate to severe RA who do not respond to certain treatment options. This drug works by stopping the inflammation caused by a specific type of protein and if licensed, it may be an option that can be used earlier in the treatment pathway.

TARGET GROUP

Rheumatoid arthritis (RA) in adults (active; moderate to severe) - after failure of conventional disease-modifying anti-rheumatic drugs (DMARD) or biologic DMARDs.

TECHNOLOGY

DESCRIPTION

Upadacitinib (ABT-494) is under development for the treatment of moderate to severe RA in adults.[1]

Upadacitinib is a Janus-kinase (JAK) 1 inhibitor. JAK is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the JAK/signal transducer and activator of transcription (STAT) pathway and are located in the cytoplasm of cells. The JAK-STAT pathway plays a key role in blood cell production and immune and inflammatory responses in the body. When activated, JAKs stimulate a cascade involved in the production of pro-inflammatory cytokines. Over activation of JAK can lead to inflammation and tissue destruction. Each JAK protein has specificity for a different set of cytokine receptors. Blocking of the JAK family may lead to the alleviation of the condition.[1]

Upadacitinib is in development in a number of phase III clinical trials[2,3,4, 5,6,7] and is administered orally via tablet formulation, at a dose of 15 mg or 30 mg daily for 240 weeks.

Upadacitinib is not licensed in the EU for any other indications.

Upadacitinib is also in phase II and phase III development for the following conditions:[1]

- Ulcerative colitis
- Psoriatic arthritis
- Atopic dermatitis
- Crohn's disease
- Giant cell arteritis
- Ankylosing spondylitis

INNOVATION and/or ADVANTAGES

For RA patients who have responded inadequately to biologic therapies, treatment options are extremely limited and there is a high unmet medical need.[8] The European League Against Rheumatism indicate that JAK inhibitors could be used earlier in the treatment pathway of RA.[9,10] Therefore if licensed, upadacitinib will offer an additional treatment for those with moderate to severe active rheumatoid arthritis who have failed conventional synthetic DMARDs or biologic DMARDs.

DEVELOPER

AbbVie Ltd

PATIENT GROUP

BACKGROUND

Rheumatoid arthritis (RA) is a chronic, inflammatory, multi-system, progressive autoimmune disease affecting the synovial joints, typically the small joints of the hands and feet, which are often affected bilaterally and symmetrically. Clinical features of RA include joint pain (usually worse after periods of rest or inactivity), joint swelling, stiffness and loss of function. On palpation, affected joints are tender, warm and give a 'boggy' feel. Extra-articular presentations may include lymphadenopathy, rheumatoid nodule (occurring over extensor surfaces in 20-30% people with RA), cardiopulmonary disease (e.g. pleurisy, intrapulmonary nodules, diffuse interstitial fibrosis and atherosclerosis), eye disease (including keratoconjunctivitis, dry eyes/sicca, episcleritis and corneal ulcerations) and rheumatoid vasculitis (typically ischaemic mononeuropathy and progressive scleritis).[11] Systemic features include morning stiffness, malaise, fatigue, fever and weight loss. Symptoms may be insidious, palindromic (waxing and waning) or explosive in onset. Rarely, patients may present with fever, joint pain or weight loss. Risk factors for RA include a genetic predisposition, which is oligogenic (including the shared epitope on chromosome 6), and environmental triggers, including smoking in susceptible individuals.[12]

The severity of the disease is measured using the composite disease activity score (DAS28), which consists of the assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein. DAS28 <3.2 indicates low disease activity, DAS28 ≥3.2 and ≤5.1 indicates moderate activity, and DAS28 >5.1 indicates high activity.[13] Additionally the severity of RA can be defined by the stage of disease. As the disease progresses beyond the early stage (stage I), there is a spread of inflammation in synovial tissue, affecting joint cavity space across joint cartilage. This inflammation gradually results in cartilage destruction, accompanied by a narrowing of the joint, and characterises stage II or moderate RA. Severe RA (stage III) is marked by formation of pannus in the synovium and loss of joint cartilage which exposes bone beneath the cartilage. These joint changes and deformities become evident on x-ray. Stage IV is referred to as end stage RA during which the inflammatory process subsides and formation of fibrous tissue and/or deformity of the bone results in ceased joint function. This stage may be associated with formation of subcutaneous nodules.[14]

Without adequate treatment, at 20 years after diagnosis, more than 60% of patients with RA may develop significant functional impairment (stage III), including need of mobility aids, loss of ability for self-caring, and requirement of joint replacement.[10] The overall impact of RA is that it can lead to progressive disability and a decrease in quality of life and functional status,[15] resulting in overall impaired health-related quality of life, and loss of productivity and social functions.[16] Approximately one-third of people stop work within two years of onset, and after ten years, 30% of patients are considered severely disabled.[17,18] People with RA have reduced life expectancy and excess cardiovascular mortality.[19]

CLINICAL NEED and BURDEN OF DISEASE

The estimated prevalence of RA in England is 0.86%, equivalent to around 346,000 people.[20] The annual incidence of RA is 1.5 per 10,000 in males and 3.6 per 10,000 in females, which equates to

approximately 12,000 new diagnoses each year in the UK.[14] Peak age of onset is 40-70 years and the disease is severe in around 15% of patients.[13] Around 10% of patients with RA (approximately 34,600 people) are eligible to receive current available biological treatments after the failure of conventional DMARDs.[14] In 2015-16, there were 61,142 admissions for RA (ICD-10 M06) in England resulting in 62,315 finished consultant episodes and 19,021 bed days.[21]

There is a 47% increased risk of death compared to the general population in patients with RA. Additionally 31% of early deaths in those with RA are due to cardiovascular disease, and a further 29% of all deaths are caused by pulmonary problems.[22] In 2015, 858 deaths from RA (and juvenile arthritis) were registered in England and Wales.[23]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Tofactinib for moderate to severe rheumatoid arthritis (TA480). October 2017.
- NICE technology appraisal. Baricitinib for moderate to severe rheumatoid arthritis (TA466). August 2017.
- NICE technology appraisal. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (TA415). October 2016.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375) January 2016.
- NICE technology appraisal. Tocilizumab for the treatment of rheumatoid arthritis (TA247). February 2012.
- NICE technology appraisal. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (TA225). June 2011.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195). August 2010.
- NICE technology appraisal. Certolizumab pegol for the treatment of rheumatoid arthritis (TA186). February 2010.
- NICE quality standards. Quality standard for rheumatoid arthritis (QS33). June 2013.
- NICE clinical guidelines. Rheumatoid arthritis in adults (CG79). February 2009. [updated December 2015]

NHS ENGLAND and POLICY GUIDANCE

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

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis. (123). 2011.

- American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. 2015
- European League Against Rheumatism (EULAR). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. 2017

CURRENT TREATMENT OPTIONS

RA is currently incurable; however, symptoms can usually be managed. The goal of management is to suppress disease, control pain, reduce functional limitation, reduce risk of permanent joint damage and achieve clinical remission. The clinical management of RA includes physical therapy, surgical interventions and a range of pharmacological treatments.[15] The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend targeting inducement of remission or low disease activity.

Joint damage, which may begin early in the disease course, is shown to have high correlation with impaired physical function and long-term disability. With a modern strategy of early treatment, slowing or halting the progression of underlying joint damage is usually achievable. Not all patients respond to current biologic or small molecule DMARDs and some patients may experience loss of efficacy or require discontinuation of therapy due to adverse events (AEs), which emphasises the need for additional or alternative treatment options. There is an unmet need for alternative treatment options for a subgroup of around 10-15% of patients who are unresponsive to, or intolerant of all existing treatment options.[24]

There are three main types of pharmacological therapies for RA, including;,[14, 15, 16, 25]

1. Non-biologic therapies:

- Corticosteroids.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Cyclo-oxygenase-2 (COX-2) inhibitors.
- Conventional DMARDs: e.g. methotrexate, sulfasalazine, leflunomide and azathioprine (first line treatment). Usually administered within three months of diagnosis, either as combination therapy (methotrexate and at least one other conventional DMARD) or as monotherapy (when combination therapy is deemed inappropriate).

2. Biologic DMARDs:

- TNF-α inhibitors: e.g. etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. TNFα inhibitors work by modulating a key costimulatory signal required for full activation of T lymphocytes expressing CD28.
- IL-6 inhibitors: IL-6 inhibitor, tocilizumab, is currently recommended for use in combination with methotrexate for patients with RA with a DAS28 score >5.1 after failure of at least two conventional DMARDs, including methotrexate.
- Abatacept

If methotrexate is unsuitable, treatment with biologic DMARDs may be used as monotherapy. However, amongst patients who have responded to TNF-α inhibitors, a significant number of patients discontinue therapy over time due to loss of efficacy, intolerance or AEs. In a systematic study of European registries, after 5-years pooled drug survival rates of TNF-α inhibitors were 37-52%

depending on the TNF-α inhibitor. In patients receiving TNF-α inhibitors, switching to an IL-6 inhibitor may be more effective than switching to a second (or third) anti-TNF-α.

Rituximab in combination with methotrexate is recommended for patients with severe active RA who have had an inadequate response to, or are intolerant of other DMARDs, including at least one TNF-α inhibitor. Where rituximab is unsuitable or ineffective, biologic DMARDs may be used in combination with methotrexate or as monotherapies.

3. Targeted synthetic DMARDs:

- Baricitinib in combination with methotrexate, is recommended as an option for treating severe (DAS28 >5.1) active RA in adults whose disease has responded inadequately to intensive therapy with conventional DMARDS), if the company provides baricitinib with the discount agreed in the patient access scheme. Additionally baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, with treatment continued only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy.
- Tofacitinib in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs, if the disease is severe (a disease activity score [DAS28] of more than 5.1) and the company provides tofacitinib with the discount agreed in the patient access scheme. Tofacitinib in combination with methotrexate, is also recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot have, other DMARDs, including at least 1 biological DMARD, only if disease is severe (a DAS28 of more than 5.1) and they cannot have rituximab. Additionally tofactinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, with treatment continued only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy.

EFFICACY and SAFETY	
Trial	SELECT-EARLY; NCT02706873; upadacitinib (dose A) vs upadacitinib (dose B) vs methotrexate; phase III
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl UK), USA and other countries
Design	Randomised, double blind, active-controlled study

Participants	n=975 (planned); aged ≥18 years old; rheumatoid arthritis patients who are naïve to methotrexate or, if already on it, have received no more than 3 weekly methotrexate doses with requirement to complete a 4-week methotrexate washout before the first dose of study drug; those with prior exposure to conventional synthetic DMARDs other than methotrexate may be enrolled if completed the washout period
Schedule	Randomised to upadacitinib dose A once daily monotherapy and methotrexate matching placebo orally once weekly; or upadacitinib dose B once daily monotherapy and methotrexate matching placebo orally once weekly; or active comparator methotrexate orally once weekly and upadacitinib matching placebo orally once daily.
Follow-up	The study had an active treatment period of 52 weeks.
Primary Outcomes	Proportion of participants achieving American College Rheumatology (ACR) 50 response Proportion of subjects achieving clinical remission (CR) based on Disease Activity 28 (DAS28) C-Reactive Protein (CRP)
Secondary Outcomes	Change in modified Total Sharp Score (mTSS) Change in DAS28 CRP ACR70 response rate Change in Health Assessment Questionnaire Disability Index (HAQ-DI) ACR20 response rate Change in Short Form-36 Physical Component Score Proportion of subjects achieving low disease activity Proportion of subjects with no radiographic progression
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date March 2021.

Trial	SELECT-BEYOND; NCT02706847; upadacitinib (dose A) vs upadacitinib (dose B) vs placebo followed by upadacitinib dose A vs placebo followed by upadacitinib dose B; phase III
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[3] Press release[8]
Location	EU (incl UK), USA and other countries

Design	Randomised, double blind, active comparator study
Participants	n=648 (planned); aged ≥18 years old; rheumatoid arthritis patients who have been on oral or parenteral methotrexate therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to first dose of study drug; must have discontinued all conventional synthetic DMARDs (other than MTX) ≥ 4 weeks prior to first dose of study drug.
Schedule	Randomised to upadacitinib dose A once daily for 240 weeks; upadacitinib dose B once daily for 240 weeks; methotrexate for 14 weeks followed by upadacitinib dose A for 226 weeks; methotrexate for 14 weeks followed by upadacitinib dose B for 226 weeks
Follow-up	Active treatment period of 240 weeks
Primary Outcomes	Proportion of participants achieving American College of Rheumatologist (ACR) 20 response Low disease activity (LDA) based on Disease Activity Score (DAS) 28 C-Reactive protein
Secondary Outcomes	Change in DAS28 (CRP) Change in Heath Assessment Questionnaire and Disability Index (HAQ-DI) ACR50 response rate ACR70 response rate Change in Short Form-36 (SF-36) Physical Component Score Proportion of participants achieving clinical remission (DAS28 [CRP] < 2.6) Change from baseline in morning stiffness (severity)
Key Results	Results showed that after 12 weeks of treatment, both once-daily doses of upadacitinib (15 mg and 30 mg) met the study's primary endpoints of ACR20* and low disease activity (LDA)**.1 All ranked secondary endpoints were also achieved with both doses. Both doses achieved low disease activity in over 40 percent of patients at week 12 and over 50 percent of patients at week 24.
Adverse effects (AEs)	In this study, the safety profile of upadacitinib was consistent with previously reported Phase 2 trials and the Phase 3 SELECT-NEXT clinical trial.1-4 No new safety signals were detected.1 During the placebo-controlled period, serious adverse events occurred in 5/7/0 percent of patients in the 15 mg/30 mg/placebo groups, respectively.1 There were two deaths reported during the study
Expected reporting date	Estimated study completion date August 2020.

Trial	SELECT-MONOTHERAPY; NCT02706951; upadacitinib (dose A) vs upadacitinib (dose B) vs placebo followed by upadacitinib dose A vs placebo followed by upadacitinib dose B; phase III
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (not incl UK), USA and other countries
Design	Randomised, double blind, active-controlled study
Participants	n=648 (planned); aged ≥18 years old; rheumatoid arthritis patients who have been on oral or parenteral methotrexate therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to first dose of study drug; must have discontinued all conventional synthetic DMARDs (other than MTX) ≥ 4 weeks prior to first dose of study drug.
Schedule	Randomised to upadacitinib dose A once daily for 240 weeks; upadacitinib dose B once daily for 240 weeks; methotrexate for 14 weeks followed by upadacitinib dose A for 226 weeks; methotrexate for 14 weeks followed by upadacitinib dose B for 226 weeks
Follow-up	Active treatment period of 240 weeks
Primary Outcomes	Proportion of participants achieving American College of Rheumatologist (ACR) 20 response Low disease activity (LDA) based on Disease Activity Score (DAS) 28 C-Reactive protein
Secondary Outcomes	Change in DAS28 (CRP) Change in Heath Assessment Questionnaire and Disability Index (HAQ-DI) ACR50 response rate ACR70 response rate Change in Short Form-36 (SF-36) Physical Component Score Proportion of participants achieving clinical remission (DAS28 [CRP] < 2.6) Change from baseline in morning stiffness (severity)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date October 2020
Trial	SELECT-NEXT; NCT02675426; upadacitinib (dose A) vs upadacitinib (dose B) vs upadacitinib (dose A) followed by placebo vs upadacitinib (dose B) followed by placebo; phase III
Sponsor	AbbVie Ltd
Status	Complete
Source of Information	Trial registry[5]

Location	EU (incl UK), USA and other countries
Design	Randomised, double blind, placebo-controlled study
Participants	n=600 (planned); aged ≥18 years old; rheumatoid arthritis ≥ 3 months, receiving conventional synthetic DMARD (csDMARD) therapy for ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug; subjects with prior exposure to at most one biologic DMARD (bDMARD) may be enrolled (up to 20% of study population) if they have documented evidence of intolerance to bDMARDs or limited exposure (less than 3 months) and have satisfied required washout periods
Schedule	Randomised to upadacitinib dose A once daily for 12 weeks (and up to an additional 5 years); upadacitinib dose B once daily for 12 weeks weeks (and up to an additional 5 years); placebo comparator once daily for 12 weeks followed by upadacitinib dose A once daily for up to an additional 5 years; placebo comparator once daily for 12 weeks followed by upadacitinib dose B once daily for up to an additional 5 years
Follow-up	Period 1: 12 weeks and period 2: up to 5 years
Primary Outcomes	Proportion of participants achieving American College of Rheumatologist (ACR) 20 response Low disease activity (LDA) based on Disease Activity Score (DAS) 28 C-Reactive protein
Secondary Outcomes	Change in DAS28 (CRP) Change in Heath Assessment Questionnaire and Disability Index (HAQ-DI) Change in Short Form-36 (SF-36) Physical Component Score Proportion of participants achieving clinical remission (DAS28 [CRP] < 2.6) Change in functional assessment of chronic illness therapy (FACIT-F) Change from baseline in morning stiffness (severity) Low Disease Activity (LDA) (DAS28 [CRP] < 2.6) Low Disease Activity based on Clinical Disease Activity Index (CDAI < 10)
Key Results	Results at week 12 showed that of patients receiving a 15 mg or 30 mg oral, once-daily dose of upadacitinib, 64 percent and 66 percent achieved ACR20, respectively, compared to 36 percent of patients receiving placebo.1 Patients receiving upadacitinib achieved ACR50 responses of 38 percent and 43 percent in the 15 mg and 30 mg groups, respectively, compared to 15 percent of patients receiving placebo. ACR70 responses were achieved by 21 percent and 27 percent of patients in the 15 mg and 30 mg groups, respectively, compared to 6 percent of patients receiving placebo.1 Low disease activity was achieved by 48 percent of patients receiving either dose of upadacitinib,

	compared to 17 percent of patients receiving placebo.1 Additionally, clinical remission was achieved by 31 percent and 28 percent of patients receiving 15 mg or 30 mg of upadacitinib, respectively, compared to 10 percent receiving placebo.1 All primary and key secondary endpoints achieved p-values of <0.001 versus placebo for both doses.[a]
Adverse effects (AEs)	Serious adverse events were 4 percent and 3 percent in the 15 mg and 30 mg dose arms, respectively, compared to 2 percent in placebo. No deaths were reported
Expected reporting date	-

Trial	SELECT-COMPARE; NCT02629159**;** upadacitinib vs adalimumab vs placebo followed by upadacitinib
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[6]
Location	EU (incl UK), USA and other countries
Design	Randomised, double blind study
Participants	n=1500 (planned); aged ≥18 years old; rheumatoid arthritis ≥ 3 months; patients who have been on oral or parenteral methotrexate therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to first dose of study drug; must have discontinued all conventional synthetic DMARDs (other than MTX) ≥ 4 weeks prior to first dose of study drug.
Schedule	Randomised to upadacitinib once daily; placebo comparator once every two weeks for subcutaneous injection and once daily for oral tablet for 26 weeks, followed by upadicitinib once daily for up to 5 years; adalimumab subcutaneous injection every two weeks
Follow-up	Active treatment period 1: 48 weeks and period 2: up to 5 years
Primary Outcomes	Proportion of participants achieving American College of Rheumatologist (ACR) 20 response Proportion of patients achieving clinical remission (CR) based on DAS28 (CRP< 2.6)
Secondary Outcomes	Change in DAS28 (CRP) Change in modified Total Sharp Score (mTSS) Change in Heath Assessment Questionnaire and Disability Index (HAQ-DI) ACR50 response rate ACR70 response rate Change in Short Form-36 (SF-36) Physical Component Score

[a] Company information

	Change in functional assessment of chronic illness therapy (FACIT-F) Change in Work Instability Score for Rheumatoid Arthritis (RA-WIS) Change from baseline in morning stiffness (severity) Proportion of patients achieving Low Disease Activity (LDA) Proportion of patients with no radiographic progression Low disease activity (LDA) based on Disease Activity Score (DAS) 28 C-Reactive protein
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date Jan 2021

Trial	SECLECT-CHOICE; NCT03086343; upadacitinib vs abatacept followed by upadacitinib
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[7]
Location	EU (incl UK), USA and other countries
Design	Randomised, double blind, active-controlled
Participants	n=550 (planned); aged ≥18 years old; rheumatoid arthritis ≥ 3 months, treated with 1 bDMARD for ≥ 3 months but continue to exhibit RA or had to discontinue
Schedule	Upadicitinib once daily for 24 weeks during period 1 and up to 5 years during period 2; Abatecept IV infusion at baseline, week 2, 4, 8, 12, 16, and 20 followed by upadicitinib starting at week 24 up to 5 years
Follow-up	Active treatment period: 24 weeks
Primary Outcomes	Change in Disease Activity Score (DAS) 28 C-Reactive Protein (CRP) (non-inferiority)
Secondary Outcomes	Change in Disease Activity Score (DAS) 28 C-Reactive Protein (CRP) (superiority) Proportion of patients achieving clinical remission (CR) based on DAS28 (CRP< 2.6)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date July 2019

ESTIMATED COST and IMPACT

COST

The cost of upadacitinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☒ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1]GlobalData. *Upadacitinib.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=249319 [Accessed 30 October 2017]

[2]ClinicalTrials.gov. *A Study to Compare ABT-494 Monotherapy to Methotrexate Monotherapy in Subjects With Rheumatoid Arthritis (RA) Who Have Not Previously Taken Methotrexate (SELECT-EARLY).* Available from: https://clinicaltrials.gov/ct2/show/NCT02706873 [Accessed 30 October 2017]

[3]ClinicalTrials.gov. *A Study to Compare ABT-494 to Placebo in Subjects With Rheumatoid Arthritis on Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response or Intolerance to Biologic DMARDs (SELECT-BEYOND).* Available from: https://clinicaltrials.gov/ct2/show/NCT02706847 [Accessed 30 October 2017]

[4]ClinicalTrials.gov. *A Study Comparing ABT-494 Monotherapy to Methotrexate (MTX) Monotherapy in Subjects With Rheumatoid Arthritis (RA) Who Have an Inadequate Response to MTX (SELECT-MONOTHERAPY).* Available from: https://clinicaltrials.gov/ct2/show/NCT02706951 [Accessed 30 October 2017]

[5]ClinicalTrials.gov. *A Study Comparing ABT-494 to Placebo in Subjects With Rheumatoid Arthritis on a Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response to csDMARDs Alone (SELECT-NEXT).* Available from: https://clinicaltrials.gov/ct2/show/NCT02675426 [Accessed 23 November 2017]

[6]ClinicalTrials.gov. *A Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects With Rheumatoid Arthritis Who Are on a Stable Dose of Methotrexate and Who Have an Inadequate Response to Methotrexate (SELECT-COMPARE).* Available from: https://clinicaltrials.gov/ct2/show/NCT02629159 [Accessed 23 November 2017]

[7]ClinicalTrials.gov. *A Phase 3 Study to Compare Upadacitinib to Abatacept in Subjects With Rheumatoid Arthritis on Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response or Intolerance to Biologic DMARDs (SELECT-CHOICE).* Available from: https://clinicaltrials.gov/ct2/show/NCT03086343 [Accessed 23 November 2017]

[8]AbbVie. *Pressroom.* Available from: https://news.abbvie.com/news/abbvies-upadacitinib-abt-494-meets-all-primary-and-ranked-secondary-endpoints-in-second-phase-3-study-in-rheumatoid-arthritis.htm [Accessed 30 October 2017]

[9]GlobalData. *PharmaPoint: Rheumatoid Arthritis – Global Drug Forecast and Market Analysis to 2025.* Avaialble from: https://pharma.globaldata.com/Reportsview.aspx?DocID=51426 [Accessed 30 October 2017]

[10]Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Annals of the rheumatic diseases.* 2017 Jun 1;76(6):960-77.

[11]Johns Hopkins Arthritis Center. *Rheumatoid Arthritis Signs and Symptoms.* Available from: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-symptoms/. [Accessed 30 October 2017]

[12]NIHR Horizon Scanning Research & Intelligence Centre. *Masitinib for rheumatoid arthritis – second and subsequent line*. Available from: www.hsc.nihr.ac.uk [Accessed 30 October 2017]

[13]National Institute of Health and Care Excellence. Committee papers: Baricitinib for treating moderate to severe rheumatoid arthritis. Technology appraisal TA466. London NICE; August 2017.

[14]Rheumatoid Arthritis.net. *Understanding RA Stages and Progression*. Available from: https://rheumatoidarthritis.net/what-is-ra/stages-and-progression/ [Accessed 30 October 2017]

[15]Singh JA, Beg S and Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2010; doi: 10.1002/14651858.CD008331.pub2.

[16]Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis. National clinical guideline 123. Edinburgh: SIGN; February 2011.

[17]National Institute for Health and Care Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. Technology appraisal TA195. London: NICE; August 2010

[18]National Institute for Health and Care Excellence. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. Clinical guideline CG79. London: NICE; February 2009

[19]Goodson N, Marks J, Lung M et al. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Annals of Rheumatic Disease* 2005;65:1595-1601.

[20]National Institute for Health and Clinical Excellence. Costing statement: golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. London: NICE; June 2011.
[21]Health and Social Care Information Centre. Hospital Episodes Statistics for England. Inpatient statistics 2015-16. http://www.hscic.gov.uk/
[22]Arthritis Research UK. *State of musculoskeletal health 2017.* Available from: https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/state-of-musculoskeletal-health.aspx [Accessed 30 October 2017]
[23]Office for National Statistics. Death Registrations Summary Tables - England and Wales, 2015. www.ons.gov.uk
[24]Kinet JP. The essential role of mast cells in orchestrating inflammation. *Immunological Reviews* 2007; 217:5-7
[25]National Institute of Health and Care Excellence. Baricitinib for treating moderate to severe rheumatoid arthritis. Technology appraisal TA466. London NICE; August 2017.