NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Filgotinib for moderate to severe rheumatoid arthritis

1 Recommendations

1.1 Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a 2 or more conventional disease-modifying antirheumatic drugs (DMARDs), only if:

- disease is moderate or severe (a disease activity score [DAS28] of 3.2 or more) and
- the company provides filgotinib according to the commercial arrangement (see section 2).

1.2 Filgotinib, with methotrexate, is 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 and
- the company provides filgotinib according to the commercial arrangement (see section 2).

1.3 Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if:

- disease is severe (a DAS28 of more than 5.1) and

- the company provides filgotinib according to the commercial arrangement (see section 2).

1.4 Filgotinib can be used as monotherapy when methotrexate is contraindicated or if people cannot tolerate it, when the criteria in sections 1.1, 1.2 or 1.3 are met.

1.5 Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary from person to person because of differences in how the drugs are taken and treatment schedules.

1.6 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. If this initial response is not maintained at 6 months, stop treatment.

1.7 When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.

1.8 These recommendations are not intended to affect treatment with filgotinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with severe rheumatoid arthritis have a number of advanced treatment options (biological and targeted synthetic DMARDs) available to them if their disease has not responded well enough to 2 or more conventional DMARDs. These advanced treatment options are currently not available for people with moderate rheumatoid arthritis.

Clinical trials show that filgotinib with methotrexate or other conventional DMARDs is more effective than adalimumab with methotrexate or methotrexate alone for treating moderate to severe rheumatoid arthritis that has not responded well enough to 2 or more conventional DMARDs. It is also more effective than conventional DMARDs alone for treating moderate to severe active rheumatoid arthritis that has not responded well enough to 1 or more biological DMARDs.

There are no trials comparing filgotinib with the full range of biological and targeted synthetic DMARDs in severe disease. However, an indirect comparison shows that filgotinib with conventional DMARDs (including methotrexate) works as well as the biological and targeted synthetic DMARDs recommended by NICE.

The most likely cost-effectiveness estimates show that filgotinib with methotrexate is an acceptable use of NHS resources for some people with moderate and severe rheumatoid arthritis (see sections 1.1 to 1.3).

The cost effectiveness of filgotinib monotherapy is more uncertain but is still likely to be within what NICE considers an acceptable use of NHS resources, therefore it is recommended.

2 Information about filgotinib

Marketing authorisation indication

2.1 Filgotinib (Jyseleca, Gilead) is 'indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to 1 or more disease-modifying anti-rheumatic drugs (DMARDs). Filgotinib may be used as monotherapy or in combination with methotrexate'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for filgotinib is £863.10 per bottle of 30-day pack (company submission). The average cost for each patient per year is estimated at £10,508 based on the list price. The company has a commercial arrangement (simple discount patient access scheme). This makes filgotinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Gilead, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved or partially resolved during the technical engagement stage:

- Using direct head-to-head trial data from the overall moderate population to model the efficacy of filgotinib in people with moderate rheumatoid arthritis
- Modelling the efficacy of best supportive care based on the placebo plus methotrexate arm of the FINCH1 trial
- Using the company's approach to utility values, that is, estimating pain scores from Health Assessment Questionnaire Disability Index (HAQ-DI).

However, the committee discussed these issues further. Also, after technical engagement, there were a number of outstanding uncertainties in the analyses. The committee considered these in its decision making.

Treatments for rheumatoid arthritis

Additional treatment options for rheumatoid arthritis are important, especially for moderate disease

3.1 The patient expert explained that rheumatoid arthritis is a lifetime condition that has a large effect on mental and physical health and emotional wellbeing, causing fear, anxiety, stress, pain and fatigue. It can severely reduce quality of life and affect ability to work, everyday activities and relationships with children and other family members. The clinical expert stated that conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are inadequate for many people with active rheumatoid arthritis. Although a range of biological and targeted synthetic DMARDs are available for severe rheumatoid arthritis (see section 3.2), none of these treatments are currently available for people with moderate disease activity. Patient experts explained that currently people with moderate disease activity that has not responded adequately to conventional DMARDs have no effective treatment options. They feel that their disease needs to get worse before they can be offered effective treatments. They explained that progression in rheumatoid arthritis is relentless if not adequately treated. The clinical expert also added that for a significant proportion of people with severe disease who are eligible for treatment with biological DMARDs, their disease responds inadequately to these treatments, or they cannot tolerate the treatment. Both the clinical and patient experts said it would be helpful to have new treatments for various points in the treatment pathway. Clinical and patient experts also said that an oral drug taken daily may be preferable, especially for patients who are needle phobic or who have a significant hand disability. The committee concluded that a range of treatment options was important in rheumatoid arthritis and that filgotinib would be a welcome additional option, especially for moderate disease.

There is NICE technology appraisal guidance for different points in the severe rheumatoid arthritis treatment pathway

3.2 Disease severity is assessed using the disease activity score (DAS28). A DAS28 of more than 5.1 indicates severe disease, between 3.2 and 5.1 indicates moderate disease, between 2.6 and 3.2 indicates mild disease, and 2.6 or less indicates disease remission. The NICE pathway on drug treatments for rheumatoid arthritis summarises NICE technology appraisal guidance which currently recommends the following biological and targeted synthetic DMARDs, all with methotrexate, for severe active rheumatoid arthritis that has responded inadequately to:

- intensive treatment with a combination of conventional DMARDs (that is, responded inadequately to 2 or more conventional DMARDs): adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept, tofacitinib, baricitinib, sarilumab and tocilizumab
- at least 1 TNF-alpha inhibitor: rituximab
- at least 1 biological DMARD and rituximab is contraindicated or not tolerated: adalimumab, etanercept, infliximab, abatacept, certolizumab pegol, golimumab, tofacitinib, baricitinib, sarilumab and tocilizumab
- at least 1 biological DMARD and to rituximab: sarilumab and tocilizumab.

Of these, adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are tumour necrosis factor (TNF)-alpha inhibitors. Tofacitinib and baricitinib are Janus kinase (JAK) inhibitors and sarilumab and tocilizumab are interleukin-6 (IL-6) inhibitors. For people who cannot take methotrexate because it is contraindicated or because they cannot tolerate it, adalimumab, baricitinib, certolizumab pegol, etanercept, tofacitinib, sarilumab and tocilizumab can be used alone. Treatment should start with the least expensive drug (taking into account administration costs, dose needed and product price per dose). It should only be continued if there is a moderate response using European League

Against Rheumatism (EULAR) criteria at 6 months, and should be stopped if at least a moderate EULAR response is not maintained.

In moderate disease, the most appropriate position for filgotinib is after an inadequate disease response to 2 or more conventional DMARDs

3.3 Filgotinib's marketing authorisation covers its use in people with moderate rheumatoid arthritis whose disease has responded inadequately to 1 or more conventional DMARDs. However, the company's submission covers filgotinib's use in moderate rheumatoid arthritis for people whose disease has responded inadequately to 2 or more conventional DMARD. The committee agreed with the company's positioning of filgotinib in moderate disease. It noted such positioning is aligned with the use of biologic and targeted synthetic DMARDs in severe disease. The clinical expert explained that people whose disease has an inadequate response to 2 or more conventional DMARDs are usually offered continued treatment with the same conventional DMARDs. Corticosteroids can be used to manage disease flares. The committee concluded that the appropriate position for filgotinib in moderate disease is after inadequate response to 2 or more conventional DMARDs. It also agreed that the relevant comparator for this population is best supportive care, consisting of previously used conventional DMARDs with optional corticosteroids.

In severe disease, filgotinib could be used at all 4 different points in the treatment pathway, with multiple comparators at each point

3.4 Filgotinib's marketing authorisation and the company's submission cover its use at all 4 points in the severe disease treatment pathway for which other biologic and targeted synthetic DMARDs are recommended (see section 3.2). The committee agreed with this positioning. It noted that the marketing authorisation includes the use of filgotinib alone or with methotrexate. The committee agreed that all treatments listed in section 3.2, all used with methotrexate, are relevant comparators for filgotinib with methotrexate, when used at the same position in the treatment pathway. For people who cannot have methotrexate, relevant comparators for

filgotinib monotherapy are adalimumab, baricitinib, certolizumab pegol, etanercept, tofacitinib, sarilumab and tocilizumab, depending on the position in the treatment pathway.

Clinical effectiveness

The clinical trials are acceptable for decision making but do not include all relevant comparators for severe disease

3.5 The company's clinical evidence came from 2 randomised controlled trials in people with moderate to severe rheumatoid arthritis:

- FINCH1 enrolled patients with inadequate disease response to methotrexate. A total of 24% of patients had moderate disease, and 76% had severe disease. Filgotinib was used with methotrexate and the comparators were adalimumab with methotrexate or placebo with methotrexate.
- FINCH2 enrolled people with inadequate disease response to at least 1 biological DMARD. A total of 21% of patients had moderate disease and 79% had severe disease. Filgotinib was used with conventional DMARDs and the comparator was placebo with conventional DMARDs.

The committee concluded that the trials were relevant and acceptable for decision making but did not include all relevant comparators for severe disease (see section 3.2).

For moderate to severe disease that has responded inadequately to conventional DMARDs, filgotinib with methotrexate is more clinically effective than adalimumab with methotrexate or placebo with methotrexate

3.6 In FINCH1, filgotinib with methotrexate showed a statistically significant improvement in the primary endpoint, American College of Rheumatology responses (ACR20) at 12 weeks, compared with adalimumab with methotrexate or placebo with methotrexate (76.6% compared with 70.5% and 49.9%, respectively, $p < 0.05$ for both comparisons). Filgotinib also

showed improvement in key secondary endpoints at both 12 and 24 weeks, including ACR50, ACR70 or EULAR responses. The committee concluded that filgotinib with methotrexate was more clinically effective than adalimumab with methotrexate or placebo with methotrexate in people with moderate to severe disease that has responded inadequately to conventional DMARDs.

For moderate to severe disease that has responded inadequately to biological DMARDs, filgotinib with conventional DMARDs is more clinically effective than placebo with conventional DMARDs

3.7 In FINCH2, filgotinib with conventional DMARDs showed a statistically significant improvement in the primary outcome, ACR20 at 12 weeks, compared with placebo with conventional DMARDs (66.0% compared with 31.1%, $p < 0.05$). Filgotinib also showed improvement in key secondary endpoints at both 12 and 24 weeks, including ACR50, ACR70 or EULAR responses. The committee concluded that filgotinib with conventional DMARDs was more clinically effective than placebo with conventional DMARDs in people with moderate to severe disease that has responded inadequately to biological DMARDs.

The clinical efficacy of filgotinib monotherapy is uncertain

3.8 FINCH1 and FINCH2 trials included filgotinib only with methotrexate or with conventional DMARDs, respectively. Therefore, no clinical efficacy data are available for filgotinib monotherapy in people with moderate to severe disease that has responded inadequately to conventional or biological DMARDs. The clinical expert explained that in the FINCH3 trial, which enrolled people who had not previously had methotrexate (that is, methotrexate-naive population), filgotinib monotherapy showed improved clinical outcomes compared with placebo. The committee noted that all biological and targeted synthetic DMARDs are recommended with methotrexate, unless methotrexate is contraindicated. This is because combination therapy is thought to be more clinically effective than monotherapy. The committee concluded that the clinical efficacy of

filgotinib monotherapy is uncertain because there is no clinical trial data in the target population.

Direct and indirect comparisons

Network meta-analyses show that filgotinib with conventional DMARDs works as well as other biological and targeted synthetic DMARDs

3.9 A direct comparison was only possible with adalimumab and placebo, informed by FINCH1 and FINCH2 trials. To compare with other biological and targeted synthetic DMARDs, the company did 2 network meta-analyses for:

- people whose disease responded inadequately to 2 or more conventional DMARDs,
- people whose disease responded inadequately to 1 or more biological DMARDs.

The results showed that for both populations, filgotinib gave similar EULAR response rates to other biological and targeted synthetic DMARDs. Filgotinib also gave better EULAR response rates than conventional DMARDs alone (the exact rates are confidential and cannot be reported here). However, the committee noted several limitations of the network meta-analyses:

- They contained a mixed population of people with moderate and severe rheumatoid arthritis. Separate network meta-analyses for people with moderate and severe disease were not possible because most trials did not report efficacy results by disease severity.
- They relied on EULAR responses mapped from ACR responses. This was because most trials did not report EULAR responses.
- They assumed that the same treatment effect applied regardless of the position in the treatment pathway. This does not reflect clinical practice because treatments used later in the treatment pathway are likely to have a lower response rate.

- The company assumed equal efficacy of filgotinib monotherapy and combination therapy (with methotrexate or conventional DMARDs). This was because no clinical trial data exists to inform efficacy of filgotinib monotherapy in the target population (see section 3.8).
- They excluded potentially relevant studies. The ERG explained that the company excluded studies published before 1999, and studies for monotherapies.

The committee agreed that for severe disease, there was limited direct trial evidence. Therefore, it accepted the network meta-analyses for decision making, bearing in mind their limitations. It agreed that using data from the moderate to severe population was appropriate to inform efficacy estimates for the severe population, because this was aligned with populations in other studies included in the network meta-analysis. The committee accepted that, in the absence of data, the efficacy of filgotinib combination therapy may be used as a proxy for the efficacy of filgotinib monotherapy, but noted this approach has limitations and could overestimate the efficacy of filgotinib monotherapy.

Direct head-to-head trial data is most appropriate to model efficacy of filgotinib and best supportive care in moderate rheumatoid arthritis

3.10 Although the network meta-analysis was used for decision making for people with severe disease (see section 3.8), the technical team noted that for moderate disease it may be more appropriate to use FINCH1 trial data because:

- the trial included all relevant comparators (with placebo plus methotrexate arm of the trial used as a proxy for best supportive care, see section 3.13)
- this avoids limitations associated with company network meta-analysis (see section 3.8)

- using direct head-to-head evidence is in line with NICE's guide to the methods of technology appraisal.

In response to technical engagement, the company used direct head-to-head trial data to inform the efficacy of filgotinib and best supportive care in the moderate population. The committee agreed with this approach, noting that the FINCH1 trial data were more appropriate for decision making for moderate disease than the network meta-analyses.

Data from the overall moderate population of FINCH1 trial is appropriate for decision making

3.11 The ERG explained that the FINCH1 trial enrolled people who had had 1 or more conventional DMARDs, and that about half the patients with moderate disease had only had 1 previous conventional DMARD. Therefore, FINCH1 data may not be generalisable to the target population (that is, after 2 or more previous conventional DMARDs). In response to technical engagement, the company provided pairwise comparisons of clinical efficacy data for patients with moderate disease who had had 1 previous conventional DMARD compared with those who had had 2 or more previous conventional DMARDs. The company highlighted that these are exploratory post-hoc analyses based on small patient numbers, and FINCH1 was not powered for such a comparison. However, the number of previous conventional DMARDs did not appear to have any notable effect on clinical efficacy estimates. The company also provided exploratory cost-effectiveness analyses for the population who had had 2 or more previous DMARDs. The committee considered all evidence provided by the company and concluded that using the overall moderate population from FINCH1 is more appropriate for decision making. It noted that this is preferred to using small post-hoc subgroup data.

EULAR data from the FINCH1 trial should be used when modelling the efficacy of filgotinib and best supportive care in the moderate population

3.12 The revised company submission used direct head-to-head trial data to model the efficacy of filgotinib (see section 3.10). The FINCH1 trial collected EULAR response data. However, the company mapped the EULAR responses from ACR responses. The ERG explained this approach was aligned with the approach taken for the severe population, but noted it preferred to use the EULAR responses from FINCH1 directly in the model. This is because using direct data gives more precise estimates of clinical efficacy than using mapped values. The committee agreed with the ERG that EULAR response should be used directly in the model, instead of the mapped values.

Modelling best supportive care in the moderate population

Using the placebo plus methotrexate arm of the FINCH1 trial to model the efficacy of best supportive care has limitations but is acceptable

3.13 The revised company base case modelled the efficacy of best supportive care based on the response rates seen in the placebo plus methotrexate arm of the FINCH1 trial. The clinical expert explained that best supportive care is not expected to give an EULAR response in clinical practice. However, the committee noted that a considerable response rate was seen in the placebo plus methotrexate arm of the FINCH 1 trial, as well as in other clinical trials in rheumatoid arthritis. It noted that this response could have been caused by several factors, including a placebo effect, disease resolving naturally over time, regression to the mean, response bias and variation in symptoms. Some of these factors might have also contributed to the response to filgotinib in the FINCH 1 trial. Therefore, the committee agreed it would not be appropriate to assume full clinical efficacy for filgotinib while assuming no response to best supportive care. It agreed with revised company analyses, which used FINCH1 response rates for both filgotinib with methotrexate and placebo plus methotrexate (a proxy for best supportive care). However, it acknowledged that these

analyses had limitations because they did not fully reflect what is expected to happen in clinical practice.

Comparators and treatment sequences for severe disease

The comparators and treatment sequences modelled by the company are sufficient for decision making

3.14 Rheumatoid arthritis is a heterogenous disease and treatment choices are influenced by many factors (see section 3.1). Because of the large number of possible treatment sequences, it was not practical to model them all. However, the clinical expert confirmed that the company model included the most relevant comparators and treatment sequences that are used in NHS clinical practice. One exception to that, noted by both clinical and patient experts, was that further advanced therapies would be used instead of best supportive care in clinical practice. The committee acknowledged this as a limitation but noted that this approach was aligned with previous NICE technology appraisals. It also noted that this is likely to have a limited effect on the cost-effectiveness estimates in severe disease, but could be important to consider for the moderate population in the treatment sequence upon progression to severe disease (see section 3.16).

Modelling progression from moderate to severe rheumatoid arthritis

The rate of progression from moderate to severe disease is uncertain but the company approach to model this is acceptable for decision making

3.15 In the revised company base case, the company used patients' mean baseline DAS28 and expected DAS28 trajectory, to estimate patients' progression from moderate to severe disease. Using this approach, the modelled progression rate with best supportive care was 11% at 2 years and 39% at 5 years. The clinical expert mentioned one study that reported

5% progression rate at 1 year. Another study (ERAN database) reported that 19% of people with moderate disease activity 1 year after diagnosis had severe disease activity at a 2-year visit. The committee noted this estimate may be uncertain because of small patient numbers in the registry and single assessment of disease activity at both timepoints (so results could be subject to temporary fluctuation in disease activity, including flares). It also noted no data were available to inform long-term progression rates. The clinical expert highlighted that although published data on the progression rates are lacking, the rates modelled by the company seem reasonable. The committee discussed that some patients could start treatment for severe disease when they have a flare that temporarily increases their disease activity to a severe level. This could mean that the initiation of severe treatment sequences in NHS clinical practice is higher than modelled by the company. The patient and clinical experts explained that a single flare would usually trigger a change of treatment (start of severe treatment sequence) only for patients with their usual disease activity in the higher end of the moderate disease activity range (that is, close to the severe disease activity level). However, such a change after a single flare was unlikely for patients with disease activity in the lower end of disease activity range. The committee agreed the rate of progression in NHS clinical practice is uncertain but noted that higher progression rates would result in lower incremental cost-effectiveness ratios (ICERs) for filgotinib compared with best supportive care. This was because with higher progression rates, quality-adjusted life years (QALYs) and costs are increasing in both treatment arms, but to a higher degree in the best supportive care arm. The committee concluded that although the rates of progression from moderate to severe disease in NHS clinical practice is uncertain, the company approach to model this is reasonable. It also noted that if the true rates of progression are higher than those estimated in the model, the cost-effectiveness estimates for filgotinib would improve.

Alternative treatment sequences after progression from moderate to severe disease are plausible

3.16 The committee recalled that rheumatoid arthritis is a heterogenous disease and it was not practical to model all possible treatment sequences (see sections 3.1 and 3.14). The clinical expert explained that generally, they would follow the standard treatment sequence for severe disease once patients' disease progresses to severe disease activity. This would generally be:

- for people who can have methotrexate: a TNF-alpha inhibitor, followed by rituximab and then by an IL-6 inhibitor (all given with methotrexate)
- for people who cannot have methotrexate: a TNF-alpha inhibitor, followed by IL-6 inhibitor (most frequently), abatacept, or rituximab (only in some trusts), and then a drug with an alternative mode of action (all given as monotherapy or with an alternative conventional DMARD).

The clinical expert explained that there was no evidence to suggest treatment for severe disease would change if filgotinib was used for moderate disease, except the lower likelihood of considering another JAK inhibitor. However, the committee recalled that an alternative treatment sequence was considered plausible in NICE's technology appraisal guidance on upadacitinib for previously treated moderate active rheumatoid arthritis. This is because JAK inhibitors (such as filgotinib) and IL-6 inhibitors are targeting a similar signalling pathway. Using a drug with a distinct mechanism of action, such as abatacept, instead of an IL-6 inhibitor could be preferred in people who have already had filgotinib for the moderate disease. However, the committee agreed this is uncertain and may depend on clinician and patient preferences. Clinical experts explained that filgotinib could be used after progression to severe disease, if it was not used for the moderate disease. However, the committee agreed not to consider this treatment sequence further because there is uncertainty about how filgotinib would be used in NHS practice. The

committee concluded that a range of treatment sequences for severe disease are plausible and agreed to consider them all (Table 1). It also agreed that there is even higher uncertainly about treatment sequences after progression when methotrexate is not suitable, and considered this in its decision making.

Table 1 Relevant treatment sequences for people whose disease progresses from moderate to severe disease and can have methotrexate

Scenario	Treatment arm	First-line treatment for severe disease	Second-line treatment for severe disease	Third-line treatment for severe disease
Base case	Filgotinib	Adalimumab	Rituximab	Tocilizumab
Base case	Best supportive care	Adalimumab	Rituximab	Tocilizumab
ERG scenario	Filgotinib	Etanercept	Rituximab	Tocilizumab
ERG scenario	Best supportive care	Etanercept	Rituximab	Tocilizumab
Scenario 1	Filgotinib	Adalimumab	Rituximab	Sarilumab
Scenario 1	Best supportive care	Adalimumab	Rituximab	Sarilumab
Scenario 2	Filgotinib	Adalimumab	Rituximab	Abatacept (subcutaneous)
Scenario 2	Best supportive care	Adalimumab	Rituximab	Tocilizumab (or sarilumab)
Scenario 3	Filgotinib	Adalimumab	Rituximab	Tocilizumab (or sarilumab)
Scenario 3	Best supportive care	Adalimumab	Rituximab	Baricitinib

Utility values

The company's mapping algorithm to link HAQ and pain scores is appropriate for decision making

3.17 In the company's base case, health-related quality-of-life data was mapped from patients' long-term HAQ-DI score trajectory using a published mapping algorithm. In addition to HAQ-DI, the algorithm used patients' current age, sex, and visual analogue scale pain scores to determine a utility value at any point in the model. In the company's base

case, the VAS pain scores were mapped from HAQ-DI as per NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. The ERG explained their initial concerns about the mapping algorithm, which seemed to provide distinct utility values than those based on EQ-5D data collected in the trial. However, in response to technical engagement, the company provided corrected validation of their mapping algorithm, using individual patient data. The ERG was satisfied that the QALY outputs are fairly similar using the 2 methods. Therefore, it agreed with the company's approach and followed it in the revised ERG base case. The committee noted this approach is consistent with a number of previous appraisals. It concluded that the company's approach may have limitations but is appropriate for decision making.

Cost-effectiveness results

Because of uncertainty in the cost-effectiveness estimates, an acceptable ICER is around £20,000 per QALY gained

3.18 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee concluded that the cost-effectiveness results for moderate disease were uncertain because:

- the response rates in the placebo arms of the trials did not reflect clinical practice. It is unlikely that a EULAR response would be seen after an inadequate response with 2 conventional DMARDs (see section **Error! Reference source not found.**)

- the long-term rate of progression from moderate to severe disease is uncertain (see section 3.15)
- there is uncertainty about the most appropriate treatment sequence for people whose disease progresses from moderate to severe disease state (see section 3.16).

Because of this uncertainty, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.

In moderate disease, filgotinib with methotrexate is cost effective after 2 or more conventional DMARDs

3.19 The committee noted that the revised company analyses applied the following committee preferences:

- FINCH1 trial data (whole moderate population) were used to model the efficacy of both filgotinib and best supportive care (see sections 3.10, 3.11 and 3.13).
- The modelled rate of progression was uncertain but was judged to be reasonable by the clinical expert (see section 3.15).
- A range of alternative treatment sequences were explored (see section 3.16).
- Mapping algorithm from NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed was used to estimate utility values (see section 3.17).

However, it noted that company analyses were based on EULAR responses mapped from ACR responses, instead of directly using EULAR responses from FINCH1 (see section 3.12). Therefore, the committee preferred to use the ERG analyses, which used trial-based EULAR responses. The ERG analyses also applied confidential discounts for treatments used after progression from moderate to severe disease. Because of these confidential discounts, exact ICERs are confidential and

cannot be reported here. The committee noted that all analyses with alternative treatment sequences produced ICERs around £20,000 per QALY gained for filgotinib with methotrexate compared with best supportive care. The only exception was a treatment sequence assuming filgotinib use in the comparator arms for patients who did not have it for moderate disease. But the committee recalled that it had agreed this sequence was less relevant to decision making (see section 3.16). The committee also recalled that although the exact rate of progression from moderate to disease severity in NHS clinical practice is uncertain, a higher rate of progression would improve cost-effectiveness estimates for filgotinib. The committee concluded that it could recommend filgotinib with methotrexate as a cost-effective use of NHS resources for people with moderate rheumatoid arthritis whose disease had responded inadequately to 2 or more conventional DMARDs.

In severe disease, filgotinib with methotrexate is cost effective after 2 or more conventional DMARDs

3.20 The ERG did analyses for people with severe rheumatoid arthritis whose disease had responded inadequately to 2 or more conventional DMARDs, applying confidential discounts for filgotinib, comparators and subsequent treatment options. Filgotinib with methotrexate provided a higher net health benefit (that is, was more cost effective) than alternative therapies used with methotrexate. Therefore, the committee concluded that it could recommend filgotinib with methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to 2 or more conventional DMARDs.

In severe disease, filgotinib with methotrexate is not cost effective after 1 or more biological DMARDs if rituximab is a treatment option

3.21 The ERG did analyses for people with severe disease whose disease had responded inadequately to 1 or more biological DMARDs, applying confidential discounts for filgotinib, rituximab and subsequent treatments. Filgotinib with methotrexate was dominated by rituximab with

methotrexate (that is, filgotinib with methotrexate was more costly and less effective than rituximab with methotrexate). Therefore, the committee concluded that it could not recommend filgotinib with methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to 1 or more biological DMARDs if rituximab is a treatment option.

In severe disease, filgotinib with methotrexate is cost effective after 1 or more biological DMARDs, if rituximab is not a treatment option

3.22 The ERG did analyses for people with severe disease whose disease had responded inadequately to 1 or more biological DMARDs and rituximab is not a treatment option, applying confidential discounts for filgotinib, comparators and subsequent treatment options. Filgotinib with methotrexate provided a higher net health benefit (that is, was more cost effective) than alternative therapies used with methotrexate. Therefore, the committee concluded that it could recommend filgotinib with methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to 1 or more biological DMARDs, if rituximab is not a treatment option.

In severe disease, filgotinib with methotrexate is cost effective after 1 or more biological DMARDs and rituximab

3.23 The ERG did analyses for people with severe disease whose disease had responded inadequately to 1 or more biological DMARDs and rituximab, applying confidential discounts for filgotinib, comparators and subsequent treatment options. Filgotinib with methotrexate provided a higher net health benefit (that is, was more cost effective) than alternative therapies used with methotrexate. Therefore, the committee concluded that it could recommend filgotinib with methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease had responded inadequately to 1 or more biological DMARDs and rituximab.

The cost effectiveness of filgotinib monotherapy is more uncertain but it is likely to represent a good use of NHS resources if methotrexate is not suitable

3.24 The committee noted that cost-effectiveness estimates for filgotinib monotherapy were uncertain because filgotinib monotherapy has not been studied in its target population (see section 3.8). The committee also recalled that company model assumed equal effectiveness of filgotinib monotherapy and combination therapy, which has limitations (see section 3.9). Also, for moderate disease, it recalled there was higher uncertainty related to treatment sequences after progression from moderate to severe disease (see section 3.16). However, the committee concluded that despite these limitations, filgotinib is likely to represent a good use of NHS resources for people for whom methotrexate is not suitable and so it recommended filgotinib monotherapy in the same positions as combination therapy. It also noted that this population is much smaller than population of patients who can have methotrexate. It agreed that the small number of people who could not tolerate methotrexate should not be treated differently from other people with moderate to severe disease, as far as possible.

Other factors

Healthcare professionals should consider any disabilities or communication difficulties when using the DAS28 measure

3.25 A potential equality issue was raised in NICE's technology appraisal guidance on upadacitinib for treating severe rheumatoid arthritis in rheumatoid arthritis, about people with rheumatoid arthritis who have difficulty communicating. For these people, it may be more difficult to assess outcomes when using the DAS28 measure. The committee agreed that this equality issue was also important to consider for this appraisal. The committee concluded that healthcare professionals should consider any physical, psychological, sensory or learning disabilities, or

communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.

Healthcare professionals should choose the most appropriate treatment after discussing the options with the person having treatment

3.26 The committee recalled that having a range of treatment options was important in rheumatoid arthritis (see section 3.1). It also recalled that a range of biological and targeted synthetic DMARDs are already available for severe rheumatoid arthritis (see section 3.2). It noted that a number of NICE technology appraisals are currently ongoing for moderate rheumatoid arthritis (GID-TA10759 and GID-TA10586). The committee concluded that healthcare professionals should choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, they should start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary from person to person because of differences in how the drugs are taken and treatment schedules.

The benefits of filgotinib were adequately captured in the cost-effectiveness analysis

3.27 Filgotinibis taken orally, which is valued by patients. The committee noted that for severe rheumatoid arthritis, other oral treatments with a similar mechanism of action are already available. But no biological or targeted synthetic DMARDs are currently available for people with moderate disease. The committee agreed that filgotinib is an important treatment option for these people. It concluded that all the benefits of filgotinib were adequately captured in the model.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information

Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has rheumatoid arthritis and the doctor responsible for their care thinks that filgotinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
January 2021

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ewa Rupniewska
Technical lead

Alexandra Filby
Technical adviser

Gavin Kenny
Project manager

ISBN: [to be added at publication]