Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 20th April 2023

		Present	Apologies
Members			
Prof A Hingorani	NCL JFC Chair	✓	
Dr B Subel	NCL JFC Vice Chair	✓	
Ms W Spicer	RFL, Chief Pharmacist	✓	
Dr P Jasani	RFL, DTC Chair		✓
Dr K Boleti	RFL, DTC Chair		✓
Dr A Scourfield	UCLH, DTC Chair	✓	
Mr J Harchowal	UCLH, Chief Pharmacist; NCL ICS, Interim Chief Pharmacist	✓	
Dr R Urquhart	UCLH, Divisional Clinical Director	✓	
Dr K Tasopoulos	NMUH, DTC Chair	✓	
Ms S Stern	NMUH, Chief Pharmacist		✓
Dr M Kelsey	WH, DTC Chair	✓	
Mr S Richardson	WH, Chief Pharmacist	✓	
Dr S Ishaq	WH, Consultant Anaesthetist	✓	
Dr A Worth	GOSH, DTC Chair		✓
Ms J Ballinger	GOSH, Chief Pharmacist		✓
Mr V Raman	RNOH, DTC Chair	✓	
Mr A Shah	RNOH, Chief Pharmacist	✓	
Prof A Tufail	MEH, DTC Chair		✓
Ms N Phul	MEH, Chief Pharmacist		✓
Ms K Delargy	BEH, Chief Pharmacist	✓	
Ms L Reeves	C&I, Chief Pharmacist		✓
Dr L Waters	CNWL, Consultant Physician in HIV	✓	
Ms R Clark	NCL ICB, Head of Medicines Management (Camden)	✓	
Mr P Gouldstone	NCL ICB, Head of Medicines Management (Enfield)		✓
Ms E Mortty	NCL ICB, Interim Head of Medicines Management (Haringey)	✓	
Ms M Singh	NCL ICB, Head of Medicines Management (Barnet)	✓	
Mr A Dutt	NCL ICB, Head of Medicines Management (Islington)	✓	
Dr D Roberts	NCL ICB, Clinical Director (Islington)	✓	
Mr T Dean	Patient partner		✓
Attendees			
Ms S Amin	IPMO Programme Team, JFC Principal Pharmacist	✓	
Mr G Grewal	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms S Maru	JFC Support Pharmacist	✓	
Ms P Varu	JFC Support Pharmacist	✓	
Ms I Samuel	RFL, Formulary Pharmacist	✓	
Mr H Shahbakhti	RFL, Formulary Pharmacist		✓
Ms H Bouattia	RFL, Formulary Pharmacist		✓
Mr A Barron	UCLH, Principal Pharmacist	✓	
Mr S O'Callaghan	UCLH, Formulary Pharmacist	✓	
Ms A Gabriela	UCLH, Formulary Pharmacist	✓	
Ms A Sehmi	NMUH, Formulary Pharmacist	✓	
Ms H Thoong	GOSH, Formulary Pharmacist	✓	
Mr D Sergian	MEH, Formulary Pharmacist	✓	

Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	✓	
Ms A Blochberger	NHSE, Specialised Commissioning Pharmacist	✓	
Ms A Fakoya	NCL ICB, Contracts & Commissioning Pharmacist	✓	
Dr A Hosin	UCLH, Clinical Pharmacology Registrar		✓
Ms EY Cheung	NCL ICB, Deputy Head of Medicines Management (Camden)		✓
Ms K Mistry	RNOH, Formulary Pharmacist	✓	
Ms S Ahmed	WH, Formulary Pharmacist		✓
Ms L Garubova	WH, Formulary Pharmacist		✓
Mr J Flor	WH, Finance, Business and Performance Pharmacist		✓
Ms M Thacker	RFL, Clinical Lead Pharmacist	✓	
Mr G Purohit	RNOH, Formulary Pharmacist		✓
Ms J Bloom	MEH, Associate Chief Pharmacist	✓	
Ms C Weaver	Senior Prescribing Advisor, NCL ICB (Camden)	✓	
Ms G Gungor	NCL ICB, Assistant Director of Transformation	✓	
Dr N Halliday	RFL, Academic Clinical Lecturer in Hepatology	✓	
Ms R McGaw	RFL Hepatology Pharmacist	✓	
Ms R Clark	NCL ICB, Head of Medicines Management (Camden)	✓	
Ms J Toft	UCLH, Gastroenterology Pharmacist	✓	
Ms N Taherzadeh	RFL, Gastroenterology Pharmacist	✓	
Mr D McLornan	UCLH, Haematology Consultant	✓	
Mr A Tailor	UCLH, Haematology Pharmacist	✓	

1. Meeting observers and members

Prof Hingorani welcomed members, applicants and observers to the meeting (see above).

2. Members' declaration of interests

The Declarations of Interests register for Committee members was included for information. Dr L Waters declared that she held a talk on interactions with Paxlovid for Pfizer. The applicant, Dr D McLornan, for item 8.2 declared that he was the Chief Investigator for the SIMPLIFY-2 and MOMENTUM studies for momelotinib.

3. Minutes of the last meeting

Minutes and abbreviated minutes were accepted as an accurate reflection of the March 2023 meeting.

4. Matters arising

4.1 Lenalidomide FOC scheme ending

Deferred to the May 2023 meeting.

4.2 Testosterone minutes amendment

Deferred to the May 2023 meeting.

5. Review of action tracker

Action tracker included for information.

6. JFC outstanding items & work plan

These items were included for information only. Any questions should be directed to Ms Amin.

7. Local DTC recommendations / minutes

Nil

8. New medicine reviews

8.1 Budesonide for autoimmune hepatitis

The Committee considered an application for oral budesonide (Budenofalk®), a corticosteroid, for the induction and maintenance of remission in patients with autoimmune hepatitis (AIH). The proposed place in therapy is first-line as an alternative option to prednisolone, in patients who have experienced or are likely to experience severe steroid-specific side effects (SSSE) from prednisolone treatment. Treatment with budesonide would be restricted to non-cirrhotic patients and those without significant risk of portosystemic shunting. In a small number of patients, budesonide monotherapy may be considered if all other current standard of care options have been exhausted or

are unsuitable. The proposed dose of oral budesonide would be; induction 6-9mg/day, and maintenance; 3-6mg/day.

Mann at. al (2010, n=203) was a 6-month prospective double-blind, randomised, phase IIb trial (segment A) with a further 6-month open-label phase (segment B). Patients were aged 10-70 years, with either a first diagnosis of acute AIH or were experiencing relapse after a previous diagnosis of AIH. Patients were randomised to budesonide (n=100) or prednisone (n=103). The primary endpoint, was complete response to therapy, defined as complete biochemical remission (i.e. serum AST and ALT within normal range) and the absence of pre-defined SSSE at the patient's last visit of segment A which was significantly better with budesonide [47/100 (47%)] compared to prednisone [19/103 (18.4%)] (P<0.001; CI: 16.2). Secondary endpoints were complete biochemical remission and the occurrence or absence of steroid-specific side effects. At 6 months, complete biochemical remission occurred in 60/100 (60%) of patients given budesonide versus 40/103 (38.8%) of those given prednisone (P=0.001; CI: 7.7); 72% (72/100) of those in the budesonide group did not develop pre-defined SSSE versus 46.6% (48/103) in the prednisone group (P<0.001; CI: 12.3).

Key limitations of the study were that budesonide was given at a high dose until a response was observed and treatment was response guided (i.e dose escalation and de-escalation were permitted in the trial), however the prednisone arm was not. The prednisone dose was tapered down according to the fixed-dose regimen (either high or low) which was selected at week 2, potentially introducing a bias in the trial. Additionally, there was no baseline data on whether patients were at high risk of steroid-related side effects so stratification in terms of baseline risk was not possible. The trial was sponsored by Dr Falk Pharma Ltd (the manufacturer of Budenofalk®).

In terms of safety and risks, the administration risks for budesonide are the same as prednisolone, except that there is only one preparation licensed for AIH, therefore care when prescribing/dispensing is required to ensure the correct product is supplied. The Mann et. al study shows that budesonide had a lower risk of pre-defined SSSE compared to prednisone (as above).

In terms of budget impact, the cost of budesonide varies according to the stage of treatment and different dosing regimens. The comparative cost of budesonide vs. prednisolone treatment for Year 1 is estimated to be £675 vs. £74-108 per patient and the cost of Year 2 is estimated to be £270-540 vs. £25 per patient, respectively. The NCL budget impact requires consideration of; i) the number of new patients initiated within NCL, ii) the number of patients stopping steroid treatment after Year 2, iii) the tertiary hepatology service at RFL and costs of treating these patients which would need to be excluded from the NCL budget impact. Therefore, the estimated NCL budget impact was based on the following assumptions; i) 30 patients will be initiated each year, ii) patients will be on treatment for at least 24 months, iii) 50% of patients would stop steroid treatment after 24 months. Based on this, the estimated cost of budesonide treatment in Year 3 is £32,422-44,580 compared to £3,333–5,554 for prednisolone treatment. However, the estimated cost for Year 3 would be lower if non-NCL patients (approximately 60% of the total RFL patient number per annum) who access the RFL tertiary service are excluded. The estimated cost of budesonide treatment in Year 3 excluding non-NCL patients would be £17,703-26,553.

The Committee heard from Dr Halliday that AIH is a very heterogeneous disease and therefore patient treatment is individualised. The proportion of patients who achieve remission is approximately 60% due to steroid-related side effects; steroids are a core treatment in hepatology patients so there is a need to manage the side effect burden. It was acknowledged that the evidence base is limited and therefore if patients are not responsive to budesonide, clinicians would consider switching to prednisolone. The place in therapy would be as a first-line option or as an alternative to prednisolone in patients with significant steroid side effect burden.

The biochemical response is well correlated with the histological response and there is good evidence that normal biochemistry correlates with normal histology. There is data from RFL and other centres that normal biochemistry results in improved long-term outcomes. The Mann et. al study used the licensed 6mg daily dose for maintenance of remission, however, if remission can be achieved on 3mg daily, clinicians will reduce the dose to 3mg daily to reduce pill burden and toxicity. The use of prednisone as a comparator in the Mann et. al study may have not been a fair comparator in hepatic patients as it requires activation by the liver, hence the study has been criticised. However, other studies have shown that budesonide achieves remission, and it was highlighted that this was the key question as opposed to comparative efficacy with prednisolone for this patient cohort.

The transfer of prescribing to primary care after stabilisation would benefit patients, especially those being referred to the RFL tertiary service as many continue life-long steroid treatment. Treatment monitoring would be the same as for prednisolone. The aim for standard of care is steroid-free monotherapy with a steroid-sparing agent, i.e. azathioprine or mycophenolate, so clinicians will aim to reduce or stop the steroid where possible. Dr Halliday confirmed it would be feasible to develop clinician criteria for identifying AIH patients suitable for budesonide treatment.

In camera, the Committee acknowledged the limited evidence base and limitations of the available RCT. However, the metabolism of budesonide and inactivation in the liver provides assurance that it is less likely to cause side effects, specifically in AIH patients. Based on the biological plausibility, the Committee were in support of the use of budesonide in a limited number of patients subject to the development of specific criteria for use, including switching from prednisolone and discontinuation criteria for both. In addition to the criteria, the Committee requested data collection on use after 12 months to confirm adherence to the agreed criteria. The time frame for the transfer of care from initiation to GP prescribing needs to be agreed upon. It is expected that the electronic shared care database would be utilised at RFL.

In summary, the Committee agreed to add budesonide to the NCL Joint Formulary for the induction and maintenance of remission in patients with AIH, subject to the development and receipt of specific criteria for initiation and discontinuation.

Decision: Approved
Prescribing: Secondary care initiation, Primary care continuation
Tariff status: In tariff
Funding: Trust/ICB commissioned
Fact sheet or shared care required: Deferred to the NCL Shared Care Group
Additional information: Subject to the development and receipt of specific criteria for initiation and discontinuation and data collection on adherence to agreed criteria at 24 months.

8.2 FOC Scheme: Momelotinib for myelofibrosis

The Committee considered a free-of-charge (FOC) scheme for unlicensed momelotinib (as 200mg tablets daily), a JAK-inhibitor (JAKi), for anaemic, symptomatic myelofibrosis patients with splenomegaly in a first-, second- or third-line setting. The Committee reviewed three randomised controlled trials and one open-label extension study examining the use of momelotinib in myelofibrosis patients.

In a first-line setting, SIMPLIFY-1 (2017; n=432) was a 24-week, phase III, randomised, active-comparator controlled, double-blind, double-dummy, non-inferiority study to compare the efficacy and safety of momelotinib and ruxolitinib for JAKi-naïve patients with myelofibrosis. The primary endpoint was spleen response rate (SRR24), defined as a ≥35% in spleen volume from baseline at week 24 as assessed by MRI or CT scan. Non-inferiority of momelotinib was determined by whether the lower bound of the two-sided 95% CI for the non-inferiority difference (SRR24 of momelotinib – 0.6xSRR24 of ruxolitinib) was >0. Momelotinib was significantly non-inferior compared to ruxolitinib for the primary endpoint of SRR24 (26.5% vs. 29%; non-inferiority proportion difference (NIPD): 0.09 [95% CI: 0.02–0.19]; p=0.011). Momelotinib did not meet its key secondary non-inferiority outcome, symptom response rate, SyRR24, defined as the proportion of patients who achieved a ≥50% reduction from baseline to week 24 based on the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (mMPN-SAF TSS) (28.4% vs. 42.2%; NIPD: 0.00 [95% CI: -0.08–0.08]; p=0.98). As the non-inferiority margin for the key secondary endpoint was not met, the authors of the study stopped formal sequential testing for other end points and therefore only nominal values for the other secondary endpoints were reported. For the secondary endpoint of transfusion independence rate (TIR24), defined as the proportion of patients who were transfusion-independent (absence of RBC transfusions and no Hb <8g/dL in the prior 8 weeks) from baseline to week 24, 1.9% lost transfusion independence in the momelotinib arm compared to 20.7% in the ruxolitinib arm (p<0.001). Key limitations of the study were the non-inferiority study design which considered momelotinib to be non-inferior to ruxolitinib for the primary outcome if it achieved 60% of the SRR24 of ruxolitinib. Additionally, the study did not report on whether any adjunctive treatments were used for anaemia in the control arm, but the applicant states that to his knowledge anaemia adjunctive therapies were not used. The study design did not allow for statistical analysis of other secondary endpoints if the key secondary endpoint was not met.

In a second-line or third-line setting, SIMPLIFY-2 (2018; n=156) was a 24-week phase III, randomised, open-label, active-comparator controlled superiority trial to compare the efficacy and safety of momelotinib to best available therapy (BAT) in JAKi pre-treated patients with myelofibrosis. In the BAT arm, 89% of patients were on ruxolitinib. The primary endpoint, spleen response rate at week 24 (SRR24) was not significantly better than BAT (7% vs 6%; proportion difference (PD): 0.01 (95% CI: -0.09–0.10, p=0.90). As the primary outcome was not achieved, the authors reported that "statistical significance could not be claimed for further multiplicity testing of secondary endpoints per the sequential testing procedure". Therefore, nominal values were reported for all secondary outcomes. For the secondary outcome, symptom response rate at week 24 (SyRR24), momelotinib was nominally better than BAT (26% vs 6%, p=0.0006). For the secondary endpoint, transfusion independence rate at week 24 (TIR24), 12% of patients gained transfusion independence in the momelotinib arm compared to 16% that lost transfusion independence in the BAT arm. Key limitations of the study were the open-label study design, sub-therapeutic doses of ruxolitinib being used in the BAT arm which could result in poorer outcomes, and no wash-out period was allowed prior to study enrolment which may have confounded results. Additionally, the study did not report on whether any adjunctive treatments were used for anaemia in the control arm, but the applicant states that to his knowledge anaemia adjunctive therapies were not used. The study design did not allow for statistical analysis of other secondary endpoints if the key secondary endpoint was not met.

Another limitation was that the manufacturer, designed, and conducted this study, co-ordinated data collection, data analysis and interpretation. Moreover, the initial draft of the manuscript was prepared by the funder and a professional medical writer was paid by the funder and worked in collaboration with the authors on the manuscript.

Mesa et al (2022; n=574) reported the open-label, extended access study following the SIMPLIFY-1 and SIMPLIFY-2 randomised trials to assess the long-term safety profile of momelotinib in JAKi-naïve and experienced patients. Overall survival and leukaemia-free survival were secondary outcomes of the study. There was no difference in overall or leukaemia free survival between the patient groups from SIMPLIFY-1 or SIMPLIFY-2. In an exploratory analysis there was an association between transfusion independence response at week 24 and overall survival in patients with myelofibrosis. There was a statistically significant improvement in overall survival in JAKi-naïve momelotinib randomised patients from the SIMPLIFY-1 study (HR [TI vs non-TI]: 0.323; p<0.0001) but not those randomised to momelotinib from the SIMPLIFY-2 study. The results were not statistically significant for ruxolitinib patients randomised to momelotinib in the SIMPLIFY-1 study and all JAKi-experienced patients in the SIMPLIFY-2 study.

In a second- or third-line setting, MOMENTUM (2023; n=195) was a phase III, double-blind, double-dummy, randomised, active-comparator controlled study to compare the efficacy and safety of momelotinib to danazol in JAKi-treated patients with myelofibrosis. The primary endpoint, symptom response rate at week 24 (SRR24), defined as the proportion of patients with a 50% or more reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline, was significantly superior to danazol (25% vs 9%; p≤0.05). As per the study design, the key secondary endpoints were to be evaluated in hierarchical order only if the primary outcome showed significance in favour of momelotinib. The key secondary endpoint, transfusion independence rate at week 24 (TIR24) was tested by non-inferiority testing. TIR24 for momelotinib was non-inferior to danazol (30% vs 20%). The next secondary endpoint, splenic response rate (SRR24), was significantly superior for momelotinib compared to danazol (23% vs 3%, p≤0.05). A key limitation of this study was that danazol was used as an active comparator. However, danazol is not used as a disease-modifying agent for treating myelofibrosis in real-world practice and is often used either alone or as an adjunct with ruxolitinib for treating anaemia associated with myelofibrosis.

In terms of safety, from the SIMPLIFY-1 and SIMPLIFY-2 studies, momelotinib had a higher risk of i) side effects that led to discontinuation (15.7% vs 5.6%) ii) grade 3 ≥ thrombocytopenia (8.2% vs 4.6%) and iii) peripheral neuropathy (8.8% vs 5.6%) compared to ruxolitinib, respectively. Momelotinib had a lower risk of ≥grade 3 anaemia compared to ruxolitinib (6% vs 22.7%).

In terms of budget impact, momelotinib is being provided via a free of charge scheme until commissioned by the NHS or deemed clinically unsuitable as determined by the treating clinician.

The Committee heard from Dr McLornan that the 35% reduction in spleen volume is an arbitrary trial design set by pharmaceutical companies.

In real-world practice, a 5% reduction in spleen volume can lead to a reduction in transfusion needs. A majority of patients will develop a degree of anaemia through their disease course for which patients are often treated with adjunctive therapy such as epoetin and danazol. These therapies are likely to be continued long-term without a response due to lack of alternative therapies. Patients that are likely to have the best survival benefit are those that can achieve the best spleen response to ruxolitinib. This is only possible if they are able to receive the full dose-density of ruxolitinib as demonstrated by the SIMPLIFY-1 study. However, anaemic patients often have thrombocytopenia as well, requiring a ruxolitinib dose reduction of 25-50% of the actual recommended dose and therefore patients are not able to achieve the best spleen response. In comparison, the majority of anaemic patients on momelotinib can maintain the full dose density. In the real-world setting, there are several patients receiving sub-optimal doses of JAKis that are transfusion dependent despite adjunctive therapies and therefore momelotinib would be a useful treatment option. In terms of fedratinib, anaemic patients on fedratinib have been switched back to ruxolitinib and so there is an unmet need in the second-line setting. Dr McLornan also highlighted that draft British Society of Haematology guidelines will recommend momelotinib in anaemic myelofibrosis patients with symptoms or splenomegaly agnostic of line of therapy.

In camera, the Committee discussed the concerns of momelotinib used in each line of therapy.
In a first-line setting, the SIMPLIFY-1 study was a non-inferiority study of JAKi-naïve patients where momelotinib was considered non-inferior to ruxolitinib for the primary outcome of splenic response rate if it achieved 60% of the pre-specified 35% reduction in spleen size for ruxolitinib. For this outcome, momelotinib marginally met this non-inferiority primary outcome. The key secondary endpoint of symptom response rate did not specify the proportion by which momelotinib was allowed to be worse than ruxolitinib to be considered non-inferior. However, non-inferiority was not met for momelotinib compared to ruxolitinib. As this non-inferiority endpoint was not met, further secondary outcomes were nominally reported. Additionally, the study does not mention the number of patients on other adjunctive therapies like danazol or epoetin in the control arm, but the applicant states that to his knowledge anaemia adjunctive therapies were not used. Therefore, the evidence was not found to be sufficient to place it in a first-line setting ahead of licensed therapies which have positive NICE Technology Appraisals.

In a second-line setting, where momelotinib would be used after ruxolitinib, the relevant studies were SIMPLIFY-2 and MOMENTUM. SIMPLIFY-2 was a superiority study of ruxolitinib pre-treated patients compared to BAT. There was no wash-out period of prior treatments for patients in the BAT arm which may confound results. The majority of the patients in the BAT arm were on ruxolitinib, which was administered at sub-therapeutic doses weighing the study in favour of the momelotinib arm, although the sub-therapeutic dosing may have been because cytopenias limited escalation of ruxolitinib dose.

However, despite this, momelotinib was not superior to BAT as it did not meet the primary outcome of splenic response rate. The symptom response rate and transfusion independence rate showed a signal for improvement but due to the hierarchical statistical plan, statistical analysis was nominal and remained an exploratory finding. There was a higher rate of serious adverse events that led to discontinuation and peripheral neuropathy with momelotinib compared to BAT. Similar to SIMPLIFY-1, this study did not mention the number of patients on other adjunctive therapies like danazol or epoetin in the control arm, but the applicant states that to his knowledge anaemia adjunctive therapies were not used.

As momelotinib did not meet the primary endpoint, secondary endpoints were subsequently exploratory, and a worse adverse effect profile was reported compared to BAT, there was insufficient evidence to support its use in a second-line setting.

For the MOMENTUM study, in JAKi-experienced patients, the comparator used in the study was danazol monotherapy. However, in real world practice, danazol is not used as a disease-modifying agent for treating myelofibrosis in real-world practice and is often used either alone or as an adjunct with ruxolitinib for treating anaemia associated with myelofibrosis.

Momelotinib was superior to danazol for spleen and symptom response rates. Momelotinib met the non-inferiority endpoint of transfusion independence rate compared to danazol. However, as danazol is not a disease-modifying therapy and not intended to treat spleen volume or symptoms, the use of danazol as a comparator relates only to the anaemia-related outcomes and not disease-modification and therefore, did not provide additional evidence to support use in a second-line setting. Additionally, there was no evidence to support the use of momelotinib after ruxolitinib with danazol.

In a third line setting, where momelotinib would be used after all other therapies, the relevant studies were the SIMPLIFY-2 and MOMENTUM studies. The concerns with SIMPLIFY-2 and MOMENTUM studies were similar in the third-line setting. Additionally, there was no evidence to support the use of momelotinib after ruxolitinib with danazol or fedratinib as trials in these settings have not been conducted.

In summary, based on the evidence available and the concerns highlighted above for use in each line of therapy, the Committee could not recommend the use of momelotinib as indicated in the application.

It remains possible, that some patients who are responsive to JAK-inhibitors but who have high transfusion requirements, or where JAK-inhibitor use is limited by anaemia despite adjunctive therapies for anaemia such as danazol and epoetin, that momelotinib may have utility. The applicants may wish to consider a new application for the use of momelotinib in a narrower, clearly defined cohort of such patients if this can be supported by clear evidence. This application would be subject to a new evaluation.

Decision: Not approved

Post-meeting: The applicant provided the protocol for the SIMPLIFY-1 study which states that 'any treatments for myelofibrosis including those in the proscribed list are prohibited'. Proscribed medications included erythropoiesis stimulating agents and androgens. Therefore, adjunctive medicines were not used in this study.

8.3 Review: JAK inhibitors for Ulcerative Colitis

The Committee reviewed the use of upadacitinib in preference to filgotinib for the induction and maintenance of ulcerative colitis in a second-line setting in a restricted cohort of patients at high risk of severe disease and colectomy (e.g. extensive disease, steroid-refractory, diagnosis in childhood, extraintestinal manifestations or recent admission). The induction dose for upadacitinib is 45mg daily for 8 weeks followed by a maintenance dose of 15mg or 30mg daily thereafter. The induction dose for filgotinib is 200mg daily for 10 weeks followed by a maintenance dose of 200mg daily. Both medicines are JAK-inhibitors (JAKi).

The Committee was informed that NICE Technology Appraisals exist for both medicines and therefore both treatments are considered cost-effective. NICE have not issued a treatment hierarchy but recommend that treatments with the lowest acquisition cost should be used first. Filgotinib has a lower cost per patient per annum compared to upadacitinib. In order to review upadacitinib's proposed place in therapy ahead of filgotinib, a review to identify superiority of upadacitinib compared to filgotinib in the induction and maintenance phase for ulcerative colitis patients was undertaken. The induction and maintenance studies for filgotinib were called SELECTION. The induction studies for upadacitinib were UC1 and UC2 and the maintenance study was UC3. The Committee reviewed outcomes from 2 network meta-analyses (NMAs) which included these studies.

Attaubi et al (2023) conducted a network meta-analysis for induction studies only for upadacitinib and filgotinib. The studies included the UC1 study, UC2 study and a post-hoc analysis of the SELECTION and UC1 study. The population included in the studies were a mixed population of biologic-naïve and experienced patients with ulcerative colitis. Upadacitinib 45mg OD was reported to be significantly superior to filgotinib 200mg in the induction of 'clinical response' and 'clinical remission' at week 2 ($RR_{response}$=1.47 [1.08-1.97]; $RR_{remission}$=3.00 [1.5-6.12]) and week 6 ($RR_{response}$=1.18 [0.94- 1.47]; $RR_{remission}$=1.88 [1.26-2.82]).

Lasa et al (2021) conducted a network meta-analysis for induction and maintenance studies for upadacitinib and filgotinib. In the induction setting, upadacitinib 45mg OD was reported to be significantly superior to filgotinib 200mg in the induction of 'clinical remission' (OR=4.49 [2·18–9·24]) and 'endoscopic improvement' (OR=2.91 [1.19–7.10]) at 8 weeks (for upadacitinib) and 10 weeks (for filgotinib). There were no significant differences in adverse effects or serious adverse effects, though upadacitinib trended unfavourable for AE (OR=1.46 [0.99-2.11]) but favourably for SAEs [OR=0.61 [0.24-1.52]]. In the maintenance setting, upadacitinib 30mg OD was significantly superior to filgotinib 200mg OD at 'maintaining endoscopic improvement' (OR=3.46 [1.18-10.12]) but not 'maintaining clinical remission' (OR=1.68 [0.68-4.15]) or 'maintenance of steroid-free remission' (OR=1.37 [0.35-5.35]). Upadacitinib 15mg OD was not superior to filgotinib 200mg at 'maintaining endoscopic improvement' (OR=2.04 [0.69-5.95]), 'maintaining clinical remission' (OR=1.12 [0.45-2.77]) or 'maintaining steroid-free remission' (OR=0.84 [0.21-3.26]).

Key limitations of the NMAs were that they included a mixed population of bio-naïve and bio-exposed patients, patient-level variables and trial design variables are not adjusted for.

Phase 2 dose-finding studies were reviewed for filgotinib and upadacitinib. For filgotinib induction studies in bio-experienced patients, Feagan et al (2021) reported a greater proportion of patients on filgotinib 200mg achieved clinical remission and Mayo Clinical Score remission compared to placebo at week 10 (11.5% vs 4.2%, absolute difference: 7.2% [95% CI: 1.6-12.8]; p=0.0103 and 9.5% vs 4.2%, absolute difference: 5.3% [95% CI: -0.1-10.7]; p=0.0393 respectively). The proportion of patients on filgotinib 100mg was not significantly greater than placebo at week 10 for clinical remission (9.5% vs 4.2%, absolute difference: 5.2% [95% CI: 0.0-10.5]; p=0.0645) and Mayo Clinical Score remission (6.0% vs 4.2%, absolute difference: 1.7% [95% CI: -3.1-6.6]; p=0.5308). These results suggested a dose-dependent response for outcomes. The difference was not statistically significant for inducing endoscopic remission for filgotinib 200mg or filgotinib 100mg compared to placebo at week 10 (3.4% vs 2.1%, absolute difference: 1.3% [95% CI: -2.5-5.1]; p=0.4269 and 2.1% vs 2.1%, absolute difference: 0.0% [95% CI: -3.4-3.4]; p=0.9987, respectively). For upadacitinib induction studies in a mixed population of bio-naïve and bio-experienced patients, Sandborn et al (2020) reported a statistically significant difference was met for clinical remission and endoscopic remission for all strengths of upadacitinib compared to placebo. A greater proportion of patients on upadacitinib 45mg (19.6% vs 0.0%, difference: 19.4%; p=0.002), followed by upadacitinib 15mg (14.3% vs 0.0%; difference 12.7%, p=0.013) and then upadacitinib 30mg (13.5% vs 0.0%; difference: 12.7%, p=0.011) achieved clinical remission compared to placebo at week 8. Similarly, a greater proportion of patients on upadacitinib 45mg (35.7% vs 2.2%, difference: 36.0%; p<0.001), followed by upadacitinib 15mg (30.6% vs 2.2%; difference 26.9%, p<0.001) and then upadacitinib 30mg (26.9% vs 2.2%; difference: 26.5%, p<0.001), achieved endoscopic remission compared to placebo at week 8.

UCLH, RFL and NMUH clinicians had agreed to a 70:30 split in usage of filgotinib:upadacitinib. WH currently have a higher usage of upadacitinib:filgotinib of a 60:40 split but further consultation is required with the clinical team. In terms of cost impact, 70:30 split of filgotinib:upadacitinib is expected to cost an additional £232,000 compared to 100% usage of filgotinib across all patients in NCL.

The Committee heard from Ms Toft that UCLH is a tertiary referral centre so the patients referred have quite severe disease and therefore upadacitinib would be reserved for these patients. Experience from other centres using upadacitinib has been good. While a budget impact of all therapies used for ulcerative colitis has not been conducted, greater use of JAK inihibitors (upadacitinib and filgotinib) will result in a lower cost-impact by decreasing use of the more expensive vedolizumab.

In summary, the Committee were supportive of the proposed position of using upadacitinib in a second-line setting in preference to filgotinib for the restricted cohort of patients with high risk of severe disease and colectomy (e.g. extensive disease, steroid refractory, diagnosis in childhood, extraintestinal manifestations or recent admission). The Committee agreed that a 70:30 split of filgotinib:upadacitinib usage is a suitable and appropriate audit standard and data can be brought back after 6 months to see the usage split between the JAKis.

Decision: Approved for the proposed cohort with a 70:30 usage split for filgotinib:upadacitinib, usage data to be brought back in 6 months
Prescribing: Secondary Care only
Tariff status: Excluded from tariff
Funding: ICB commissioned
Fact sheet or shared care required: N/A

9. Discontinuation of Restandol using the DHSC document (Oct 2020)

Deferred to May 2023.

10. Primary Care Pathway: Alcohol Withdrawal

The risk assessments for the medicines included in the Alcohol Primary Care Pathway were presented to the Committee for consideration and approval as part of the JFC support for the pathways transformation work agreed previously. The medicines in the pathway are currently in use within NCL and align with the NCL prescribing recommendations. The risk assessment undertaken involved a review of the place in the pathway and the evidence base for each medicine including safety, efficacy, costs and prescribing and formulary position. Overall, the Committee were supportive of the pathway and medicines included, in addition to the process undertaken to review the medicines. The Committee provided feedback to take to the clinical pathway development group on ensuring that clearer criteria for the transfer of medicines from secondary to primary care prescribing are provided. It was acknowledged that the process may be subject to further iterations as more pathways are brought to the Committee.

It was highlighted that the process for reviewing additional pathways remains probationary and there is a need to establish an upstream pre-assessment process and clearly separate those pathways that are likely to require a shorter amount of time for approval by the Committee and pre-circulate these prior to the JFC meeting. If issues are flagged during the pre-assessment process, then a separate sub-group may be required where more time is required to agree on and approve the medicines in the pathways. The interim agreement to review 18 pathways which require more urgent attention will continue to inform this process.

It was clarified that the addition of medicines to Trust formularies approved in the Primary Care pathways will depend on the services provided by individual Trusts. The medicines will be captured in the abbreviated minutes and Trusts will have the opportunity to ratify JFC decisions at local DTCs.

In summary, the medicines in the Primary Care Alcohol Pathway were approved pending ratification at the next meeting (as the Committee was not quorate when this item concluded). The process for reviewing Primary Care pathways may require further iterations and remains under review.

11. COVID-19 therapies

The Committee were informed that NICE have recently reviewed COVID therapies and had published their Final Appraisal Determination (FAD. Whilst recommendations for some medications have been published in full (NICE TA878), others have been held due to appeals from the respective manufacturers. This includes remdesivir, which was given a negative recommendation in the NICE FAD which is now being appealed. Until the appeal concludes, the recommendations in the "COVID-19 rapid guideline" remain in place (which includes use of remdesivir for up to 5 days in hospitalised patients with COVID-19 pneumonia requiring supplemental oxygen).

However, the Committee were also informed that from April 1st 2023, remdesivir is no longer commissioned by NHS England; instead, it will be commissioned by ICBs. It is estimated to cost between £2,000-£4,000 per patient per course. Early discussions have taken place with UCLH and RFL leads and have suggested that use as per the COVID-19 rapid guideline will be widespread and may not be feasible due to the financial pressure. Clinicians would like to retain remdesivir as an option in certain immunosuppressed cohorts. JFC will likely receive an application for review at the May meeting. The Committee also discussed the use of COVID-19 therapies through COVID medicines delivery units in the community; pathways are currently in development to demonstrate how medicines will be screened, prescribed and administered. These will also come to the May JFC meeting for discussion and approval (given that the JFC is the most appropriate path for medicines governance).

12. Next meeting

Thursday 18th May 2023

13. Any other business

Nil