North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 20 November 2017
G12 Council Room, South Wing, UCL, Gower Street, London WC1E 6BT

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr R Sofat	UCLH, DTC Chair	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr M Kelsey	WH, Chair DTC	
	Dr R Woolfson	RFL, DTC Chair	
	Dr M Dhavale	Barnet CCG, GP Clinical Lead Medicines Management	
	Mr S Richardson	WH, Chief Pharmacist	
	Mr T James	MEH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Dr A Mian	NMUH, Clinical Director for Specialty Medicine	
	Ms EY Cheung	Camden CCG, Deputy Head of Medicines Management	
In attendance:	Mr A Barron	NCL JFC, Support Pharmacist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Ms M Bhogal	NMUH, Formulary Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Ms E Wassuna	Enfield Community Nurse, Bone Health	
	Mr K Paik	MEH, Clinical Pharmacist	
	Dr S Naik	UCLH, Consultant Diabetologist	
	Dr M Cohen	RFL, Consultant Diabetologist	
	Dr E Karra	RFL, Consultant Diabetologist	
	Dr T Richards	UCLH, Consultant Clinical Oncologist	
	Dr K-K Shiu	UCLH, Consultant Medical Oncologist	
Apologies:	Ms R Clark	Camden CCG, Head of Medicines Management	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Dr F Gishen	RFL, Palliative Medicine Consultant	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr T Dean	Patient Partner	
	Dr D Hughes	RFL, Consultant Haematologist	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	

2. Meeting observers

Elizabeth Wassuna (Enfield Community Nurse, Bone Health) and Kuldeep Paik (MEH, Clinical Pharmacist) were welcomed as meeting observers.

3. Minutes of the last meeting

The minutes and abbreviated minutes were accepted as accurate reflections of the October meeting.

4. Matters arising

4.1 Pembrolizumab for platinum-ineligible patients in urothelial cancer

At the October 2017 meeting, JFC were asked to consider an application to use pembrolizumab under a free-of-charge scheme for patients with urothelial cancer who had either advanced whilst on platinum-based chemotherapy, or were ineligible for platinum-based chemotherapy. The Committee approved the former indication, but were unable to reach a decision on the efficacy of pembrolizumab in patients ineligible for platinum-based chemotherapy as this cohort had been excluded from the clinical trial presented (KEYNOTE 45).

Further evidence was provided in the form a recently published, single arm, phase 2 study (KEYNOTE-052; n=370), that included patients with histologically or cytologically confirmed locally advanced unresectable, or metastatic, urothelial cancer who were ineligible for cisplatin chemotherapy (based on poor performance score, poor renal function, hearing loss, peripheral neuropathy or heart failure).

All patients in this single-arm study received pembrolizumab 200 mg every three weeks until confirmed disease progression, completion of 24 months treatment, or the need to withdraw arose. The primary efficacy outcome was objective response (defined as the proportion of patients achieving an independently assessed complete or partial response). Secondary outcomes included overall survival, progression free survival, safety and tolerability. The study also aimed to establish a PD-L1 "strongly positive expression" cut-off (to estimate PD-L1 expression that acts as a positive predictor of outcomes), and to determine the duration of response.

The Committee noted that the median treatment time was 3 months (range 0.03 to 16 months), with a median follow-up of 5 months (IQR: 3 to 8.6 months). 89 patients (24%, 95% CI: 20 to 29) had a centrally assessed objective response; median time to response was 2 months (95% CI: 2 to 2.1 months). Objective response was separated into complete response (5%) and partial response (19%). Of the secondary outcomes of interest, median progression free survival was 2 months (95% CI 2 to 3); six month PFS was 30% (25 to 35%). This was based on 248 progression events or deaths recorded. Six month overall survival (based on 130 deaths recorded) was calculated as 67% (95% CI 62 – 73%).

Regarding the lack of a control arm in this study, the Committee noted that NICE has accepted this as methodologically appropriate for the same cohort of patients as published in Technology Appraisal 492 (of atezolizumab, another PD-L1 binding monoclonal antibody). As a naïve comparison to pembrolizumab, the Committee noted that atezolizumab demonstrated an objective response of 22.7% (95% CI 15.5 to 31.3) at 15 months, which was used by NHS England to fund atezolizumab under the Cancer Drug Fund.

The Committee discussed the lack of controlled clinical trial data for either PD-L1 binding agent used in this indication. Without evidence from a head-to-head trial, or of a large treatment effect from pembrolizumab compared to atezolizumab, the Committee was not convinced that there is a need to approve a second PD-L1 binding agent in addition to atezolizumab.

In summary, as atezolizumab has CDF funding and NICE approval is imminent, the Committee were of the view that pembrolizumab does not need to be added to the formulary for the 1st line treatment of locally advanced or metastatic urothelial cancer when cisplatin is unsuitable.

Decision: Not approved

4.2 Idebenone for Duchenne Muscular Dystrophy (Early Access to Medicines Scheme; EAMS)

UCLH is the only Trust commissioned to provide an adult service for Duchenne's in NCL therefore the application was passed to UCLH Use of Medicines Committee (UMC) for further consideration. UCLH UMC agreed with the JFC recommendation and deferred the application until EMA approval or outcome of the CHMP re-review following consideration of the appeal. Based on the timelines it was noted that the outcome of the EAMS appeals process would likely be published mid-February 2018.

4.3 Freestyle Libre interim position statement for glucose monitoring

The RMOC (North) published a position statement which is at odds with advice received from the London Diabetes Clinical Networks. LPP are co-ordinating a response to the position statement via the London RMOC. It was agreed that the NCL interim position statement does not require a review at the current time.

5. Declarations of relevant conflicts of interest

There were no declarations of interest

6. Local DTC recommendations / minutes

6.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
BEH	Jul-17	Paliperidone LAI 3 monthly (Trevicta®)	Schizophrenia for patients who are well controlled on a stable dose (minimum 4 months) of paliperidone LAI 1 monthly (Xeplion®)	Decision: BEH only† Prescribing: Secondary care only Tariff status: In tariff Funding: Secondary care Fact sheet or shared care required: No
RFL	Oct-17	Eliglustat	Gaucher's Disease	Decision: RFL only Prescribing: Secondary care only Tariff status: Excluded from tariff Funding: NHSE Fact sheet or shared care required: No
UCLH	Sep-17	Gilteritinib (compassionate access)	Relapsed/refractory FLT3-ITD or D835 mutation positive Acute Myeloid Leukaemia	Decision: UCLH only Prescribing: Secondary care only Tariff status: NA Funding: FOC Fact sheet or shared care required: No

† The indication approved at BEH was consistent with the product license. Trevicta was also approved by C&I in October 2016 for a smaller cohort of patients – 'Schizophrenia in patients with demonstrable non-compliance with the monthly depot'. The principle advantage of Trevicta compared with the 1 monthly injection (Xeplion®) was the longer residual effect. Trevicta and Xeplion were similarly priced however Xeplion will come off patent sooner (available data suggests 2022). BEH will consider Trevicta for some fully compliant patients (e.g. individuals who study out of the area) whereas C&I will limit approval to individuals with poor compliance in order to take maximal advantage of a generic 1 monthly injection when available.

7. New Medicine Reviews

7.1 CROSS chemoradiotherapy regimen as neo-adjuvant treatment before surgery for adenocarcinoma of the oesophagus or the gastro-oesophageal junction (Applicant: Dr G Blackman, UCLH)

The Committee considered an application to use carboplatin and paclitaxel together with radiotherapy before surgery for the treatment of adenocarcinoma of the oesophagus or gastro-oesophageal junction. Evidence from one randomised controlled trial and its follow-up study were considered by the Committee.

Van Hagen (n=366) was a randomised, controlled trial to determine the difference in overall survival in patients treated with combined chemotherapy (carboplatin and paclitaxel), radiotherapy and surgery, compared to surgery alone, in adult patients with potentially curable oesophageal or junctional cancer. The majority of the patients had adenocarcinoma (75%), though there was a sizable minority with squamous cell carcinoma (23%). Patients were stratified at randomisation based on predefined subgroups (including histological tumour subtype).

The Committee agreed that this study was necessarily unblinded to allow patients not entered into the neoadjuvant chemoradiotherapy arm to receive their surgery as soon as possible. The median wait time for surgery was 24 days for those entered into the surgery arm, compared to 97 days for patients receiving chemoradiotherapy first.

The median overall survival in the chemoradiotherapy-surgery group was 49.4 months versus 24.0 months in the surgery group (HR 0.657; 95% CI 0.495 to 0.871, p=0.003). An estimation of the 5-year overall survival depending on tumour type reported a statistically significant difference with the CROSS regimen for adenocarcinoma when the univariate analysis was reported (HR 0.732, 95% CI 0.524-0.998, p=0.049), but when multivariate analysis (adjusted for baseline covariates) was reported 5 year overall survival with CROSS was no longer statistically significant (HR 0.741, 95% CI 0.536-1.024, p=0.07). Hazard ratios for effect of CROSS on squamous cell carcinoma (outside this application) was statistically significant on both the univariate and multivariate analyses. Other subgroups in whom CROSS treatment did not demonstrate a statistically significant benefit over surgery alone include women, patients with a clinical N stage of 1, and patients with a WHO performance score of 1. Chemoradiotherapy was successful at reducing the proportion of patients unable to proceed with surgery because either primary tumour or lymph nodes were unresectable (4% vs. 13%, p=0.002). An R0 resection was achieved in 92% of chemoradiotherapy patients, compared to 69% of surgery only patients (p<0.001).

The Committee also reviewed evidence provided by Shapiro *et al*, which reported the long term follow up of the van Hagen study reported above. The median overall survival for the chemoradiotherapy arm changed slightly in the follow up study (to 48.6 months), resulting in a marginally higher HR 0.68 (95% CI 0.53 to 0.88). For the adenocarcinoma arm, the median overall survival was 43.2 months (24.9 to 61.4 months) in the neoadjuvant group versus 27.1 months (13 to 41.2 months) in the surgery alone group (HR 0.73 [95% CI 0.55 to 0.98], p=0.037) on univariate analysis. As in van Hagen, this stopped being statistically significant when multivariable analysis was performed.

For combined tumour types, median progression free survival (PFS) HR was 0.64 [95% CI 0.49 to 0.82] in favour of chemoradiotherapy. For the adenocarcinoma arm the HR=0.69 [95% CI 0.52 to 0.92]. Similarly as found in the van Hagen paper, this study confirmed the lack of statistical significance for chemoradiotherapy versus surgery alone, when used in women, and when used in cN1 and in patients with a WHO performance score of 1. In the multivariable analysis, treatment failed to show statistical significance in the adenocarcinoma arm.

The Committee heard from the clinical experts to ascertain the need for both this regimen and the FLOT regimen (discussed under item 7.2 below) to be added to the NCL Joint Formulary. The Committee was assured that the cohort for whom CROSS chemoradiotherapy will be used differs from that which will receive FLOT, with a MDT involved in the decision-making. CROSS is required for patients whose circumferential margins are threatened, as chemotherapy alone is less effective at preparing these patients for surgery. The clinical experts acknowledged that there was no clinical trial data supporting this hypothesis, but believed there was a firm rationale and that clinical trial data were expected in a couple of years. CROSS is not proposed for use in patients with gastric cancer (i.e. no junctional or oesophageal involvement) because it is difficult to target radiotherapy here; these patients would receive a chemotherapy regimen. The clinical experts remained convinced about the clinical benefit from the CROSS regimen in patients with adenocarcinoma, despite the lack of statistical significance in the results for this subgroup, as the hazard ratio for survival trended convincingly towards superiority with this regimen.

In camera, the Committee was convinced that the very large increases in overall survival witnessed from the CROSS regimen justified its addition to the formulary. The Committee was satisfied that the clinical oncologists and radiologists were utilising a multi-disciplinary approach to identify the most appropriate regimen for patients, and were employing the same team to monitor outcomes.

In summary, the Committee agreed to add the CROSS chemoradiotherapy regimen to the NCL Joint Formulary to treat adenocarcinoma of the oesophagus or the gastro-oesophageal junction.

Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: As per other chemotherapy regimens (varies across Trusts)
Fact sheet or shared care required: No

7.2 **FLOT chemotherapy regimen in gastric or gastro-oesophageal junction adenocarcinoma (Applicant: Dr K-K Shiu, UCLH)**

The Committee considered an application to use the peri-operative FLOT chemotherapy regimen (docetaxel, oxaliplatin, disodium folinate and 5-FU) in the treatment of resectable adenocarcinoma of the

stomach or gastro-oesophageal junction. This regimen represents an alternative to three regimens already in use locally: cisplatin plus capecitabine; cisplatin plus 5-FU; and mFOLFOX. The data considered was limited to one fully published phase 2 study and a phase 3 study published as an abstract.

Al-Batran (n=716) was a phase 3 trial presented in abstract form at the 2017 ASCO conference. Adult patients were randomised to receive either the FLOT regimen, an ECF regimen (epirubicin, cisplatin, 5-FU) or ECX regimen (epirubicin, cisplatin, capecitabine) for treatment of adenocarcinoma of either the stomach or gastro-oesophageal junction. Although there was limited information available in the abstract, the Committee was encouraged by the large treatment effect reported for the FLOT regimen versus ECF/X. The overall survival for FLOT was 50 months compared to 35 months for ECF/X (HR=0.77 [95% CI 0.63 to 0.94], p=0.012). The three-year overall survival was higher for the FLOT regimen (57%) than the ECF/X regimen (48%), as was PFS (FLOT: 30 months vs. ECF/X: 18 months [HR=0.75; 95% CI 0.62 to 0.91; p=0.004]).

Al-Batran had earlier published the phase 2 part of the trial described above (n=300). The primary outcome considered was the proportion of patients with pathological complete regression in the primary tumour (proportion of patients with pathological complete regression over the total number of patients evaluated centrally by the study pathologist). The FLOT regimen demonstrated a higher proportion of pathological complete regression (TRG1a) than did the ECF/X regimens (16% vs. 6%; p=0.02). Secondary outcomes reviewed were margin-free resection (R0) (85% in FLOT vs. 74% in ECF/X), serious adverse events (25% of FLOT patients vs. 40% ECF/X patients reported at least one serious peri-operative medical or surgical adverse event), and 30-day mortality (2% for FLOT vs. 4% for ECF/X).

In camera, the Committee acknowledged the lack of fully published phase 3 data to support use of this regimen, however considered the large improvements in overall survival (15 months) to be sufficiently encouraging to support approval of the FLOT regimen for addition to the NCL Joint Formulary for this indication. The Committee was satisfied that the clinical oncologists and radiologists were utilising a multi-disciplinary approach to identify the most appropriate regimen for patients, and were employing the same team to monitor outcomes.

Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: As per other chemotherapy regimens (varies across Trusts)
Fact sheet or shared care required: No

7.3 Insulin degludec (Tresiba) for adults with Type 1 diabetes – appeal with new data (Applicants: Dr S Naik [UCLH], Dr E Karra [RFL] and Dr M Cohen [RFL])

This agenda item was considered in parallel with item 7.4.

7.4 Insulin degludec (Tresiba) for paediatrics and adolescents with Type 1 diabetes – evaluation results (Applicant: Dr B White, UCLH)

The Committee considered an appeal for insulin degludec for patients from the age of 1 year with Type 1 diabetes who have (i) intermittent adherence to basal insulin leading to recurrent DKA or HbA1c ≥9.5% despite regular intervention from MDT or (ii) problematic hypoglycaemia. Problematic hypoglycaemia was defined as (a) two or more episodes per year of severe hypoglycaemia (requiring assistance from a third party), or (b) one episode associated with impaired awareness of hypoglycaemia, extreme glycaemic lability/variation, or major fear and maladaptive behaviour.

The Committee considered the evidence for insulin degludec pertaining to reducing hypoglycaemia, in the form of new / published data following the original appeal in 2016.

SWITCH 1 (n=501) was a randomized, double-blind, crossover, multi-centre, treat-to-target trial to assess whether insulin degludec is non-inferior or superior to insulin glargine in reducing the rate of symptomatic hypoglycaemia. Adults with T1DM treated with HbA1c ≤10%, BMI ≤45Kg/m^2 who fulfilled at least one of risk criteria for developing hypoglycaemia and/or had an episode of hypoglycaemia within the last 12 weeks were included. Patients were randomised 1:1 to insulin degludec or insulin glargine. The primary endpoint was the rate of overall 'severe or blood glucose confirmed (<3.1 mmol/L) hypoglycaemia' during the maintenance period. Secondary endpoints included rates of nocturnal 'severe or confirmed hypoglycaemia' and 'severe hypoglycaemia'. Results found degludec was associated with a lower rate of overall hypoglycaemia: 22.0 vs. 24.6 episodes per patient year of exposure (PYE) for degludec and glargine respectively (rate ratio = 0.89 [95% CI: 0.84 to 0.94], NNT = 1 patient for 3 years to avoid 8 overall confirmed hypo). Degludec was also associated with a lower rate of severe hypoglycaemia:

0.4 vs. 0.7 episodes per PYE for degludec and glargine respectively (rate ratio = 0.65 [95% CI: 0.48 to 0.89], NNT = 1 patient for 3 years to avoid 1 severe hypo). There was a trend towards a small increase in HbA1c.

A poster presentation of observational data from ABCD National Audit included a subgroup analysis of people who switched to degludec due to hypoglycaemia (n=101); of these 65% experienced some reduction in minor hypoglycaemia, 53% experienced some reduction in severe hypoglycaemia and 64% experienced some reduction in nocturnal hypoglycaemia. A larger open-label observational study 'EU-TREAT' (n=1717) found a significant reduction in all types of hypoglycaemia after 6 & 12 months of degludec. By contrast, a smaller open-label observational study in Germany/Austria (n=360) found no significant changes observed regarding rates of severe hypoglycaemia although results were trending in the correct direction.

The Committee considered the new supportive evidence for insulin degludec for patients who had intermittent adherence to basal insulin. An audit in SEL, which included patients with recurrent DKA, found a 67% reduction in DKA-related admissions (absolute values not presented). No other data were identified.

The price of insulin degludec had dropped from £72.00 for 5 x 300 unit pens to £46.60 for 5 x 300 unit. Patients treated with degludec on average inject fewer units of basal insulin compared to Lantus® therefore the annual cost per patient is expected to be similar. Insulin degludec will be 15% more expensive than biosimilar glargine however the overall budget impact is expected to be low provided prescribing is restricted.

The Committee heard from the clinical experts about the negative consequences of severe hypoglycaemia; harm from falling, risk of fatality and the consequences of long term fear of insulin. Avoiding any hypoglycaemic episode was therefore considered beneficial. The Committee considered the discrepancy between the proposed indication and the SWITCH 1 inclusion criteria; the trial included three cohorts which were not at high risk of hypoglycaemia therefore it remained unknown how effective degludec would be in clinical practice. Experts hypothesised the relative risk reduction for degludec on severe hypoglycaemic in the proposed cohort would be similar to that observed in the trial (35%). It was agreed that insulin pumps are the direct comparator to degludec in this cohort, which cost up to £12,000 for 4 years and require a large amount of clinic time and patient education. Reduction in severe hypoglycaemia with insulin pump was thought to be approximately 25% (although NICE TA151 reports a risk reduction of 75%). There was uncertainty amongst clinicians as to whether insulin degludec would delay time to pump therapy for eligible individuals.

The Committee heard from clinical experts that patients with intermittent adherence to basal insulin would not be candidates for insulin pumps and the protracted duration of action of degludec was expected to provide some protection from DKA. Each episode of DKA costs approximately £3,000; given the minimal budget impact degludec compared with Lantus, degludec is likely to be cost-effective for this indication.

There was no evidence that degludec reduces HbA1c in the general Type 1 diabetes population; treat-to-target randomised controlled trials trended against degludec use, EU-TREAT showed a small but not clinically meaningful reduction from baseline (-0.2%) and the German/Austrian found no difference in HbA1c.

In camera, the Committee considered their objections to the original applications had largely been resolved by the price drop and SWITCH 1 data. The overall risk to the health economy of adopting degludec was therefore considered low. The Committee were in agreement that the small treatment effects observed in the clinical studies would be unlikely to have a significant impact on outcomes in the real-world, as proven by the conflicting observational data. Given this uncertainty, the Committee agreed degludec should not displace other commissioned therapies for the same indication – namely insulin pumps where clinically appropriate. In summary, the Committee approved insulin degludec for patients with Type 1 diabetes who had (i) intermittent adherence to basal insulin leading to recurrent DKA or HbA1c ≥9.5% despite regular intervention from MDT or (ii) problematic hypoglycaemia and were not eligible for an insulin pump. Problematic hypoglycaemia was defined as (i) two or more episodes per year of severe hypoglycaemia [requiring assistance from a third party], or (ii) one episode associated with impaired awareness of hypoglycaemia, extreme glycaemic lability/variability, or major fear and maladaptive behaviour. Patients initiating degludec for hypoglycaemia should demonstrate an improvement between pre- and 6-month post Gold and Clarke hypoglycaemia questionnaires *and* experience no inpatient admission for hypoglycaemia.

The Committee asked for the support of the endocrinology community in increasing the uptake of biosimilar glargine to offset the additional cost of degludec.

Decision: Approved with additional restriction
Prescribing: Secondary care initiation, continuation in primary care
Tariff status: In tariff
Funding: Hospital and GP
Fact sheet or shared care required: No

7.5 Faster acting insulin aspart (Fiasp®) for adults with Type 1 diabetes and gestational diabetes (Applicants: Dr S Naik [UCLH], Dr E Karra [RFL] and Dr M Cohen [RFL])

The Committee considered an application for Fiasp® for patients with Type 1 who (i) require greater flexibility in dosing times or (ii) prefer to inject post-meals. An application was simultaneously considered for the use of Fiasp in pregnancy.

ONSET 1 was a 26-week, multicentre, randomised controlled trial to compare double-blind mealtime Fiasp with mealtime NovoRapid (n=761). A 26-week open-label group with postmeal Fiasp provided a second comparison (n=382). Adults with T1DM treated with basal-bolus insulin and HbA1c 7.0-9.5% were included. Patients were randomised 1:1:1 to mealtime Fiasp, mealtime NovoRapid or postmeal Fiasp (mealtime defined as injecting 0-2 minutes before a meal; postmeal defined as injecting 20 minutes after the start of the meal). The study was powered to confirm non-inferiority of HbA1c between mealtime Fiasp and mealtime NovoRapid in terms of change from baseline after 26 weeks of treatment (primary end point). Secondary endpoints included 1, 2, 3 & 4 hour post-prandial glucose (PPG) levels after a standard liquid meal test (80 g carbohydrate consumed within 12 min) after 26 weeks treatment, and 7-9-7-point self-monitoring of plasma glucose (SMPG) profile before clinic visits at weeks 0, 12 and 26. For the comparison of mealtime Fiasp with mealtime NovoRapid, Fiasp was shown to be non-inferior to NovoRapid for 'change in HbA1c from baseline' (estimated treatment difference –0.15% [95% CI: –0.23 to –0.07]) with any numerical difference being smaller than the minimally clinically important difference (typically reported to be 0.3 to 0.4%). Mealtime Fiasp was shown to have lower 1 & 2 hour 'standard meal PPG levels' and correspondingly, there was a statistically significant increase in the number of 'severe or BG confirmed hypoglycaemic events within 1 hour of a meal' (275 vs 131; rate ratio = 1.48 [95% CI: 1.11 to 1.96]), however the number of events that occurred during this window was only a small fraction of the overall number (~2%). Mealtime Fiasp did not lead to an overall increase in the number of severe or BG confirmed hypoglycaemic events (RR=1.01 [95% CI: 0.88 to 1.15]). Despite observed differences in 1 & 2 hour 'standard meal PPG levels', there were no differences in the average 7-9-7-point SMBG profile. For the comparison of postmeal Fiasp with mealtime NovoRapid, Fiasp was shown to be non-inferior to mealtime NovoRapid for 'change in HbA1c from baseline' (estimated treatment difference 0.04% [95% CI: –0.04 to 0.12]). Postmeal Fiasp was shown to have higher 1 hour 'standard meal PPG level' but was similar in terms of 2, 3 & 4 hours 'standard meal PPG levels' and severe or BG confirmed hypoglycaemic events (RR=0.92 [95% CI: 0.81 to 1.06]).

It was noted that the observed differences in post-prandial glucose (PPG) control with Fiasp had no meaningful impact on self-monitoring of blood glucose (7-9-7 point SMBG), disease orientated outcomes (HbA1c) or patient orientated outcomes (hypos). Furthermore, reducing glycaemic variability alone is not known to be correlated with micro and macrovascular complications.

The formulation difference between Fiasp and NovoRapid is the addition of nicotinamide which increases the time to maximum concentration of insulin in the plasma by 7.3 minutes. The SPCs however specify very similar administration requirements (administer immediately before a meal or soon after a meal).

The Committee heard from the clinical experts that Fiasp would allow a change in practice from recommending injecting 15 to 20 minutes pre-meal to recommending injecting 2 minutes pre-meal. Fiasp would also offer fast onset of action if a patient forgets to inject pre-meal. Avoiding rises in PPG is particularly important in pregnancy due to the association of adverse outcomes on both mother and baby but is also important in non-pregnant individuals to achieve tight glycaemic control. The Committee noted the benefit of reducing PPG would only be observed if Fiasp was injected at the same time pre-meal as NovoRapid which is inconsistent with the plan to bring forward the injection time by 18 minutes. Fiasp might be beneficial when used in insulin pumps however this remained to be determined in a Phase III study.

Fiasp and NovoRapid both cost £30.60 therefore no budget impact is expected in the short term. NovoRapid is no longer under patent protection; however a biosimilar aspart remains several years away.

In camera, the Committee concluded Fiasp was a slightly better insulin but offered no meaningful advantage as part of multiple-daily dosing injection regimens from the perspective of patient outcomes (HbA1c or hypoglycaemia). The Committee did not agree that the data for Fiasp supported a delay in recommended injection time of 18 minutes (from 20 minutes pre-meal to 2 minutes pre-meal). The risks of a large-scale switch to Fiasp were proposed as a detrimental effect on the adoption of biosimilar NovoRapid in the future, and the risk of medication errors with availability of a slightly different and unknown insulin aspart to the formulary. With regards to use of Fiasp in pregnancy, it was not clear from the experts whether Fiasp would be used to reduce PPG levels (i.e. injecting Fiasp at the same time as NovoRapid currently is) or used to reduce the inconvenience of meal time injection (i.e. injecting Fiasp 18 minutes nearer the meal), the latter being unsupported by the trial data.

Decision: Not approved

8. **JFC Work plan**

This item was included for information only. Any questions should be directed to Mr Barron.

9. **Next meeting**

Monday 15 January 2018, G12 Council Room, South Wing, UCL, Gower St. WC1E 6BT

10. **Any other business**

Nil