Drugs Group Minutes 10th March 2016

Members in attendance (or on telecon): Dr Susan O'Reilly, Dr Roy Browne, Dr Kevin Kelleher, Dr Valerie Walsh, Dr David Hanlon, Anne Marie Hoey, Dr Laura McCullagh (for Prof Barry), Ms Angela Fitzgerald, Dr Helen Flint

Apologies: Dr Philip Crowley, Prof Michael Barry, Dr Aine Carroll

In attendance: Mr Shaun Flanagan, Ms Kate Mulvenna

A. The minutes of the previous meetings were agreed
   a. 19th November
   b. Telecon 21st December

B. Matters Arising
   Mr Flanagan updated the group on revised control procedures required by the DOH and DPER as part of NSP 2016. This included a requirement that a significant number of medicines would become the subject of government memos.

C. Reviews of Medicines
   1. Apremilast for Plaque Psoriaisis
      There was a second indication (psoriatic arthritis) for which a HTA was ongoing and the group considered that recommendations in relation to pricing and reimbursement should be considered when the full implications of all licensed indications was understood.

   2. Ceritinib for Alk + NSCLC
      The Drugs Group considered that despite the uncertainties, the product would only be used post Crizotinib in a group of patients clearly identifiable by a biomarker thereby limiting the possible budget impact. The medicine would most likely result in some improvements in quality of life for patients with an extremely poor prognosis and few treatment options i.e. patients with high unmet need. The Drugs Group would recommend in favour of reimbursement.

   3. Idelalisib for CLL & FL
      The Drugs group was uncomfortable with the approach taken by the pharmaceutical company to the Health Technology assessment. The Drugs Group was unable to arrive at a recommendation in relation to the product and requested that clinical experts at the NCCP be asked whether there were significant advantages of Idelalisib over Ibrutinib or vice versa.

   4. Olaparib for Ovarian Cancer
      The Drugs Group requested additional information in relation to the plan for BRCA testing from the NCCP and also advice as to how many platinum courses should be required to qualify for reimbursement. In addition NCCP / CPU were asked to re-engage with the company.

   5. Pembrolizumab for Malignant Melanoma
      The Drugs group recognised that the medicine appeared to be an improvement over Ipilimumab and would be supported by clinicians. The Drugs group noted that the product was cost effective when compared to Ipilimumab but noted Ipilimumab was cost ineffective. The Drugs Group felt it would wish to approve 1st line but subject to improved commercial offering and greater certainty around the likely level of use of Ipilimumab post pembrolizumab. The NCCP / CPU were requested to seek an improved commercial offering and to seek to arrive at an estimate of likely 2nd line Ipilimumab use. The Drugs Group would consider the issue of 2nd line Pembrolizumab use on the basis of any revised commercial offering. It noted 2nd line use did not appear to be cost effective.

   6. Ponatinib for certain CML and ALL cohorts
   7. Vedolizumab for Ulcerative Colitis and Crohns Disease
   8. Vismodegib for basal cell carcinoma
      There was insufficient time available to consider these 3 medicines.

Contains Commercially Confidential Information – All Budget Impacts, All Cost Effectiveness Numbers if released would breach commitments made in commercial negotiations and impact on State's ability to negotiate discounts in the future

Drugs Group Meeting - 8.30am - 1st June 2016

Pembrolizumab for Malignant Melanoma

First Line Treatment Recommendation

The Drugs Group recommend funding of Pembrolizumab as 1st line monotherapy. However, the Drugs Group recommends that 2nd line use of Ipilimumab post Pembrolizumab is not reimbursed except in circumstances where patients are unable to tolerate Pembrolizumab. The Drugs Group recommends that the National Cancer Control Programme should establish a Melanoma Board / Advisory Committee to provide clinical advice on the optimal sequencing and role of the new and existing Immuno-modulatory agents (Ipilimumab, Pembrolizumab and Nivolumab), combinations of same, existing high cost oral agents (Dabrafenib, Vemurafenib) and soon to be considered new oral agents such as the MEK Inhibitors (Cobimetinib and Trametinib).

Clinical Evidence: The Keynote-006 clinical trial established that Pembrolizumab is more effective than Ipilimumab demonstrating improvements in progression free survival (PFS) and overall survival (OS). It is also better tolerated than Ipilimumab.[i]

	Pemb 2mg/kg every 2 weeks	Pemb 2mg/kg every 3 weeks	Ipilimumab
Median OS @ IA2 Hazard ratio	NR	NR 0.69 (95% CI: 0.52, 0.9; p=0.00358)	NR
OS @ 12 months (estimated)	74.1%	68.4%	58.2%
PFS @ IA1 Hazard Ratio		0.58 (95% CI: 0.47, 0.72; p<0.00001)	
PFS @ 6 months (estimated)	47.3%	46.4%	26.5%
Response Rate	33.7%	32.9%	11.9%
Grade 3+ Adverse Events		33.2%	36.7%
Serious Adverse Events		24.9%	30.1%
Treatment related adverse events (G3 – 5 severity)	13.3%	10.1%	19.9%

Cost Effectiveness: Pembrolizumab has been compared to Ipilimumab a medicine which is itself very cost inefficient (despite robust commercial discussions in 2012). Ipilimumab represents the existing standard of practise. Based on the current pricing position for Ipilimumab, Pembrolizumab would satisfy a cost effective threshold of €20,000 per QALY. The Corporate Pharmaceutical Unit / NCCP sought to negotiate terms which would improve overall cost effectiveness i.e. to arrive at a position where Pembrolizumab provided more benefit at lower cost than Ipilimumab [redacted] that would achieve that goal.

Budget Impact: The projected 5 year total spend on Pembrolizumab was originally estimated at around €64m. Commercial negotiations have [redacted]. The net budget impact of Pembrolizumab depends on the level of Ipilimumab use post Pembrolizumab. There is no clinical information available to guide decision makers on the likely percentage that might apply if this was allowed. If Ipilimumab is not allowed post Pembrolizumab then it is probable that Pembrolizumab could be introduced at near to budget neutral costs. If Ipilimumab is used post Pembrolizumab the 5 year net budget impact would most likely range somewhere between [redacted]m (12% of patients receive Ipilimumab use post Pembrolizumab) to [redacted]m (40% receive Ipilimumab).

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Second Line Treatment Recommendation

The Drugs Group recommend reimbursement as 2nd line monotherapy based on the revised commercial terms negotiated.

Clinical Evidence: The Keynote-002 trial demonstrated a modest (0.2 month) difference in median progression free survival when compared with physician choice of chemotherapy and little or no difference in overall survival. However UK NICE reported that 48% of patients in the chemotherapy group had crossed over to Pembrolizumab in the Keynote-002 trial. NICE had accepted a company model which corrected for crossover and resulted in a suggested overall survival benefit of 3.5 months.

	Pemb 2mg/kg Q3W	Pemb 10mg/kg Q3W	Inv Choice Chemotherapy
Median PFS Hazard Ratio	2.9 months (2.8, 3.8) 0.57 (95% CI: 0.45, 0.73; p<0.0001)	2.9 months (2.8, 4.7) 0.50 (0.39, 0.64; p<0.0001)	2.7 months (2.5, 2.8)
Median OS	11.4 months (10.2, NR)	12.5 months (9.7, NR)	11.6 months (9.0, 16.3)
Hazard Ratio (immature survival data / confounded by crossover)	0.88 (0.64, 1.22; p=0.229)	0.78 (0.56, 1.08; p=0.066)	
Median OS (adjusted for crossover)	11.4 months		7.9 months
Hazard Ratio (adjusted for crossover)	0.63 (0.45, 0.88; p=0.007)		
	No clinically meaningful or statistically significant differences betweeen Pembrolizumab arms. For Pembrolizumab: Mean PFS = 25.43 weeks Mean OS = 46.8 weeks @ 73 weeks max follow up		

Cost Effectiveness: Pembrolizumab has not demonstrated cost effectiveness as a second line treatment post Ipilimumab. The incremental cost effectiveness ratio is estimated at [redacted] per quality adjusted life year at the revised commercial offering.

Budget Impact: The expected budget impact is modest and is likely to be lower in future years as the existing cohort of patients who have failed Ipilimumab and would be candidates to receive Pembrolizumab (or competitors) second line will reduce because Pembrolizumab will be used first line. 5 Year budget impact is estimated at around [redacted]m, the majority of this will occur in the first 12 months.

Other Information - Nivolumab is under consideration for the following indications:

- Monotherapy for malignant melanoma (HTA complete: not cost effective at price submitted)
- Combination therapy for malignant melanoma (HTA process ongoing)
- Non squamous non-small cell lung cancer (HTA process ongoing)
- Squamous non-small cell lung cancer (HTA complete: not cost effective at price submitted)
- Renal cell carcinoma (HTA process ongoing)

BMS has sought to [redacted], a number of which have health technology assessments ongoing. The Drugs group was not in a position to [redacted] on the basis of cost effectiveness reports completed to date.

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Olaparib (oral medicine) for Ovarian Cancer

The Drugs Group was unable to arrive at a consensus position on the reimbursement of Olaparib following a very detailed discussion.

Clinical Evidence: In pre-planned sub group analysis of a Phase 2 placebo controlled study (NCT00753545 - Study 19) Olaparib demonstrated a 6.9 month improvement in median (investigator assessed) progression free survival over placebo in the subset of patients with BRCA-mutated ovarian cancer. No overall survival benefit was demonstrated in this subgroup. Following post-hoc analysis (which exclude sites where patients received PARP inhibitor post progression) olaparib showed a 7.6 month improvement in overall survival (which did not reach statistical significance) over placebo (34.9 months vs 27.3 months @ 70% maturity). There is very significant uncertainty around that estimate.

Cost Effectiveness: The NCPE estimate a cost of [redacted] per QALY which is significantly over the standard decision thresholds (whether €20,000 / QALY or €45,000 / QALY). There is significant uncertainty around this estimate.

Budget Impact: the 5 year (2016-2020) budget impact is estimated at €[redacted]m (following commercial discussions). 9 to 17 patients would be treated per annum

Unmet Need: The Drugs Group discussed in detail unmet need and the poor prognosis for women with ovarian cancer. It was unable to arrive at a consensus around recommending olaparib. There was consensus that measures to increase early diagnosis were likely to be the best mechanisms to address poor survival rates.

[i] IA1 = Interim Analysis 1, IA2 = Interim Analysis 2

Minutes of Drugs Group

Date: Thursday, 23rd June 2016, 8.30am

Venue: 3rd Floor meeting room, Offices of the Dublin Midlands Hospital Group, Block D 3rd Floor Park Gate Business Centre, Park Gate Street, Dublin, D08 YFF1

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Roy Browne, Dr Valerie Walsh, Prof Michael Barry, Dr Helen Flint, Dr David O'Hanlon, Dr Kevin Kelleher (by phone), Ms Anne Marie Hoey

Apologies Received: Ms. Angela Fitzgerald, Dr Áine Carroll

In attendance: Mr Shaun Flanagan, Ms Kate Mulvenna, Ms Joan Donegan (new member joining)

A. Minutes of previous meetings
The minutes of the previous meetings of the 10th March 2016 and 1st June 2016 had only been circulated within the previous 24 hours. The minutes were agreed in principle subject to any errors noted by the members being corrected.

B. Matters arising from minutes and update on previous recommendations
   a. Pembrolizumab monotherapy for malignant melanoma had been recommended by the Group at its meeting of 1st June 2016. SF / SOR confirmed that the HSE Leadership had considered and approved the recommendations.
   b. In relation to Olaparib for ovarian cancer SF / SOR reported the feedback from the Directorate that it could only consider formal recommendations from the Drugs Group. SF was asked to revert to the pharmaceutical company to establish whether there was any additional information (clinical or economic) available that would enable the Group to arrive at a formal recommendation.
   c. SF confirmed that the HSE had been made aware that the government had considered Ibrutinib (CLL, Mantle Cell Lymphoma and Waldenstrom macroglobinaemia) and the DOH was completing the paper work necessary to formally communicate the position to the HSE. Ibrutinib had recently received an extension to 1st line CLL therapy and an additional assessment process would commence. In the interim reimbursement would only apply to the indications for which government support was in place. A key learning from this first experience with the new process was the importance of making clear that following a Government decision the HSE has to go through a number of implementation steps to enable reimbursement (i.e. communicate with applicant, communicate with contractors, put product code and price in place, confirm product available in market etc).

C. **Reviews of Medicines on previous meeting agenda** (insufficient time had been available to consider these medicines at the previous meeting).

1. Apremilast for Plaque Psoriaisis
The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. Clinical efficacy was modest. There were a range of reimbursed alternatives available. The group noted that that Apremilast was significantly more expensive than other non biologic therapies. There were concerns around the economic models provided by the applicant. The group believed that it was unlikely that the medicine would result in cost savings in the long term as patients would sequence through therapies. The group noted that all considerations in relation to economic value were highly dependent on the sequence in which therapies would be used. The Drugs groups considered that a lower price would be required to enable a recommendation in favour of reimbursement of this medicine. If a lower price was to emerge from commercial negotiations the Group agreed that it would reconsider its recommendation in parallel with guidelines around prescribing and sequencing.

2. Idelalisib for CLL & FL
The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. The Group was aware of the review ongoing at the EMA (commenced 11th March 2016). Pending the outcome of this review the Group did not review Idelalisib.

3. Ponatinib for certain CML and ALL cohorts
The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. The group considered that this medicine offered an additional end of line of therapy for a small number of patients. The medicine was associated with significant adverse reactions in some patients which would limit its use. In the absence of a response treatment is recommended to be stopped after 3 months. Numerically it satisfied a cost effectiveness threshold of €45,000 per quality adjusted life year albeit that there were some concerns related to the modelled clinical efficacy estimates. The budget impact was relatively modest. (Note: information provided by the pharmaceutical company Ariad indicated just [redacted] patients had received treatment under a compassionate access programme). The pharmaceutical company was not agreeable to a price reduction due to the small market size. The group recommended in favour of reimbursement given ponatinib would only be used as an additional option for patients for whom treatment options were limited.

4. Vedolizumab for Ulcerative Colitis and Crohns Disease
The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. The Group noted that the medicine had market authorisation for a number of years in Ireland. The group was concerned to learn that the product had been marketed to (and purchased by) Irish hospitals in advance of the completion of the review (and at a price significantly above the application price). The group advised that improved communications were required with the Acute sector in relation to medicines under consideration.
In relation to Ulcerative Colitis, the concerns of the NCPE in relation to the clinical and economic modelling were discussed. The potential impact of more frequent dosing and the absence of a stop rule at 12 months on cost effectiveness were noted. The group noted the concerns raised by the NCPE in relation to the Crohns Disease indication. The Drugs Group agreed unanimously that a substantial price reduction would be required to enable it to support funding of Vedolizumab for Crohns disease in the Acute Hospital system. The Drugs group requested that the HSE re-engage with Takeda to substantively improve the price on offer.

5. Vismodegib for Basal Cell Carcinoma
The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. This was the 3rd time the medicine had been considered by the group. The group noted that this medicine was used to symptomatically treat lesions for which there were very limited treatment options. Some of these lesions were visually disturbing and were associated with very significant morbidity. The NCPE report from 2014 had shown that at the price submitted the value for money associated with this medicine had failed to approach any reasonable cost effectiveness threshold. The original budget impact estimate had indicated a potential budget impact of €14.7m over 5 years but Roche were now offering [redacted] would mean that the cost per QALY was most likely around [redacted] (In 2014, NCPE had advised that a 61% reduction would be required to satisfy €100,000 / QALY). Following a discussion a vote ensued. The group arrived at a majority decision to recommend in favour of reimbursement. A number of members opposed the recommendation.

D. New Medicines not on previous meetings agendas

6. Nintedanib for Idiopathic Pulmonary Fibrosis and Non-Small Cell Lung Cancer
The Group had been provided with the HTA reports in relation to this medicine. The Drugs Group was unable to complete its deliberations and agreed that an additional meeting would be held in July to consider this and other medicines in the pipeline in detail.

7. Ataluren for Duchenne Muscular Dystrophy
   The Group had been provided with the HTA reports and a slide set summarising information in relation to this medicine. The Drugs Group was unable to complete its deliberations and agreed that an additional meeting would be held in July to consider this and other medicines in the pipeline in detail.

8. Nivolumab monotherapy for Malignant Melanoma
9. Nivolumab monotherapy for Squamous Cell Non-Small Cell Lung Cancer
   The Group had been provided with the HTA reports in relation to the above indications for this medicine. In addition the Group were made aware of the [redacted] (including indications for which assessments were ongoing or planned such as combination therapy for melanoma, non-squamous NSCLC and renal cell carcinoma) which BMS was taking. The Drugs group noted the various compassionate access programmes which were or had been in place. The Drugs Group was unable to complete its deliberations and agreed that an additional (previously unplanned) meeting would be held in July to consider this and other medicines in the pipeline in detail.

AOB: Dr Helen Flint confirmed she would be replaced on the Group by Joan Donegan. On behalf of the Drugs Group the Chair thanked Dr Flint for her service and contribution to the Drugs Group and wished her well in her future endeavours.

It was agreed that the next meetings would in the PCRS building in Finglas.

Meeting of Drugs Group (to address agenda items from 23rd June 2016)

Date: Thursday 21st July 2016 8.30am

Venue: 4th Floor Annex, PCRS, Exit 5, M50, Finglas, Dublin 11

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Valerie Walsh, Prof Michael Barry, Dr David O'Hanlon, Dr Kevin Kelleher (by phone), Dr Philip Crowley (by phone), Ms Anne Marie Hoey, Ms Joan Donegan

Apologies Received: Ms. Angela Fitzgerald, Dr Áine Carroll, Dr Roy Browne,

In attendance (non-voting): Mr Shaun Flanagan, Ms Ellen McGrath, Ms Kate Mulvenna,

1. Nintedanib for Idiopathic Pulmonary Fibrosis and Non-Small Cell Lung Cancer.
   The Group had been provided with the HTA reports for both indications and a slide set summarising information in relation to the IPF indication. The group noted that the HSE had approved (in 2013) the reimbursement of Pirfenidone a competitor product for IPF following a commercial-in-confidence offer of improved commercial terms. The group noted that the cost effectiveness of Nintedanib versus Pirfenidone was highly dependent on relative pricing. Neither Nintedanib nor Pirfenidone appeared to be cost effective when compared to best supportive care. A number of members raised the issue of whether there was information available to the HSE in relation to the impact of Pirfenidone in practise. It was agreed the Medicines Management Programme would liaise with key opinion leader(s) in relation to establishing same. The group considered that Nintedanib was somewhat more expensive than Pirfenidone and that a revised price should be explored with the company (over and above previous progress). A number of members believed that a hard budget cap on these medicines should be considered given the modest clinical benefit. The group would consider the smaller budget impact indication (NSCLC) in the context of any revised commercial offering.

2. Ataluren for Duchenne Muscular Dystrophy
   The Group had been provided with the HTA report and a slide set summarising information in relation to this medicine. The group discussed the medicine in detail. The group agreed that Duchenne Muscular Dystrophy was a Rare Disease with a very significant unmet need which the Health System would wish to address. The group considered the clinical information in relation to Ataluren. Ataluren could treat a sub-group of the patients with Duchenne Muscular Dystrophy. The group considered that the scientific data was uncertain. The group noted a trend in favour of the lower dose in the clinical trials on surrogate markers at the week 48 time point for 6MWD only (primary outcome) but noted that when a higher daily dose of Ataluren was used it produced clinical results which appeared inferior to or no better than placebo for this outcome. The company rationalised this to the EMA as explainable via a bell shaped curve response. This higher dose was not approved by the EMA. The group noted that Ataluren had received conditional marketing authorisation (by majority opinion) from the European Medicines Agency but had not received marketing authorisation in the USA from the US FDA thereby confirming the uncertainty around the clinical information. The lack of serious side effects was considered by the EMA as relevant to its decision. The Group noted that the HSE was required to consider the magnitude of the clinical effects and its impact on cost effectiveness. Ataluren was an expensive medicine. Even when using favourable cost estimates (e.g. lower median body weight, later commencement of treatment in model resulted in lower estimates of cost) the costs per life year gained or quality adjusted life year gained exceeded €1 million/ QALY. The HSE had engaged with the pharmaceutical company to achieve an improved commercial offering but the cost per QALY would still exceed €500,000 (at best). The group noted that the budget impact was relatively modest i.e. [redacted]m over 5 years. The group was unable to recommend reimbursement due to the uncertainty around clinical evidence and the impact on the ability to fund other services or needs if Ataluren were to be funded. The group considered that [redacted]m was a substantial amount of funding. The group confirmed it would be eager to review Ataluren in the future should more robust clinical information emerge.

3. Nivolumab monotherapy for Malignant Melanoma
The Group had been provided with the HTA report and a slide set summarising information in relation to this medicine. In additional preliminary information (slide sets) in relation to combination therapy with Ipilimumab was also provided. The Drugs Group agreed that it was almost impossible to consider decisions around reimbursement for melanoma without fully understanding the evidence around the benefits and the costs of combination therapy. The group noted that Pembrolizumab had recently been funded for monotherapy and was administered every 3 weeks. Pembrolizumab does not have market authorisation approval for combination therapy. Nivolumab was required to be administered every 2 weeks. The group agreed that it would not be possible to put in place a monitoring system to restrict access to Nivolumab monotherapy if reimbursement was agreed. Very significant budget impacts would accrue over 5 years. The group noted that BMS had [redacted]. The group considered that it could not recommend reimbursement of future indications in advance of completing due digilance on each indication. SF was instructed to seek improved commercial terms for the melanoma indication.

4. Nivolumab monotherapy for Squamous Cell Non-Small Cell Lung Cancer
The Group had been provided with the HTA report and a slide set summarising information in relation to this medicine. The NCCP Therapeutic Review process had recommended that reimbursement be approved subject to a substantial reduction in price. Clinicians on the NCCP review had clearly flagged their view that the medicine was clinically effective but also had recognised that there were significant concerns around cost effectiveness and budget impact. Nivolumab was associated with a 3.22 month survival advantage. The NCPE estimated a cost per QALY of at least €136,000. Commercial discussions resulted [redacted] with an NCPE estimated cost per QALY of at least [redacted] for this indication. The estimated net budget impact was €[redacted] per annum to treat approximately 140-150 patients per annum. The group noted that BMS had made a [redacted]. The group considered that it could not recommend reimbursement of future indications in advance of completing due digilance on each indication. SF was instructed to seek improved commercial terms for the squamous cell NSCLC indication.

Additional preliminary slide sets were provided detailing relevant information around non-squamous NSCLC and metastatic renal cell carcinoma to assist members to understand [redacted].

AOB: Members discussed the importance of reviewing previous reimbursement decisions to ensure that intended and expected outcomes were being delivered. Members also discussed the importance of examining current reimbursed items to ensure economic head room was available to fund new services.

Next meeting: 15th September 2016, PCRS Finglas

Drugs Group Minutes Meeting 2016.05

Date: Thursday, 15th September 2016, 8.30am

Venue: 4th Floor Annex, PCRS, Exit 5, M50, Finglas, Dublin 11

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Roy Browne, Dr Valerie Walsh (by phone), Prof Michael Barry, Dr David O'Hanlon, Dr Kevin Kelleher (by phone), Ms Anne Marie Hoey, Ms Joan Donegan (by phone)

Apologies Received: Ms Angela Fitzgerald, Dr Áine Carroll, Dr Philip Crowley

In attendance (non-voting): Mr Shaun Flanagan (Secretary, CPU PCRS), Ms Kate Mulvenna (Head of Pharmacy Function, PCRS), Ms Jennifer McCartan (CPU PCRS)

Meeting Business:

1. Minutes for the previous meetings of 10th March 2016, 1st June 2016, 23rd June 2016 and 21st July 2016 were approved.

2. Update on Medicines previously considered – recommendations with Leadership
   A. Ataluren for Duchenne Muscular Dystrophy had not been recommended by the Group at its meeting of 21st July 2016. SF confirmed that the HSE Leadership had considered the Drugs Group recommendations and he understood that reimbursement would not be granted for this medicine. Formal written confirmation of the decision was awaited.

   B. Ceritinib for Alk + NSCLC had been recommended by the Group at its meeting of 10th March 2016. SF confirmed that the HSE Leadership had considered the Drugs Group recommendation and he understood had approved the recommendation. Formal written confirmation of the decision was awaited.

   C. Ponatinib for certain CML and ALL cohorts had been recommended by the Group at its meeting of June 2016. SF confirmed that the HSE Leadership had considered the Drugs Group recommendation and he understood had approved the recommendation. Formal written confirmation of the decision was awaited.

   D. Vismodegib for BCC had been recommended by the Group at its meeting of 23rd June 2016. SF confirmed that the HSE Leadership had considered the Drugs Group recommendation and he understood was minded to approve the recommendation but under NSP 2016 was required to submit the intended decision to Government for review.

3. Any other matters arising: no additional matters arose for discussion

4. Medicines for Consideration

   A. Reviews of Medicines on previous meeting agenda

      1. Apremilast for Plaque Psoriasis/ Psoriatic Arthritis

The Group had been provided with the results of commercial negotiations with Celgene and an update on countries where a positive indication had been given. The Group noted that the revised commercial terms negotiated by CPU had [redacted]. Concerns were expressed that with oral dosing providing convenience and a different safety profile compared to some of the current first line inexpensive oral therapies, the budget impact for this molecule may be larger than anticipated. Members expressed concern over the financial uncertainty and risk involved. A minority of the committee was minded to reimburse. The Group agreed that the medicine was more effective than placebo, was most likely less effective than biologics and that the key issue was whether it would be

used prior to less expensive oral therapies as that would drive budget impact. The Drugs Group decided that input from an expert group in Dermatology would be sought via the Clinical Strategy & Programmes Division. The expert group would be asked to provide clarity surrounding most likely sequencing through therapies, to provide expert opinion on whether there would be first-line use and to propose a set of conditions to be applied to the prescribing of this medicine. The Drugs Group would then re-consider the issue of reimbursement. SF to provide slide set with commercial information redacted to the clinical group when identified.

2. Nintedanib for Idiopathic Pulmonary Fibrosis

The Group had been provided with the revised commercial offering from Boehringer Ingelheim which it noted resulted in Nintedanib being probably more effective and [redacted] than Pirfenidone. The Group was made aware of representations from expert physicians in support of this medicine. The Group considered that those representations were not unexpected and were not uncommon for the medicines which it was required to consider. The Drugs Group considered the issue of whether best supportive care or Pirfenidone was the appropriate comparator. The Drugs Group considered that it was reasonable to consider Pirfenidone as the appropriate comparator. The revised commercial terms were noted to satisfy all cost effectiveness thresholds when compared to Pirfenidone and the Drugs Group unanimously supported reimbursement of Nintedanib for this indication.

3. Olaparib for Ovarian Cancer

The HSE had been provided with additional information from Study 19 (academic in confidence) by AstraZeneca which the pharmaceutical company believed would aid certainty surrounding economic analysis. The Drugs Group noted that despite the trial being at [redacted]. The Drugs Group considered that based on imperfect information there appeared to be an identifiable patient group who would gain benefit on treatment with the medicine due to their genetic mutation and who had previously failed platinum-based therapies. The Drugs Group noted that the treatment cohort was approximately 13 patients per year with currently very limited treatment options. The 5 year budget impact of €[redacted] was not insignificant. The Drugs Group expressed concerns surrounding the trial data, potential for bias and the immaturity of data presented to date. It noted that the SOLO-2 trial was ongoing and it should provide better clinical evidence and data on which to formulate a recommendation. If that data were to be available in the near future it would not be sensible for the Drugs Group to make any recommendation given its ongoing concerns. SF to engage with AZ to determine when exactly Solo-2 would report and to revert to the Group.

4. Vedolizumab for Ulcerative Colitis and Crohn's Disease

The Group had been provided with details of a revised commercial offer from Takeda [redacted] and post IPHA agreement. The NCPE had advised that vedolizumab may be considered cost effective in Ulcerative Colitis for TNF-α naïve patients (if a threshold of €45,000 per QALY applied) but that for UC patients who have previously been treated with TNF-α antagonists and patients with Crohn's Disease Vedolizumab was not cost effective. The Drugs Group discussed concerns around potential for escalation of dosing schedule from every eight weeks to every four weeks. SF detailed that this concern had been flagged during commercial negotiations and that the company argued that real world data suggested ~ [redacted] of usage would be at the eight week dose. The Drugs Group noted that the company had offered no commercial security around this figure. The potential impact of more frequent dosing remained a concern for the Drugs Group. The Group decided that reimbursement approval could only be on the basis of eight weekly treatment dosing schedule. The Drugs Group noted the NCPE recommendation that a 37% discount

would be needed to ensure the ICERs were cost effective at a threshold of €45,000 per QALY for the Crohn's indication. The Group discussed the possibility of diagnostic separation as there was a positive inclination towards reimbursement for Ulcerative Colitis but negative towards Crohn's Disease. The Group discussed the challenges this scenario would bring. The Group considered that there was potential for some cross-over of diagnosis between UC and CD. It was noted that the commercial offer as proposed was dependent on [redacted]. The Drugs Group agreed that a managed reimbursement application system would be scoped for Vedolizumab for conditional reimbursement applying to the UC indication only. Reimbursement would only apply to the eight week dose schedule, a consultant application establishing patient suitability and reimbursement would be contingent on the overall offer being applied to UC indication reimbursement only. As this was a hospital medicine, ND Acute Division signature would be required.

B. New Medicines (or indications) not discussed on previous meetings agendas

1. Pertuzumab for HER2-positive Breast Cancer: neo-adjuvant use

The Drugs Group had been provided with a slide set summarising information in relation to this indication (in addition to the NCPE reports). The Group noted that this indication most likely represented less than 5% of the overall cohort of patient with breast cancer. Pertuzumab was already reimbursed for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Roche had presented an economic model for neo-adjuvant use which numerically resulted in the medicine appearing cost effective. The NCPE had expressed concerns surrounding the modelling used and a number of parameters including the number of cycles of chemotherapy included in the model. The Drugs Group discussed the response to treatment and the extent to which it might equate to overall increase in survival or long term benefit to patients. The budget impact was considered to be significant at €12m over five years. The Drugs Group considered that whilst the pathological response was of interest it could not accept the face validity of the model. There was significant uncertainty around the extent to which this response would reduce the risk of the disease recurring and result in longer survival i.e. the clinical information was of interest but immature. The Drugs Group decided that the most appropriate decision was to await the outcome of ongoing clinical trials that would enable more robust economic modelling.

2. Nintedanib for Non-Small Cell Lung Cancer

The Drugs Group had been provided with the revised commercial offering from Boehringer Ingelheim, a slide set summarising key issues and the NCPE reports. The Group noted the significant unmet need for this patient cohort and discussed that although the progression-free survival benefits were relatively modest they were statistically significant in a patient group with very poor prognosis. The NCPE had advised that Nintedanib did not satisfy cost effective thresholds for this indication however the budget impact was modest at €220,000 over five years and [redacted] would apply to this medicine. The Drugs Group supported recommendation for this indication.

3. Trifluridine/Tipiracil for Metastatic Colorectal Cancer

The Group had been provided with a slide set summarising information in relation to this medicine. CPU / NCPE provided an update in relation to pricing against regorafenib following commercial negotiations [redacted]. The Drugs Group considered that notwithstanding the small overall survival improvement in clinical trials this medicine would be cost effective compared to Regorafenib and no net budget impact was likely to accrue due to [redacted]. The group recommended unanimously in favour of reimbursement.

C. Requests for Consideration of Early Access Proposals

1. Osimertinib for Non-small cell lung cancer

The Group had been provided with a slide set summarising information in relation to this medicine, a Rapid Review Assessment and Astra Zeneca's proposal for early commercial access pre-HTA. The Group noted that the immature clinical evidence indicated promising response rates but was insufficient for informing questions surrounding the cost effectiveness of this therapy. A proposed budget impact of €[redacted]m over five years was regarded as conservative. The Drugs Group recognised that while trial data indicated good response rates, a reimbursement recommendation at this point was not possible. The Group looked forward to the availability (imminently) of clinical trial data that would enable cost-effectiveness modelling to be carried out. The Group noted that it had a legislative responsibility under the Health Act and it had to ensure that it could stand over all decisions. It was noted that Pharmaceutical Companies requesting early reimbursement whilst medicines were undergoing clinical trials could decide to offer patients access through a compassionate access scheme.

5. **IPHA Agreement 2016:** New requirements in relation to transparency and process agreed between the State and Industry were included in a Slide set for the Group. The importance to the State of overall affordability and consideration of cost effectiveness at a range of thresholds (€20,000/QALY and €45,000/QALY) were detailed within the accompanying documents to the Agreement.

Drugs Group Minutes

Date: Thursday, 13th October 2016, 8.30am

Venue: 4th Floor Annex, PCRS, Exit 5, M50, Finglas, Dublin 11

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Roy Browne, Dr Valerie Walsh (by phone), Prof Michael Barry, Dr David O'Hanlon, Dr Ann Dee (on behalf of Dr Kevin Kelleher), Ms Anne Marie Hoey, Ms Joan Donegan, Dr Philip Crowley, Ms Angela Fitzgerald

Apologies Received: Dr Áine Carroll,

In attendance (non-voting): Mr Shaun Flanagan (Secretary, CPU PCRS), Ms Kate Mulvenna (Head of Pharmacy Function, PCRS).

1. The Draft Minutes circulated for the Meeting of 15th September were agreed.

2. The Group was provided with the following updates in relation to previous Drugs Group recommendations to reimburse
    a. Apremilast for Psoriasis and Psoriatic Arthritis: Dermatology review pending
    b. Ceritinib in (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib: HSE Leadership / Directorate had decided it was within their authority to approve Certinib.
    c. Ponatinib in CML and ALL: HSE Leadership / Directorate had decided it was within their authority to approve Certinib.
    d. Vismodegib for symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma: The HSE had written to the DoH and it was likely that a government memo would be required.
    e. Nintedanib for Idiopathic Pulmonary Fibrosis: HSE Directorate deliberations were pending.
    f. Nintedanib for NSCLC: HSE Directorate deliberations were pending.
    g. Trifluridine/Tipiracil for Metastatic Colorectal Cancer: HSE Directorate deliberations were pending

3. Update on previous Drugs Group recommendations not to reimburse at this time
    a. Ataluren for Duchenne Muscular Dystrophy: Government memo process was only to be actioned in relation to decisions to reimburse which fell outside of affordability criteria.
    b. Pertuzumab for breast cancer (neoadjuvent use): The HSE was awaiting a response from Roche and when that response was received the recommendation may be required to be presented to the HSE Directorate
    c. Osimertinib (early access proposal) for NSCLC: Drugs Group position notified to company

4. Responses from companies following on from Drugs Group feedback
    a. Olaparib for BRCA+ ovarian cancer: The HSE was awaiting company response.
    b. Vedolizumab for ulcerative colitis: awaiting response.

5. New Medicines for Decision: None this month

6. Update on negotiation on Lumacaftor/Ivacaftor (Orkambi) for CF and request for advice on next steps. The Drugs Group reviewed information in relation to Orkambi to provide oversight on the commercial negotiaton process. The Drugs Group recommended that significant additional movement would be required from Vertex. The prices proposed to date were unreasonable.

7. The next Meeting Date was confirmed as 17th November 2016. It was hoped that the Final Agenda would be confirmed by 4/11/2016 and papers would issue by 08/11/2016

8. Dates were proposed for 2017 Meetings and Schedules as follows:

26/01/2017
30/03/2017
18/05/2017
29/06/2017
14/09/2017
16/11/2017

Drugs Group Minutes, Thursday, 17th November 2016, 8.30am

Venue: 4th Floor Annex, PCRS, Exit 5, M50, Finglas, Dublin 11

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Áine Carroll, Dr Valerie Walsh, Prof Michael Barry, Dr David O'Hanlon, Dr Ann Dee (on behalf of Dr Kevin Kelleher), Ms Anne Marie Hoey,

Apologies Received: Dr Roy Browne, Ms Angela Fitzgerald, Ms Joan Donegan, Dr Philip Crowley,

In attendance (non-voting): Mr Shaun Flanagan (Secretary, CPU), Ms Ellen McGrath (CPU)

The Draft Minutes of the meeting of 11th October were not available for review.

The Drugs Group was provided with updates on progress from previous recommendations

A. Olaparib for Ovarian Cancer: AstraZeneca had confirmed Solo-2 results should be available from 13th January 2017
B. Vedolizumab: Takeda had indicated they were not willing to accept reimbursement for Ulcerative colitis only but would be willing to consider a restricted population for Crohns disease. The Drugs Group reviewed the Takeda proposal. Concerns remained around the estimates of patient numbers. The Group asked that the proportion of patients be robustly validated before a decision could be made.
C. Certinib for lung cancer: Approved by Leadership and reimbursement would be progressed
D. Ponatinib for CML/ALL: Approved by Leadership and reimbursement would be progressed
E. Ataluren (Duchenne Muscular Dystrophy): Drugs Group recommendation had been accepted. Reimbursement had not been approved by Leadership. The Drugs Group noted the EMA CHMP requirement for a Phase 3 trial and noted that additional information should therefore become available in the future to assist decision makers.
F. Nintedanib (Idiopathic Pulmonary Fibrosis /Non-Small Cell Lung Cancer): With Leadership for decision
G. Trifluridine / Tipiracil: With Leadership for decision
H. Vismodegib for basal cell carcinoma had been sent to DoH by HSE Leadership, returned with 3 Questions
    a. Can HSE fund from existing resources?
    b. Can efficiencies release resources?
    c. Could additional conditions be applied? CPU and NCCP had confirmed that a hard cap represented the strongest possible condition.

Medicines for review:

1. Sacubitril/Valsartan for Heart Failure:

The Group noted Sacubitril/Valsaratan was associated with a 20% reduction in cardiovascular death or heart failure hospitalisation over 27 months when compared to Enalapril. Individual components of the endpoints were risk of cardiovascular death (20% reduction) and 1st heart failure hospitalisation (21% reduction). Overall mortality was a secondary endpoint and a 16% reduction over 27 months was reported. The differences in effect were observed early in the trial and were observed at each interim analysis. The medicine also demonstrated improvements in quality of life scores (KCCQ clinical summary score for heart failure symptoms and physical limitations at 8 months compared with Enalapril). The company model estimated an incremental cost of €9,977 for gain of 0.37 QALYs (vs Ramipril 10mg OD) which resulted in an incremental cost effectiveness ratio of €27,080 per quality adjusted life year (QALY) and €23,942 per life year gained (LYG). The product demonstrated improved cost effectiveness against an ARB (Candesartan 16mg) ICER of €25,350/QALY and €21,252/LYG. The most influential parameter related to mortality, the main driver of the model. The product price was reduced by 6% following the 2016 IPHA Agreement and this improved ICER to €25,234/QALY (vs Ramipril). In addition Novartis had agreed [redacted]

The HSE Drugs Group recommended in favour of the reimbursement of Entresto (Sacubitril / Valsartan). The ICERs falls within a range which can be regarded as a cost effective use of HSE resources (even when compared to low cost reference priced comparators). There is a significant budget impact. The reimbursement recommendation was subject to the requirement for an online application form for reimbursement being in place to ensure reimbursement support is restricted to patients with reduced ejection fraction. Appropriate use of the medicine requires access to echocardiography and diagnostic tests. The Drugs group recommended that engagement would be needed with the clinical community and within HSE (via the Heart Failure Clinical Programme / Medicines Management Programme / Primary Care Division) to ensure that necessary supports and processes were in place to ensure optimal use of this medicine.

2. Lumacaftor / Ivacaftor for Cystic Fibrosis:

The group noted the key findings from the two pivotal Phase III clinical trials TRAFFIC and TRANSPORT for the licensed treatment group (NEJM 2015; 373(3): 220-231):

- A statistically significant improvement in the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (ppFEV1), the primary endpoint of both studies, in patients treated when compared with placebo.
- Orkambi at licensed dose led to a mean absolute increase of 2.55% in ppFEV1 at 24 weeks ($p<0.0001$). (increase of 2.8% from baseline to average of week 16 and week 24)
- Pooled trial data indicates a 39% relative reduction in pulmonary exacerbations for the licensed dose. Patients on placebo had a rate of 1.14 pulmonary exacerbations per 48 weeks. Patients on Orkambi had a rate of 0.7 exacerbations per 48 weeks.
- 61% reduction in the rate of pulmonary exacerbations events leading to hospitalisation and a 56% reduction in the rate of events leading to intravenous antibiotics over 48 weeks in patients treated with Orkambi compared to those on placebo.
- This suggests that for every 100 patients treated for 48 weeks with Orkambi, approximately 28 hospitalisations would be avoided and 34 courses of intravenous antibiotics would be avoided.
- No significant difference in the patient reported Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score (quality of life measure) for the licensed dose of Orkambi in either of the pivotal phase 3 studies.
- Incidences of adverse events were generally similar in Orkambi and placebo groups.

The Group the longer term results from the Progress study and the comparison to a historical cohort.

Following commercial negotiations, [redacted]

Following detailed review of the clinical evidence, the economic evidence and the commercial offerings, the HSE Drugs Group unanimously agreed that it was unable to support reimbursement of Lumacaftor / Ivacaftor. The modest clinical evidence was insufficient to support the price proposed by Vertex. The Drugs Group believed it was in line with other international agencies in arriving at this recommendation. Australian, Canadian and UK authorities (to date) had not supported reimbursement of Orkambi at the prices proposed by Vertex. The Drugs Group was obliged to consider the best use of resources and had to be cognescant of implications for the entirety of health services across the public health system.

Review of time available and remaining agenda:

The Drugs noted that the previous 2 deliberations had taken a lot of time due to their complexity. Due to members other commitments it would be impossible to complete all of the remaining agenda. In addition, the NCPE had been unable in the short window between receipt of some commercial offers and the meeting to provide estimates of the revised ICERs and budget impacts (due to the short window and the unavailability of key staff who had prior international commitments). The Group agreed it would arrange an additional meeting for December which would focus on 4 Nivolumab submissions. Note: this would mean that the Drugs Group had met 8 times in 2016 versus the expected commitment to 4 meetings.

3. Nivolumab monotherapy for Malignant Melanoma
4. Nivolumab for squamous cell Non-Small Cell Lung Cancer

5. Nivolumab for non-squamous cell Non-Small Cell Lung Cancer
6. Nivolumab/Ipilimumab dual therapy for Malignant Melanoma

7. Ruxolitinib for polycythaemia vera: Insufficient time remained to review Ruxolitinib.

8. Idelalisib for CLL & FL:

The Drugs noted that with the reimbursement of Ibrutinib for CLL, decision making around Idelalisib was simplified. Idelalisib was less costly that Ibrutinib and was also somewhat less likely to be used than had previously been expected (due to safety concerns). Challenges in the CLL area were more likely to be around 1st line use of Ibrutinib and the challenges presented by further new agents. The Follicular Lymphoma relapsed refractory cohort represented a small discrete number of patients. It was agreed that Idelalisib could be reimbursed.

Drugs Group Minutes Thursday, 15th December 2016, 8.30am

Venue: 4th Floor Annex, PCRS, Exit 5, M50, Finglas, Dublin 11

Members Present: Dr Susan O'Reilly (Chair), Dr Jerome Coffey, Dr Valerie Walsh, Prof Michael Barry, Dr David O'Hanlon, Dr Ann Dee (on behalf of Dr Kevin Kelleher), Ms Anne Marie Hoey, Dr Roy Browne, Ms Joan Donegan.

Apologies Received: Ms Angela Fitzgerald, Dr Philip Crowley, Dr Áine Carroll.

In attendance (non-voting): Mr Shaun Flanagan (Secretary, CPU PCRS), Ms Ellen McGrath (CPU PCRS), Ms Kate Mulvenna (PCRS).

The group was provided with an update in relation to the HSE Leadership / Directorate meeting of 12th December 2016 and the engagements at policy level which had arisen following on from recommendations around Lumacaftor / Ivacaftor.

1. **Nivolumab**

The Drugs Group noted the overall commercial offerings in relation to:

- Nivolumab monotherapy for Malignant Melanoma
- Nivolumab for squamous cell NSCLC
- Nivolumab for non-squamous cell NSCLC
- Nivolumab/Ipilimumab dual therapy for Malignant Melanoma

The group noted the individual gross budget impact following discounts over 5 years across the 4 indications. There may be overlap between the 2 melanoma indications. BMS argued that the net cost to the HSE would be [redacted]m over 5 years, but concerns remained that this was an underestimate due to the concerns about treatment extending beyond 2 years. Following review of each of the indications the group agreed that it could not support reimbursement on a single decision basis of all indications.

Melanoma Indications

The group noted that in monotherapy for melanoma Nivolumab did provide an overall survival advantage over Ipilimumab (median difference not yet established) and the NCPE estimated that the incremental cost effectiveness ratios ranged from [redacted] depending on comparator. Nivolumab was less expensive than Pembrolizumab but had the disadvantage of more frequent dosing. There was a gross budget impact of [redacted]m over 5 years, however comparators (Ipilimumab, Pembrolizumab etc) are expensive so the net budget impact is substantially lower [redacted]m over 5 years). The NCPE flagged that company estimates assume treatment does not extend beyond 2 years and there is uncertainty around same.

The group considered that it would have been imprudent to have made a recommendation on monotherapy in the absence of a formal review of combination therapy. In combination therapy, there was an absence to date of a proven overall survival advantage albeit there was evidence of improvement in progression free survival versus Ipilimumab and indications of a potential overall survival benefit. Clinicians were likely to carefully balance the current absence of proven overall survival benefits for the combination regimen in melanoma versus the additional toxicities. The combination would be likely to be cost effective at a decision threshold of €45,000 per QALY versus comparators (albeit many of the comparators would not be cost effective). The gross budget impact would be [redacted]m and BMS argued that the net budget impact would be cost saving. However the claims of net cost saving to the pharmaceutical budget would only hold if no further sequencing of therapy occurred. Given the huge changes in the treatment landscape there had to be some doubts around this claim.

The gross budget impact for both melanoma indications (assuming current package discounts on offer could apply to the melanoma indications) may be somewhat uncertain due to potential overlap between

the 2 HTA populations. BMS claimed the net budget impact to the HSE would be cost saving but there would be some uncertainty around same.

The group agreed that it could support reimbursement of both melanoma recommendations if the discounts on offer were to be equivalent to [redacted] as the medicines cost effectiveness numbers were within the range of previous decisions. From an affordability point of view, despite the significant gross impacts, there was a possibility that use in melanoma (at the requested discounts) could be cost saving albeit concerns remained that subsequent sequences of treatment would mean savings might not materialise.

Non-Small Cell Lung Cancer (NSCLC) Indications

The group noted that for squamous NSCLC the median overall survival gain of 3.2 months (from 6 months in docetaxel control arm) and the almost doubling in survival at one year. The group noted the less than one month median gain in progression free survival. The incremental cost effectiveness ratio was estimate at approximately [redacted] by BMS (package offer) or [redacted] per QALY (NCPE). The gross 5 year budget impact was estimated at [redacted]m and the net budget impact was estimated at [redacted]m.

The group noted that for non-squamous NSCLC, there was a median overall survival gain of 2.8 months (from 9.4 months in docetaxel control arm). There were reports that at 2 years, 29% vs 16% of patients were alive. The group noted that there appeared to be an "early in treatment" risk that Nivolumab performs less well for some currently unidentifiable patients but that the overall survival curve then changes in favour of Nivolumab from 6 months on. There was a median reduction in progression free survival for Nivolumab of 1.9 months. Estimates of the incremental cost effectiveness ratio ranged from [redacted] per QALY (BMS) to [redacted] per QALY (NCPE) at the [redacted] discount offered. The gross 5 year budget impact was estimated at [redacted]m and the net budget impact was estimated at [redacted]m

The group decided that it could not support reimbursement of Nivolumab for the lung cancer indications based on the offer proposed. The net budget impacts would most likely exceed [redacted]m over 5 years, the medicine did not demonstrate cost effectiveness at conventional cost effectiveness threshold and overall the medicine was not affordable at this price.

2. **Ruxolitinib**

Insufficient time was available to consider Ruxolitinib for polycythaemia vera and it was deferred to the 1st meeting of 2017.