# 5.09 PLITIDEPSIN, Powder for I.V. infusion 2 mg with 4 mL solvent, Aplidin®, Specialised Therapeutics Pharma Pty Ltd

## 1 Purpose of Application

1.1 The submission requested a Section 100 - Efficient Funding of Chemotherapy, Authority Required, Restricted Benefit listing for plitidepsin for the treatment of relapsed/refractory multiple myeloma (RRMM) in patients who are refractory (experienced treatment failure/contraindicated) to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD; third-line) or in patients who have received at least three prior treatment regimens including both a PI and an IMiD (fourth-line setting). This is the first application for plitidepsin to the PBAC.

1.2 The submission presented an indirect comparison against pomalidomide in the third-line setting and a direct comparison against dexamethasone in the fourth-line setting. Separate economic evaluations were presented in these settings: a cost-minimisation for third-line use and a cost-utility analysis for fourth-line use. The key components of the clinical issue presented in the submission are summarised in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

| Component | Description |
|---|---|
| Population | Patients with RRMM who have received at least three prior treatment regimens, including both a proteasome inhibitor (PI) and an immunomodulator (IMiD), or failure of two prior treatments if contraindicated or intolerant to a PI and IMiD. |
| Intervention | Plitidepsin in combination with dexamethasone. |
| Comparator | 3rd line treatment setting: Pomalidomide in combination with Dxm.<br>4th line treatment setting: Dxm |
| Outcomes | PFS, OS, RR, DoR, TEAEs |
| Clinical claim | 3rd line treatment setting: In patients with RRMM who have received at least two prior treatment regimens, including both a PI and an IMiD, plitidepsin + Dxm is no worse than pomalidomide + Dxm at improving progression-free survival and overall survival, with a different safety profile.<br>4th line treatment setting: In patients with RRMM who have received at least three prior treatment regimens, including both a PI and IMiD, plitidepsin + Dxm is superior in terms of effectiveness and non-inferior in terms of safety compared with dexamethasone monotherapy. |

Abbreviations: DoR = duration of response; Dxm = dexamethasone; IMiD = immunomodulatory agent; OS = overall survival; PI = proteasome inhibitor; PFS = progression free survival; RR = response rate; RRMM = relapsed/refractory multiple myeloma; TEAE = treatment-emergent adverse event.
Source: Table 1, p2 of the submission.

## 2 Requested listing

2.1 The requested listing is presented below.

| Name, Restriction, Manner of administration and form | Max Amt | №. of Rpts | Dispensed Price Max Amt | Proprietary Name and Manufacturer |
|---|---|---|---|---|
| Plitidepsin<br>Vial, 2 mg injection | 20 mg | 0 | $[redacted] | Aplidin<br>Specialised Therapeutics Pharma |

| | | |
|---|---|---|
| Category/Program: | Chemotherapy Items for Public and Private Hospital use | |
| PBS indication: | Multiple myeloma | |
| Restriction: | Authority Required - Telephone | |
| Treatment phase: | Initial treatment | Continuing treatment |
| Clinical criteria: | The treatment must be in combination with dexamethasone,<br>AND<br>Patient must have undergone or be ineligible for a primary stem cell transplant,<br>AND<br>Patient must have received at least three prior treatment regimens including both a proteasome inhibitor and an immunomodulatory agent,<br>OR<br>Patients must have experienced treatment failure with a proteasome inhibitor or be intolerant to or be contraindicated according to the TGA approved product information AND Patients must have experienced treatment failure with an immunomodulatory agent or be intolerant to or be contraindicated according to the TGA approved product information,<br>AND<br>Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, pomalidomide, bortezomib or carfilzomib. | Patient must have previously been issued with an authority prescription for this drug,<br>AND<br>Patient must not have progressive disease,<br>AND<br>The treatment must be in combination with dexamethasone,<br>AND<br>Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide pomalidomide, bortezomib or carfilzomib. |
| Prescribing information | Proteasome inhibitor or immunomodulatory agent treatment failure is the absence of achieving at least a partial response or as progressive disease during treatment or within 6 months of discontinuing treatment with these drugs.<br>*If treatment with either a proteasome inhibitor or immunomodulatory agent is contraindicated according to the relevant TGA-approved Product Information, the application must provide details of the contraindication.*<br>*If intolerance to either a proteasome inhibitor or immunomodulatory agent treatment develops during the relevant period of use which is of a severity to necessitate withdrawal of the treatment, the application must provide details of the nature and severity of this intolerance.*<br>Progressive disease defined as at least 1 of the following:<br>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or<br>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or<br>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or<br>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or<br>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or<br>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or<br>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). | |

| | |
|---|---|
| | Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein. |
| Administrative Advice | Authority applications may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). |

Abbreviations: PBS = pharmaceutical benefits scheme; Rpts = repeats; TGA = therapeutic goods administration.

2.2 The submission did not propose a special pricing arrangement for plitidepsin but acknowledged that one may be required given that pomalidomide (the comparator in the third-line setting) is listed under a special pricing arrangement.

2.3 The submission proposed an Authority required – Telephone restriction for initial treatment with plitidepsin. This may not be appropriate since plitidepsin is a first in class medicine and the requested listing is as a Section 100 -Efficient Chemotherapy Listing. In addition, the proposed comparator pomalidomide (Section 100 – Highly Specialised Drug) requires a written authority for prescription via the PBS, due to "modest activity in patients whose myeloma was refractory to both lenalidomide and bortezomib, and the tight restriction reflected this evidence and the high incremental cost effectiveness of the pomalidomide listing" (Carfilzomib PSD, Nov 2018, paragraph 5.4). The ESC advised it was appropriate for plitidepsin's restriction level to be in line with that of pomalidomide (Authority Required-written), given the submission's claim of similar efficacy to pomalidomide and high incremental cost-effectiveness. The PBAC considered an Authority Required (telephone) restriction level was inappropriate and agreed with the ESC that plitidepsin's restriction level should be consistent with that of pomalidomide.

2.4 The proposed restriction specified prior use with a PI and IMiD. However, the current pomalidomide restriction stipulates prior exposure to lenalidomide and bortezomib. By excluding specific reference to lenalidomide and bortezomib, the proposed restriction for plitidepsin may better align with the intent of simplifying the wording of the listings for drugs used to treat myeloma and allow for potential changes in the treatment landscape. The ESC noted that the product information for plitidepsin does not specify which PI and IMiD should be used before plitidepsin, whilst the pomalidomide product information specifically names lenalidomide and bortezomib.

2.5 The proposed restriction was consistent with the use of plitidepsin in the ADMYRE trial (which was the main source of the clinical evidence presented comparing plitidepsin + Dxm with Dxm monotherapy) and the TGA PI. The proposed listing and associated maximum amount assumed a body surface area (BSA) of 1.8 $m^2$. This is consistent with the proposed maximum amount (20 mg at a dose of 5 mg/$m^2$ allows for two administrations per cycle at 9 mg per dose). At a BSA of 2.2 $m^2$, a maximum amount of 22 mg would have been required. While this calculation may not have altered the proposed price (on a cost-minimisation basis), it has minor implications for the estimated financial impact. These could not be tested given the structure of the financial estimates' workbook provided.

2.6 The submission estimated 20 patients will be grandfathered from the Aplidin Access Program at the start of PBS listing. A separate grandfathering restriction is not required for patients on the Aplidin Access Program, as they would be eligible for plitidepsin under the proposed initial treatment criteria.

2.7 The Pre-PBAC response stated the original submission's estimate of the number of patients requiring grandfathering will need to be substantially increased, with an estimated 72 patients considered potentially eligible for grandfathering by the end of February 2020 from the Aplidin Access Program.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 3 Background

## *Registration status*

3.1 Plitidepsin was TGA registered on 10th December 2018 for use in combination with dexamethasone, for the treatment of patients with RRMM who have received at least three prior treatment regimens, including both a PI and an IMiD. Plitidepsin may be used after two prior lines of therapy if refractory and/or intolerant to both a PI and an IMiD.

3.2 During the TGA review process the Clinical Evaluation Report recommended the registration of plitidepsin, however, the first assigned TGA Delegate noted an intention to reject the application on the basis of an unfavourable balance of benefits to harms. The registration was subsequently approved following a meeting with the sponsor, the appointment of a second delegate and lodgement of a Section S31 request.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 4 Population and disease

4.1 Multiple myeloma arises due to malignant clonal plasma cell proliferation in the bone marrow microenvironment. The overall median survival at present is 5–6 years from diagnosis of MM; however, outcomes vary largely by the influence of biological characteristics, such as cytogenetics and age. In the RRMM setting, MM becomes typically more aggressive with successive relapses.

4.2 The submission requested PBS listing of plitidepsin in combination with Dxm for the treatment of patients with RRMM who have received two prior lines of treatment if refractory and/or intolerant to both a PI and IMiD or at least three prior treatments including both a PI and IMiD.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 5 Comparator

5.1 The submission nominated two comparators for plitidepsin: pomalidomide with Dxm (in the third-line setting) and Dxm monotherapy (in the fourth-line setting). The ESC considered the submission's nominated comparators were appropriate. However, the ESC noted that in practice, patients will often cycle through multiple therapies as they progress and options will include all appropriate PBS-listed medicines, clinical trials and compassionate access programs for novel agents. Therefore, it is unclear what the definitive 'standard of care' is in each line of treatment, with current and future PBAC submissions in the RRMM space having the potential to change the treatment paradigm in the near future.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 The sponsor requested a hearing for this item. The clinician emphasised that plitidepsin addresses an unmet clinical need as an end-stage treatment option, offering a small group of responders remission. The clinician also highlighted that plitidepsin can be used in patients experiencing haematological toxicity due to its alternative mechanism of action when compared to other agents used in the treatment of RRMM.

6.2 In response to a question from the Committee about the adverse event profile of plitidepsin, the clinician noted that in practice the observed AEs have generally been low grade 1 or 2 AEs.

## *Consumer comments*

6.3 The PBAC noted and welcomed the input from individuals (32), health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the desire for another treatment option to become available on the PBS for multiple myeloma given this patient group cycles through multiple lines of therapy due to the incurable nature of the disease and associated high rate of relapse.

6.4 Both Myeloma Australia and the Leukaemia Foundation expressed their desire to see the introduction of new regimens for the treatment of myeloma, providing patients more hope and doctors more opportunities to assist these patients. The Leukaemia Foundation urged the PBAC to consider whether plitidepsin would assist in addressing patient's concerns, including whether access to PBS-subsidised treatment would allow patients to live well for longer, feel more in control of their treatment

and better able to manage side effects, reduce out of pocket expenses and avoid time in hospital.

6.5 All comments received by health professionals were supportive of providing PBS-subsidised access to treatment for patients, including comments from three health professionals who have experience with plitidepsin and have seen their patients benefit from treatment.

## *Clinical trials*

6.6 There were no head-to-head studies comparing plitidepsin with pomalidomide. Accordingly, the submission presented two trials as the basis of an indirect comparison of plitidepsin + Dxm and pomalidomide + Dxm: the ADMYRE trial (n =255) and the NIMBUS trial (n=455), respectively. Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| ADMYRE (NCT01102426) | Pharma Mar S.A. ADMYRE: Aplidin – Dexamethasone in Relapsed/Refractory MYeloma) Randomized, multicenter, open-label, phase III study of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma. | CSR, APL-C-001-09, 2016. |
| | Pharma Mar S.A. ADMYRE: Aplidin – Dexamethasone in Relapsed/Refractory MYeloma) Randomized, multicenter, open-label, phase III study of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma. | CSR, APL-C-001-09, Addendum, 2017. |
| | Spicka I, Ocio EM, Oakervee HE, Greil R, Banh RH, Catley L *et al*. Randomized phase III study (ADMYRE) of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma. 59th Annual Meeting of the American Society of Hematology (ASH). | *Blood* 2017; 130 (Supplement 1): 1886. |
| | Gomez J, Extremera S, Nieto A. Overall Survival Results Of Randomized Phase III Study (ADMYRE Trial) Of Plitidepsin And Dexamethasone (Dxm) Vs.Dxm Alone In Patients With Relapsed/Refractory Multiple Myeloma: Evaluation Of The Crossover Impact. Poster presented at: ASCO (Chicago, USA. | *Journal of Clinical Oncology* 2018; 36 (15): 8018 |
| NIMBUS (NCT01311687) | National Institute For Health And Care Excellence. Single Technology Appraisal Final scope for the single technology appraisal of pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib. | NICE. Committee papers [ID985], 2016. |
| | European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Pomalidomide. Procedure No. EMEA/H/C/002682. | EMA. Report, 2013. |
| | San Miguel J; Weisel K; Moreau P; Lacy M; Song K; Delforge M; Karlin L; Goldschmidt H; Banos A; Oriol A; Alegre A; Chen C; Cavo M; Garderet L; Ivanova V; Martinez-Lopez J; Belch A; Palumbo A; Schey S; Sonneveld P; Yu X; Sternas L; Jacques C; Zaki M; Dimopoulos M. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized, open-label, phase 3 trial. | *Lancet Oncology* 2013*,* 14(11): 1055-1066. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | Delforge M, Dimopoulos M, Weisel K, Moreau P, Lacy M, Song K *et al*. Adverse events and management in MM-003, a phase 3 study of pomalidomide+low-dose dexamethasone (pom+lodex) vs. high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM). 18th Congress of the European Hematology Association Stockholm Sweden. | *Haematologica* 2013; 98 (Supplement 1): 329-330. |
| | Dimopoulos MA, Lacy MQ, Moreau P, Weisel KC, Song KW, Delforge M *et al*. Pomalidomide in combination with low-dose dexamethasone: Demonstrates a significant progression-free survival and overall survival advantage, in relapsed/refractory MM: A phase 3, multicenter, randomized, open-label study. 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. | *Blood* 2012; 120(21): LBA-6. |
| | Dimopoulos MA, Weisel K, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. Final analysis, cytogenetics, long-term treatment, and long-term survival in MM-003, A phase 3 study comparing pomalidomide + low-dose dexamethasone (POM + LoDEX) vs high-dose dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM). 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States. | *Blood* 2013; 122(21):408. |
| | Dimopoulos MA, Weisel K, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. Cytogenetics and long-term survival in MM-003, a phase 3 trial of pomalidomide + low-dose dexamethasone vs. Highdose dexamethasone in refractory or relapsed and refractory multiple myeloma. 19th Congress of the European Hematology Association Milan Italy. | *Haematologica* 2014; 99: 365. |
| | Dimopoulos MA, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, Moreau P, Banos A, Oriol A, Garderet L, Cavo M, Ivanova V, Alegre A, Martinez-Lopez J, Chen C, Spencer A, Knop S, Bahlis NJ, Renner C, Yu X, Hong K, Sternas L, Jacques C, Zaki MH, San Miguel JF. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. | *Haematologica* 2015; 100(10):1327-1333. |
| | Goldschmidt H, Dimopoulos MA, Weisel KC, Moreau P, Lacy M, Song KW *et al*. Pomalidomide plus low-dose dexamethasone (POM + LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): Impact of cytogenetics in MM-003. Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. | *Journal of Clinical Oncology* 2013; Conference Publication: 31(15): 8527. |
| | Hanaizi Z, Flores B, Hemmings R, Camarero J, Sancho-Lopez A, Salmonson T, Gisselbrecht C, Laane E, Pignatti F. The European Medicines Agency Review of Pomalidomide in CombinationWith Low-Dose Dexamethasone for the Treatment of Adult Patients With Multiple Myeloma: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use. | *The Oncologist* 2015; 20:329–334 |
| | San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M *et al*. Efficacy, safety, and QOL in MM-003, a phase3, multicenter, randomized, open-label study of pomalidomide (POM)+low dose dexamethasone (LoDEX) vs high-dose dexamethasone (HiDEX) in RRMM. 18th Congress of the European Hematology Association Stockholm Sweden. | *Haematologica* 2913; 98: 475-476. |
| | San Miguel JFS, Weisel K, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. Patient outcomes by prior therapies and depth of response: Analysis of MM-003, a phase 3 study comparing pomalidomide + low-dose dexamethasone (POM + LoDEX) Vs high-dose dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM). 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States. | *Blood* 2013; 122(21): 686. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | Richardson PG, Dimopoulos MA, Chen CJ, Song K, Vij R, Bahlis NJ, Baz R, Hofmeister CC, Weisel K, Jagannath S, Lonial S, Delforge M, Talpaz M, Moreau P, San Miguel JP, Karlin L, Goldschmidt H, Banos A, Oriol A, Alegre A, Garderet L, Cavo M, Ivanova VL, Martinez-Lopez J, Lacy MQ, Chen M, Casey P, Sternas L, Zaki MH, Jacques CJ, Anderson KC. Efficacy and Safety Of Pomalidomide Plus Low-Dose Dexamethasone In Advanced Multiple Myeloma: Results Of Randomized Phase 2 and 3 Trials (MM-002/MM-003). | *Blood* 2013; 122 (21) 3185. |
| | Moreau P, Weisel KC, Song KW, Gibson CJ, Saunders O, Sternas LA, Hong K, Zaki MH, Dimopoulos MA. Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS). | *Leukemia & Lymphoma* 2016; 57(12): 2839-2847. |
| | Morgan GJ, San MJ, Dhanasiri S, Lee D, Palumbo A, Facon T *et al*. Pomalidomide plus low-dose dexamethasone (POM plus LoDEX) versus high-dose dexamethasone (HiDEX) for relapsed or refractory multiple myeloma (RRMM): Overall survival (OS) results of MM-003 after adjustment for crossover. Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. | *Journal of Clinical Oncology* 2014; 32(15): 8593. |
| | Morgan G, San Miguel JF, Dhanasiri S, Lee D, Palumbo A, Facon T *et al*. Overall survival of patients with relapsed and refractory multiple myeloma: Adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone vs. High-dose dexamethasone. 19th Congress of the European Hematology Association Milan Italy. | *Haematologica* 2014; 99 (Supplement 1): 365-366. |
| | Morgan G, Palumbo A, Dhanasiri S, Lee D, Weisel K, Facon T *et al*. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone. | *British Journal of Haematology* 2015; 168(6): 820-823. |
| | San Miguel JF, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, Moreau P, Banos A, Oriol A, Garderet L, Cavo M, Ivanova V, Alegre A, Martinez-Lopez J, Chen C, Renner C, Bahlis NJ, Yu X, Teasdale T, Sternas L, Jacques C, Zaki MH, Dimopoulos MA. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. | *Haematologica* 2015; 100 (10): 1334-1339. |
| | San-Miguel JF, Weisel KC, Moreau P, Lacy M, Song KW, Delforge M *et al*. MM-003: A phase III, multicenter, randomized, open-label study of pomalidomide (POM) plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM). Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. | *Journal of Clinical Oncology* 2013; 31(15): 8510. |
| | San Miguel JF, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. MM-003, a phase 3 study of pomalidomide+low-dose dexamethasone vs. High-dose dexamethasone in refractory or relapsed and refractory multiple myeloma: Outcomes by prior therapy and response depth. 19th Congress of the European Hematology Association Milan Italy. | *Haematologica* 2014; 99 (Supplement 1): 110. |
| | Siegel DS, Weisel KC, Dimopoulos MA, Baz R, Richardson P, Delforge M, Song KW, San Miguel JF, Moreau P, Goldschmidt H, Cavo M, Jagannath S, Yu X, Hong K, Sternas L, Zaki M, Palumbo A. Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials. | *Leukemia & Lymphoma* 2016; 57(12):2833-2838. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | Song KW, Dimopoulos MA, Weisel KC, Moreau P, Palumbo A, Belch A, Schey S, Sonneveld P, Sternas L, Yu X, Amatya R, Monzini MS, Zaki M, Jacques C, San Miguel J. Health-related quality of life from the MM-003 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed and/or refractory multiple myeloma. | *Hematologica* 2015; 100(2):e63-e67. |
| | Song KW, Dimopoulos MA, Weisel KC, Moreau P, Lacy M, Delforge M *et al*. Quality of life (QOL) improvements for pomalidomide plus low-dose dexamethasone (POM + LoDEX) in relapsed and refractory multiple myeloma (RRMM) patients (pts) enrolled in MM-003. 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. | *Journal of Clinical Oncology* 2013; 31(15): 8583. |
| | Song KW, Dimopoulos MA, Weisel K, Delforge M, Karlin L, Goldschmidt H *et al*. Pomalidomide (POM) plus low-dose dexamethasone (LoDEX) improves health-related quality of life (HRQoL) vs high-dose dexamethasone (HiDEX) in relapsed refractory multiple myeloma (RRMM) patients enrolled in MM-003 phase 3 randomized trial. 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States. | *Blood* 2013; 122(21). |
| | Weisel K, Dimopoulos M, Song KW, Moreau P, Palumbo A, Belch A, Schey S, Sonneveld P, Sternas L, Yu X, Amatya R, Gibson CJ, Zaki M, Jacques C, San Miguel J. Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial. | *Clinical Lymphoma Myeloma and Leukemia* 2015; 15(9): 519-530. |
| | Weisel K, Dimopoulos M, Song KW, Moreau P, Palumbo A, Belch A *et al*. Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial. | *Clinical Lymphoma, Myeloma and Leukemia* 2015; 15(9):610. |
| | Weisel K, San Miguel JF, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. MM-003 phase 3 study of pomalidomide in combination with low-dose dexamethasone (POM+LoDEX) vs high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): POM+LoDEX is beneficial for elderly patients (> 65 years of age). 55th Annual Meeting of the American Society of Hematology, ASH 2013 New Orleans, LA United States. | *Blood* 2013; 122(21): 3198. |
| | Weisel K, San MJ, Song K, Delforge M, Lewis P, Yu X *et al*. Impact of ecog performance status on overall survival and hrqol in relapsed/refractory multiple myeloma patients from the MM-003 trial of pomalidomide + low-dose dexamethasone (DEX) vs high-dose dex. 19th Congress of the European Hematology Association Milan Italy. | *Haematologica* 2014; 99(Supplement 1): 518. |
| | Weisel KC, Dimopoulos MA, Moreau P, Lacy M, Song KW, Delforge M *et al*. Pomalidomide plus low-dose dexamethasone (POM + LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): MM-003 analysis of patients (pts) with moderate renal impairment (RI). 2013 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. | *Journal of Clinical Oncology* 2013; 31(15): 8527. |
| | Weisel KC, San Miguel JF, Song KW, Delforge M, Karlin L, Goldschmidt H *et al*. Phase 3 study of pomalidomide + low-dose dexamethasone vs. High-dose dexamethasone in relapsed/refractory multiple myeloma: MM-003 subanalysis of elderly patients (>65 and >70 years of age). 19th Congress of the European Hematology Association Milan Italy. | *Haematologica* 2014; 99(Supplement 1): 364-365. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | Weisel KC, Dimopoulos MA, Moreau P, Lacy MQ, Song KW, Delforge M *et al*. Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in refractory or relapsed and refractory multiple myeloma. | *Haematologica* 2016; 101(7): 872-878. |

Source: Table 14, pp35-39 of the submission.

6.7 The key features of the randomised trials included in the ITC are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparison**

| Trial | N | Design/ median follow-up | Risk of bias | Patient population | Outcomes | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| **Plitidepsin + Dxm vs. Dxm monotherapy** | | | | | | |
| ADMYRE | 225 | R, OL, MC<br>Plitidepsin arm: PFS: 17.1 months [cut-off Nov 2015];<br>OS: 33.4 months [cut-off May 2017];<br>Dxm arm:<br>PFS: 20.7 months [cut-off Nov 2015];<br>OS: 36.3 months [cut-off May 2017] | Low | Relapsed/ Relapsed and refractory MM patients who received prior bortezomib and lenalidomide (or thalidomide) therapies | PFS, OS, DOR, TTFST, ORR, Safety, PFS with PD confirmation. | PFS, OS, TTF in the model comparing with dexamethasone monotherapy |
| **Pomalidomide + Dxm vs. HI-Dxm** | | | | | | |
| NIMBUS | 455 | R, OL, MC<br>IRC:10 months [cut-off 1 March 2013];<br>IA: 15.4 months [cut-off 1 Sep 2013] | Low | Relapsed and/or refractory MM in patients who failed prior bortezomib and lenalidomide | PFS, OS, ORR, Safety | Not used |

Abbreviations: DOR = duration of response; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; IA = investigator's assessment; IRC = independent review committee; MC=multi-centre; N = total patients in each arm; OL=open label; ORR = overall rate of response; OS = overall survival; PD = progressed disease; PFS=progression-free survival; R=randomised; TTF = time to treatment failure; TTFST = time to subsequent first treatment

Source: Compiled during evaluation.

6.8 The ADMYRE trial was a phase III trial comparing plitidepsin (5 mg/m$^2$ IV; day 1 and 15 every four weeks) in combination with Dxm (40 mg orally; days 1,8,15 and 22 every four weeks) to Dxm monotherapy (40 mg orally; days 1,8,15 and 22 every four weeks). The NIMBUS trial was a Phase III trial comparing pomalidomide (4 mg/day orally; days 1-21 every four weeks) + Dxm (40 mg orally; days 1,8,15 and 22 every four weeks) to high-dose Dxm (HI-Dxm, 40 mg orally; days 1-4, 9-12 and 17-20 every four weeks). The difference in the common comparator between the NIMBUS trial and the ADMYRE trial may impact the interpretation of the results of the indirect treatment comparison ITC. The ESC noted the higher doses of dexamethasone, as used in the NIMBUS trial, are associated with increased toxicity.

6.9 Both the ADMYRE trial and the NIMBUS trial permitted patients in the Dxm group to crossover to the intervention group: within the ADMYRE trial crossover occurred at disease progression, while in the NIMBUS trial crossover could have occurred prior to progression. Results for OS including adjustment for crossover were reported for

both trials. Despite this, both trials were subject to a low risk of bias given their designs.

6.10 There were some differences between the patients in the ADMYRE trial and the NIMBUS trial with respect to the proportion of patients 75+ years (15.3% vs 7.9%, respectively), the median number of prior therapies (of 4 vs 5, respectively), and time from first diagnosis to randomisation (5.9 years vs 6.3 years, respectively). In the ADMYRE trial almost all patients (99.4%) received prior autologous stem cell transplantation (ASCT), while in the NIMBUS trial only 70.1% of patients had prior ASCT.

6.11 The submission presented two analyses from the ADMYRE trial for PFS, overall rate of response (ORR), duration of response (DOR) and time to first subsequent therapy (TTFST). Within the ADMYRE trial, the primary analysis was based on the independent review committee (IRC) assessment with a supportive analysis based on investigator's assessment (IA), both conducted on the same data-cuts. The IRC analysis in the NIMBUS trial was presented for an earlier data cut-off (1st March 2013), and the IA analysis for a later data cut-off (1st September 2013). Use of the IRC analyses for both studies may provide a more comparable basis for the assessment of comparative efficacy.

## *Comparative effectiveness*

Plitidepsin + Dxm compared with Dxm: the ADMYRE trial

6.12 The summary of effectiveness of plitidepsin + Dxm and Dxm monotherapy is presented from Table 4 to Table 6. The Kaplan-Meier plots for PFS and OS are presented in Figure 1.

6.13 The patients in the treatment arm (plitidepsin + Dxm) had statistically significantly longer PFS compared to patients in the control (Dxm) arm. The increase in OS was not statistically significant in ITT analysis, however after adjusting for crossover the difference in OS was statistically significant. The submission reported that the two-stage method was the preferred basis for the crossover adjustment, but did not provide a justification for this conclusion. However, since the necessary assumptions for conducting the two-stage method appeared to be met (switching soon after progression; no unmeasurable confounders; model fits the data) and the results were similar to those using the rank preserving structural failure time (RPSFT) adjustment, the evaluators considered this may be reasonable.

**Table 4: Key efficacy outcomes for plitidepsin + Dxm versus Dxm monotherapy**

| Trial ID | Plitidepsin + Dxm | | Dxm | | Difference in median, months | P value (log rank test) | Hazard ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| Data cut-off | n/N event (%) | Median PFS, mths (95% CI) | n/N event (%) | Median PFS, mths (95% CI) | | | |
| **PFS** | | | | | | | |
| IRC (ITT) | 130/171 (76.0) | 2.6 (1.9, 3.0) | 61/84 (72.6) | 1.7 (1.1, 2.0) | 0.9 | p= 0.0062 | **0.650** (0.477, 0.885) |
| IA (ITT) | 131/171 (76.6) | 2.9 (2.1, 3.7) | 72/84 (85.7) | 1.1 (1.0, 1.9) | 1.8 | p< 0.0001 | **0.512** (0.382, 0.686) |
| IRC with confirmation of PD | 80/171 (46.8) | 5.0 (3.0, 6.4) | 43/84 (51.2) | 2.0 (1.7, 3.0) | 3.0 | p=0.0007 | **0.517** (0.354, 0.756) |
| IA with confirmation of PD, Updated[a] | 105/171 (61.4) | 3.8 (2.9, 5.6) | 50/84 (59.5) | 1.9 (1.1, 2.7) | 1.9 | NR | **0.611** (0.434, 0.860) |
| **OS** | | | | | | | |
| ITT | 123/171 (71.9) | 11.6 (9.2, 16.1) | 72/84 (85.7) | 8.9 (6.0, 15.4) | 2.7 | p= 0.1273 | 0.797 (0.596, 1.067) |
| two-stage method crossover adj | 123/171 (71.9) | 11.6 (9.2, 16.1) | 72/84 (85.7) | 6.7 (5.7, 9.7) | 4.9 | p= 0.0069 | **0.667** (0.497, 0.895) |
| RPSFT method crossover adj | 123/171 (71.9) | 11.6 (9.2, 16.1) | 69/84 (82.1) | 7.2 (5.7, 10.8) | 4.4 | p= 0.0103 | **0.676** (0.500, 0.913) |

Abbreviations: CI = confidence interval; Dxm = dexamethasone; IRC= independent review committee; HR = hazard ratio; IA= Investigator's assessment; ITT = intention to treat; n= number of participants reporting data; N= total participants in group; NR = not reported; OS = overall survival; PD = progressed disease; PFS = progression-free survival; RPSFT = rank preserving structural failure time.

Note: a = after the review of the patient profiles to classify the censoring reasons according to the information provided by the investigators; a total of 25 patients in treatment arm and 11 patients in control arm, were considered to have an event that could not have been detected previously. The ADMYRE trial median follow-up Plitidepsin + Dxm arm: 33.4 months, Dxm arm : 36.3 months.

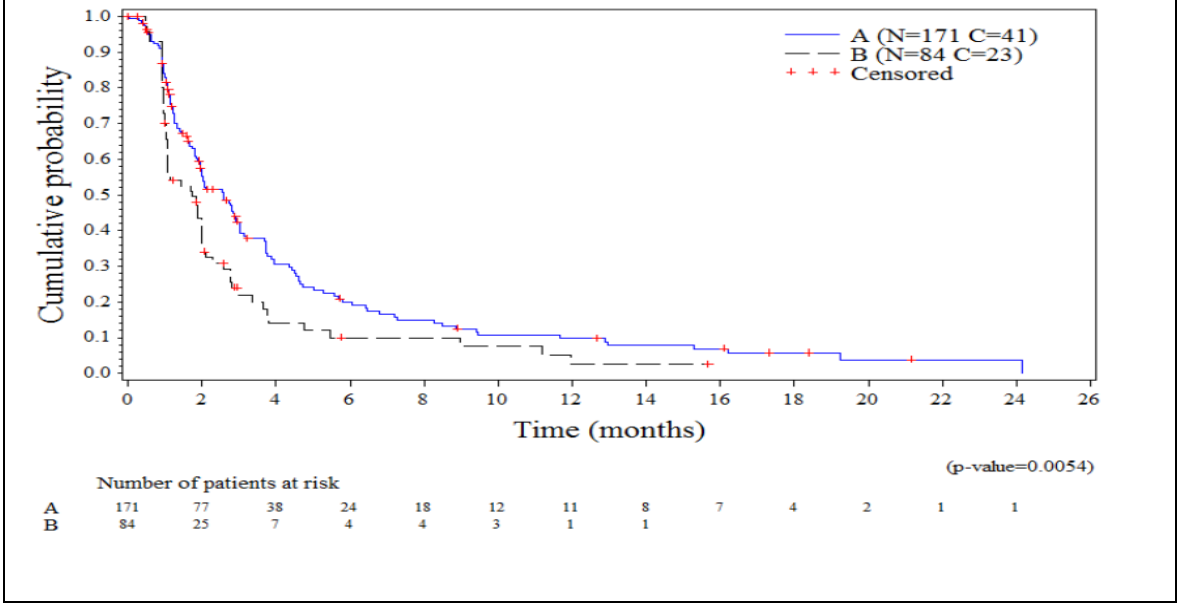
Bolded values show statistical significance.

Source: Source: PFS: Table 31, p87; Table 32, p88; Table 33, p90; Table 35, p94; Table 37, p96; OS: Table 22, p74; Table 26, p81; Table 28, p83 of the submission.

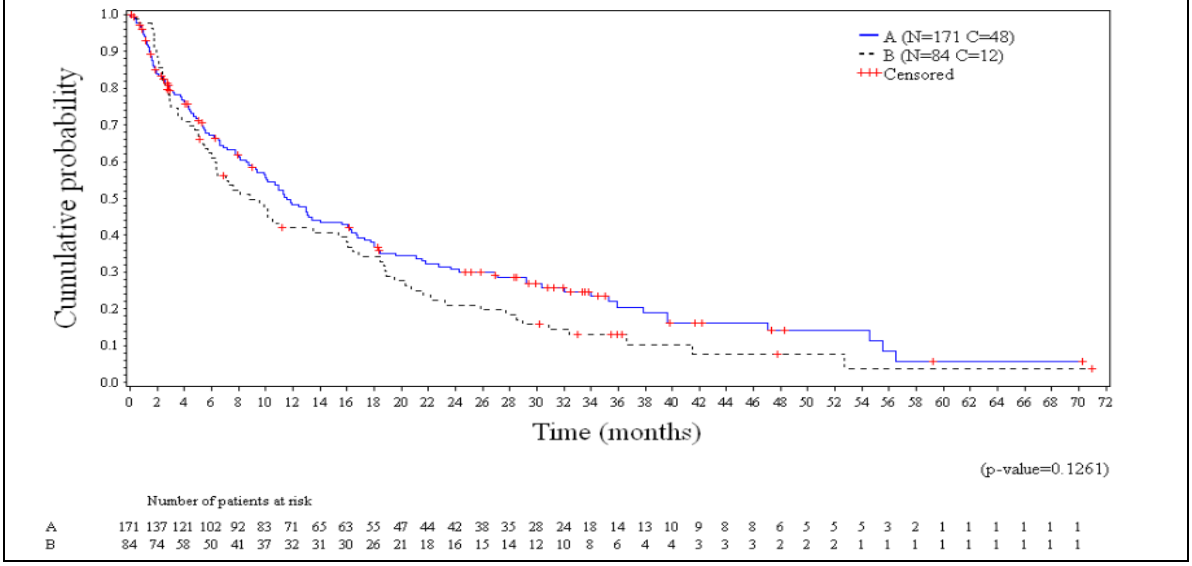
6.14 The submission stated that for both PFS and OS, the survival curves separated at 2–3 months in favour of plitidepsin + Dxm. This separation of the curves is not maintained, noting the small number of patients at risk to inform the curves toward the latter periods. Also, a median PFS difference of 0.9 months is unlikely to be considered a meaningful improvement, particularly in the context of the additional toxicity associated with plitidepsin. The ESC acknowledged the data presented in the PSCR (page 2), noting that at 24 months, the plitidepsin + Dxm arm had more than double the number of patients alive compared with Dxm alone. However, the ESC agreed with the commentary that the clinical benefit of plitidepsin + Dxm should be considered in the context of its additional toxicity.

**Figure 1: Kaplan-Meier curves of PFS and OS (IRC - ITT), the ADMYRE trial**

**PFS**




**OS**




Abbreviations: A = plitidepsin + dexamethasone treatment arm; B = dexamethasone monotherapy treatment arm; C = censored patients in each arm; ITT = intention to treat; IRC = independent review committee; N = total patients in each arm; OS = overall survival; PFS = progression-free survival. Source: Figure 11, p74; Figure 18, p87 of the submission.

6.15 The ORR favoured patients receiving plitidepsin who were more likely to respond to treatment compared to Dxm. The median duration of response in patients who received plitidepsin + Dxm was longer than for Dxm, but was statistically significant in the IA analysis only (Table 6). The results of the TTFST showed that patients in the treatment arm had 2.3 months longer until subsequent therapy or death (Table 6).

**Table 5: Results of ORR (IRC and IA, ITT), the ADMYRE trial**

| Outcome | Plitidepsin + Dxm n/N with event (%) | Dxm n/N with event (%) | RD (95% CI) | RR (95% CI) |
|---|---|---|---|---|
| IRC - ITT | | | | |
| ORR[a] | *39/171 (*22.8) | *3/84 (3.6)* | ***0.19*** *(0.12, 0.27)* | **6.39** (2.03, 20.07) |
| ORR (excluding MR)[b] | 17/171 (9.9) | 1/84 (1.2) | ***0.09*** *(0.04, 0.14)* | **8.35** (1.13, 61.70) |
| IA-ITT | | | | |
| ORR[a] | *51/171* (29.8) | 1/84 (1.2) | ***0.29*** *(0.21, 0.36)* | **25.05** (3.52, 178.18) |
| ORR (excluding MR)[b] | 20/171 (11.7) | 1/84 (1.2) | ***0.11*** *(0.05, 0.16)* | **9.82** (1.34, 71.97) |

Abbreviations: CI= confidence interval; IA = investigator's assessment; IRC= independent review committee; ITT = intention to treat; Dxm = dexamethasone; MR = minor response; ORR = overall response rate; PR = partial response; RD = risk difference; RR = relative risk; VGPR = very good partial response.
Note: a = Includes VGPR, PR and MR; b= Includes VGPR and PR (excludes MR). Bolded values show statistical significance.
Source: Table 39, p98 and Table 41, p100; Table 57, p131 of the submission. *Calculated during evaluation; CI for risk difference calculated using Review Manger 5.3 software.*

**Table 6: Results of ORR (IRC and IA, ITT), the ADMYRE trial**

| | Plitidepsin + Dxm | Dxm | Absolute difference | HR (95% CI) |
|---|---|---|---|---|
| **DOR** | | | | |
| IRC - ITT | | | | |
| Median, months | 3.7 (2.7, 10.5) | 1.8 (1.8, 5.5) | *1.9* | 0.384 (0.113, 1.303) *p-value = 0.1247* |
| Median in patients with PD confirmation, months | 18.4 (5.5-23.2) | 5.5 (1.8-5.5) | *12.9* | 0.39 (0.09, 1.75) p-value = 0.1960 |
| IA -ITT | | | | |
| Median, months | 5.1 (3.2, 6.2) | 0.0% (0.0, not estimable) | *4.2* | ***0.043*** *(0.004, 0.479) p-value = 0.0105* |
| Median in patients with PD confirmation, months | 7.1 (4.6, 10.2) | (0.9, not estimable) | *6.2* | NE |
| **TTFST or death** | | | | |
| Median, months | 4.4 (3.1. 5.8) | 2.1 (1.9. 2.6) | *2.3* | **0.479** (0.362, 0.633) p-value <0.0001 |

Abbreviations: CI = confidence interval; DOR = duration of response; HR = hazard ratio; IA = investigator's assessment; IRC= independent review committee; ITT = intention to treat; Dxm = dexamethasone; n = number of participants with event; N = total participants in group; NE = not estimable; PD = progressed disease; TTFST = time to fist subsequent therapy.
Note: Bolded values show statistical significance.
Source: DOR: Table 43, p102; Table 45, p103; TTFST: Table 30, p85 of the submission. *Table 32, p95 of CSR the ADMYRE trial.*

<u>Pomalidomide + Dxm compared with Dxm: the NIMBUS trial</u>

6.16 The efficacy results for the NIMBUS trial are presented from Table 7 to Table 9. The Kaplan-Meier plots for PFS and OS are presented in Figure 2. The patients in the pomalidomide + Dxm arm had a statistically significantly longer PFS and OS compared to patients in the HI-Dxm arm. The PBAC previously favoured the use of the two-stage method for crossover adjustment in the NIMBUS trial (Pomalidomide PSD, July 2014, point 7.7).

**Table 7: Summary of survival outcomes (IRC and IA, ITT) in the NIMBUS trial**

| Trial ID | Pomalidomide + Dxm | | HI-Dxm | | Difference in median, months | P value | Hazard ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| Data cut-off | n/N event (%) | Median PFS, mths (95% CI) | n/N event (%) | Median PFS, mths (95% CI) | | | |
| PFS, with confirmation of PD | | | | | | | |
| IRC (ITT) [cut-off 1 March 2013] | 234/302 (77.5) | *3.7 (3.0, 4.5)* | 130/153 (85.0) | *1.9 (1.6, 2.2)* | *1.8* | p-value <0.001 | **0.49** (0.39, 0.61) |
| IA (ITT) [*cut-off 1 September 2013*] | 253/302 (83.8) | 4.0 *(3.6, 4.7)* | 138/153 (90.2) | 1.9 *(1.9, 2.2)* | *2.1* | p-value < 0.001 | ***0.50** (0.41, 0.62)* |
| OS | | | | | | | |
| IRC (ITT) [cut-off 1 March 2013] | 147/302 (48.7) | 12.7 (10.4,15.5)[a] | 86/153 (56.2) | 8.1 (6.9, 10.8) | *4.6* | p-value = 0.0285 | **0.74** (0.56, 0.97)[b] |
| IA (ITT) [*cut-off 1 September 2013*] | *176/302 (58.3)* | 13.1 *(11.0, 15.4)* | *101/153 (66.0)* | 8.1 *(6.9, 9.2)* | *5* | p-value not reported | **0.72** (0.56, 0.92) |
| IRC, Two-stage method crossover adjustment | 147/302 (48.7) | 12.7 (10.4,15.5) | NR | 5.7 (4.2, 7.5) | 7 | p-value not reported | **0.52** (0.39, 0.68) |
| IRC, RPSFT method crossover adjustment | 147/302 (48.7) | 12.7 (10.4,15.5) | NR | 6.7 (4.6, 10.5) | 6 | p-value not reported | 0.49 (0.33, 1.00) |

Abbreviations: CI = confidence interval; IA = investigator's assessment; IRC= independent review committee; HI-Dxm = high-dose dexamethasone; HR = hazard ratio; IA= Investigator's assessment; ITT = intention to treat; Dxm = dexamethasone; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RPSFT = rank preserving structural failure time.

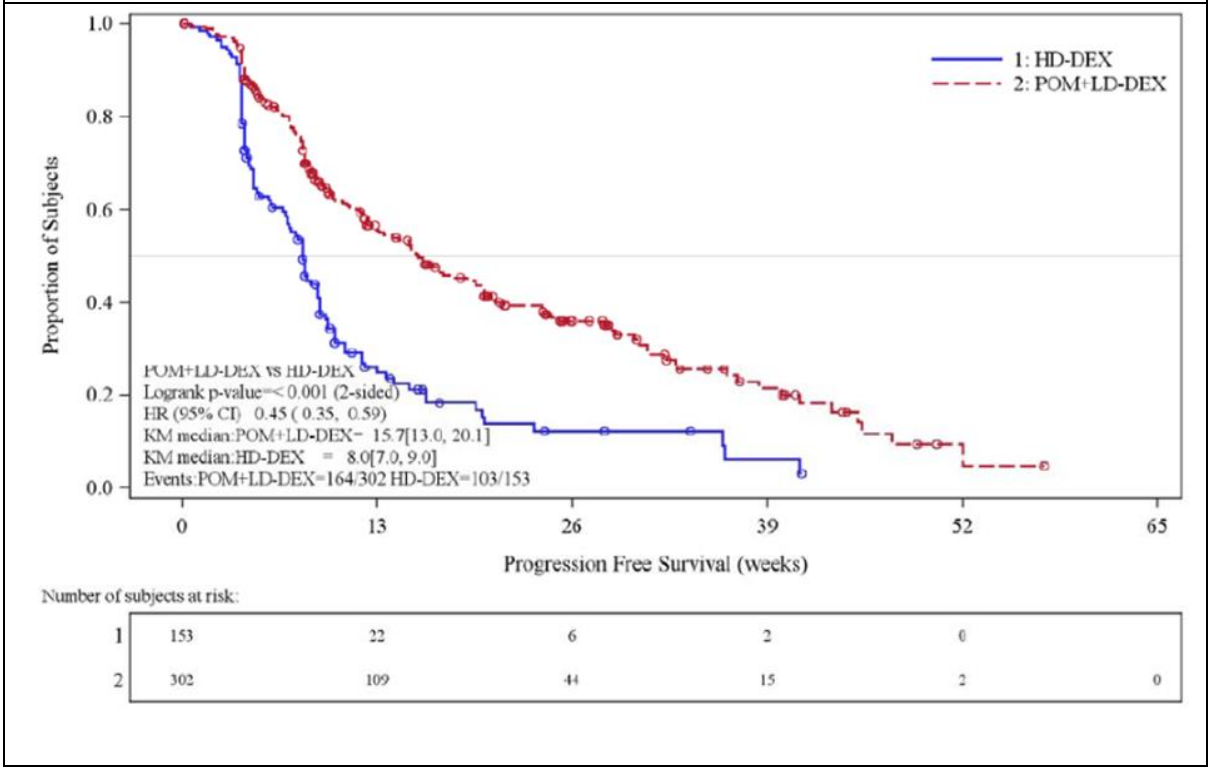
Note: a = In the NICE committee evaluation papers (Fayter et al. 2016) Table 4.9 and in Morgan et al. (2015) Table 1 overall survival is reported as 12.7 months. In the NICE committee evaluation papers (Fayter et al. 2016) Table 23 it is reported as 12.5 months.

b = In the NICE committee evaluation papers (Fayter et al. 2016) Table 4.9 HR is reported as 0.74. In the NICE committee evaluation papers (Fayter et al. 2016) Table 23 it is reported as 0.70 (95% CI: 0.54 to 0.92). Bolded values show statistical significance. The NIMBUS trial: in the IRC assessment the median follow-up was 10 months, in AI 15.4 months.

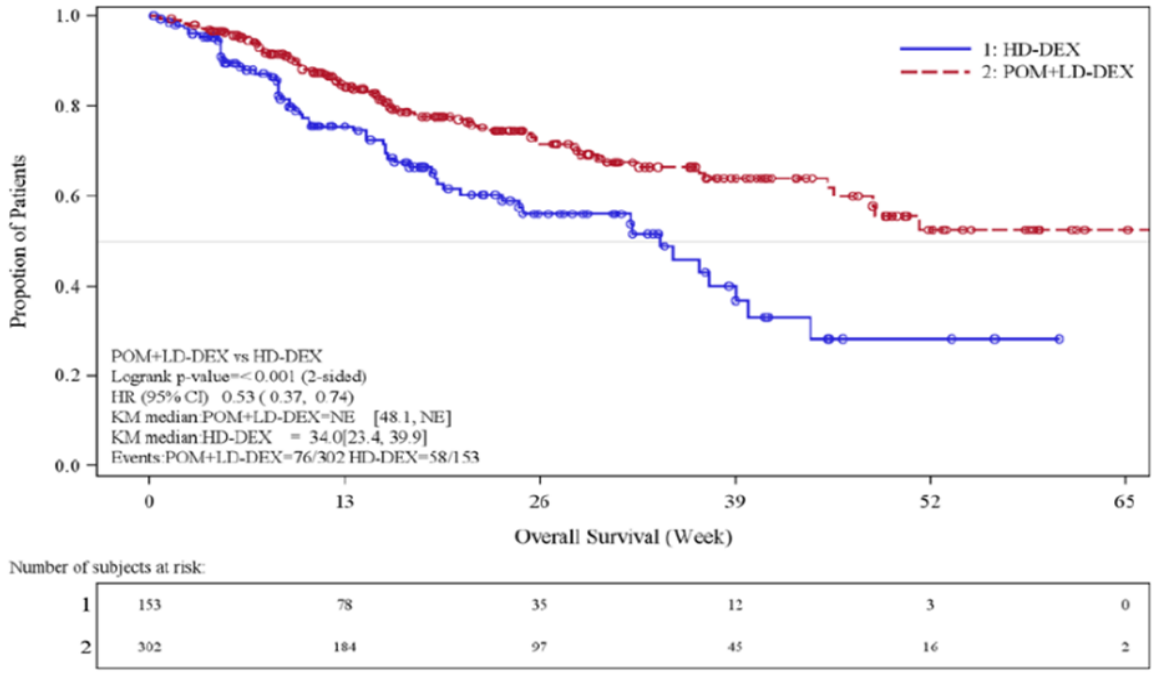
Source: PFS: Table 34, p92; Table 38, p98; OS: Table 23, p75; Table 27, p82; Table 29, p84 of the submission. *Table 22, p72; Table 23, p73 of NICE_committee-paper [ID985]. Page 1060, San Miguel et al. (2013).*

**Figure 2: Kaplan-Meier curve of PFS and OS (IRC confirmation of PD - ITT), the NIMBUS trial**

**PFS**



**OS**




Abbreviations: DEX = dexamethasone; HD = high dose; HR = hazard ratio; ITT = intention to treat; IRC = independent review committee; KM = Kaplan-Meier; LD = low dose; N = total patients in each arm; OS = overall survival; PD = progressed disease; PFS = progression-free survival; POM = pomalidomide

Source: Figure 12, p76; Figure 21, p93 of the submission.

6.17 Patients receiving pomalidomide were more likely to respond to treatment compared to HI-Dxm monotherapy (Table 8). Treatment with pomalidomide showed a statistically significantly longer duration of response based on the IA analysis (cut-off 1st September 2013) (Table 9).

**Table 8: Results of ORR (IRC-ITT and IA-ITT), the NIMBUS trial**

| Outcome | Pomalidomide + Dxm n/N with event (%) | HI-Dxm n/N with event (%) | RD (95% CI) | RR (95% CI) |
|---|---|---|---|---|
| IRC-ITT | | | | |
| ORR[a] [cut-off 1 March 2013] | 71/302 (23.5) | 6/153 (3.9) | ***0.20*** *(0.14, 0.25)* | ***6.00*** *(2.67, 13.48)* |
| IA-ITT | | | | |
| ORR[a] [cut-off 1 Sep 2013] | 97/302 (32.1) | 17/153 (11.1) | ***0.21*** *(0.14, 0.28)* | **2.89** (1.79, 4.66) |

Abbreviations: CI= confidence interval; CR = Complete Response; HI-Dxm = high-dose dexamethasone; IA= Investigator's assessment; IRC= independent review committee; ITT = intention to treat; Dxm = dexamethasone; N= total participants in group; ORR = overall response rate; PR = partial response; RD = risk difference; RR = relative risk; SCR = stringent complete response; VGPR = very good partial response.

Note: a = Includes SCR, CR, VGPR, PR. Bolded values show statistical significance.

Source: Table 40, p99 and Table 42, p101 of the submission. *Data corrected from Table 26, p78 of NICE_committee-paper [ID985]. RD calculated during evaluation using Review Manger 5.3 software.*

**Table 9: Results of DOR (IRC-ITT and IA-ITT), the NIMBUS trial**

| | Pomalidomide + Dxm | HI-Dxm | Absolute difference | HR (95% CI) |
|---|---|---|---|---|
| IRC-ITT | | | | |
| Number of events n/N (%) | 13/50 (26.0) | 2/6 (33.3) | | |
| Median months (95%CI) [cut-off 1 March 2013] | 8.1 *(6.5, 12.2)* | 6.5 *(4.6, 8.5)* | *1.6* | 0.53 (0.19, 1.51) *p-value = 0.224* |
| IA -ITT | | | | |
| Median months [cut-off 1 Sep 2013] | 7.5 *(6.0, 9.5)* | 5.1 *(1.7, 8.5)* | *2.4* | **0.52** (0.29, 0.95) *p-value = 0.031* |

Abbreviations: CI = confidence interval; DOR = duration of response; HI-Dxm = high-dose dexamethasone; HR = hazard ratio; IA = investigator's assessment; IRC= independent review committee; ITT = intention to treat; Dxm = dexamethasone; n = number of participants with event; N = total participants in group; PD = progressed disease.
Note: Bolded values show statistical significance.
Source: Table 44, p102, Table 46, p103, of the submission. *Calculated during evaluation. Section 4.7.7, p79 of NICE_committee-paper [ID985].*

Plitidepsin + Dxm vs. pomalidomide + Dxm Indirect Comparison

6.18 The submission presented an ITC between plitidepsin + Dxm and pomalidomide + Dxm using Dxm/HI-Dxm as the common reference arm. The submission based the claim of non-inferiority on the outcomes of PFS and OS (Table 10). The submission used a standard frequentist (Bucher) method. The PFS and OS results, including OS adjusted for crossover, were not statistically significant and numerically favoured pomalidomide. The submission did not propose a non-inferiority margin.

6.19 There are potential issues of transitivity between the trials:

- The dosing for the Dxm comparator arm differed between the trials. The submission stated that due to the differences in the common comparator and the difficulty of determining the relative efficacy and safety of plitidepsin and pomalidomide the ITC should be considered exploratory. The submission presented a supplementary analysis comparing Dxm and HI-Dxm, based on data from three RCTs with Dxm and HI-Dxm in combination with either lenalidomide (ECOG and MM009/010) or thalidomide (Shi 2010)). The results for PFS and crossover adjusted OS for Dxm did not differ between the trials. However, differences did arise in the safety outcomes (see below) that may support a lack of transitivity in the common comparator arm. The ESC agreed with the commentary and considered there is no evidence that efficacy is affected by the different doses of dexamethasone, however differences were evident in relation to safety between the two comparator arms.
- The definition of relapsed/refractory disease at baseline was unclear such that proportion of patients refractory to prior therapy in the ADMYRE trial was approximately 30% compared to 82.2% in the NIMBUS trial. There is a possibility that the patients are not comparable with respect to prior disease status. The ESC noted that definitions of relapsed/refractory disease in the multiple myeloma setting are highly variable, with only a small number of patients achieving true remission.

6.20 The studies differed in when they permitted crossover from their intervention arm to Dxm. The impact of this difference was mitigated by the crossover adjusted survival analysis.

**Table 10: Summary of results of the indirect comparison for PFS and OS, between ADMYRE and the NIMBUS trials**

| | Experimental Median – months (95% CI) | Common reference Median – months (95% CI) | Hazard ratio (95% CI) |
|---|---|---|---|
| **PFS** | | | |
| PFS with confirmation of PD: IRC | | | |
| Plitidepsin + Dxm vs Dxm [ADMYRE] | 5.0 (3.0, 6.4) | 2.0 (1.7, 3.0) | **0.52 (0.35, 0.76)** |
| Pomalidomide + Dxm vs Hi-Dxm [NIMBUS] | *3.7 (3.0, 4.5)* | *1.9 (1.6, 2.2)* | **0.49 (0.39, 0.61)** |
| Indirect comparison: ADMYRE vs NIMBUS | – | – | 1.06 (0.68, 1.64) |
| PFS with confirmation of PD: IA | | | |
| Plitidepsin + Dxm vs Dxm [ADMYRE] | 3.8 (2.9, 5.6) | 1.9 (1.1, 2.7) | **0.61 (0.43, 0.86)** |
| Pomalidomide + Dxm vs Hi-Dxm [NIMBUS] [cut-off 1 March 2013] | 4.0 | 1.9 | **0.49 (0.39, 0.60)** |
| Indirect comparison: ADMYRE vs NIMBUS | – | - | 1.25 (0.93, 1.87) |
| **OS** | | | |
| Plitidepsin + Dxm vs Dxm [ADMYRE] | 11.6 (9.2, 16.1) | 8.9 (6.0, 15.4) | 0.80 (0.60, 1.07) |
| Pomalidomide + Dxm vs Hi-Dxm [NIMBUS] [cut-off 1 Sep 2013] | 13.1 (11.0, 15.4) | 8.1 (6.9, 9.2) | **0.72 (0.56, 0.92)** |
| Indirect comparison: ADMYRE vs NIMBUS | – | – | 1.11 (0.76, 1.62) |
| Overall survival (two-stage method) | | | |
| Plitidepsin + Dxm vs Dxm [ADMYRE] | 11.6 (9.2, 16.1) | 6.7 (5.7, 9.7) | **0.67 (0.50, 0.90)** |
| Pomalidomide + Dxm vs Hi-Dxm [NIMBUS] [cut-off 1 March 2013] | 12.7 (10.4,15.5) | 5.7 (4.2, 7.5) | **0.52 (0.39, 0.68)** |
| Indirect comparison: ADMYRE vs NIMBUS | – | – | 1.28 (0.86, 1.92) |
| Overall survival (RPSFT method) | | | |
| Plitidepsin + Dxm vs Dxm [ADMYRE] | 11.6 (9.2, 16.1) | 7.2 (5.7, 10.8) | **0.68 (0.50, 0.91)** |
| Pomalidomide + Dxm vs Hi-Dxm [NIMBUS] [cut-off 1 March 2013] | 12.7 (10.4,15.5) | 6.7 (4.6, 10.5) | 0.49 (0.33, 1.00) |
| Indirect comparison: ADMYRE vs NIMBUS | – | – | 1.38 (0.73, 2.59) |

Abbreviations: CI = confidence interval; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; IA = Investigator's assessment; IRC = independent review committee; OS = overall survival; PD = progressed disease; PFS = progression-free survival RPSFT = Rank Preserving Structural Failure Time.

Note: Bolded values show statistical significance.

Source: Table 54, p127; Table 55, p128 of the submission. *Table 22, p72 and Table 23, p151, NICE_committee-papers [ID985].*

## *Comparative harms*

Plitidepsin + Dxm compared with Dxm: the ADMYRE trial

6.21 The summary of adverse events reported in the ADMYRE trial is presented in Table 11. Treatment with plitidepsin + Dxm was associated with more AEs than Dxm.

**Table 11: Summary of key AEs and Grade 3/4 AEs in the ADMYRE trial**

| | Plitidepsin + Dxm n with event/N (%) | Dxm n with event/N (%) | RR (95% CI) |
|---|---|---|---|
| Any TEAEs | *144/167 (86.2)* | *38/83 (45.8)* | ***1.88 (1.48, 2.40)*** |
| TE - SEA | *47/167 (28.q)* | *6/83 (7.2)* | ***3.90 (1.74, 8.73)*** |
| Grade ≥ 3 TEAEs | *86/167 (51.5)* | *9/83 (10.8)* | ***4.75 (2.52, 8.96)*** |
| TEAEs that occurred in ≥10% of patients of any grade | | | |
| Diarrhoea | *24/167 (14.4)* | *2/83 (2.4)* | **5.96 (1.44, 24.63)** |
| Nausea | *62/167 (37.1)* | *9/83 (10.8)* | **3.42 (1.79, 6.54)** |
| Vomiting | *28/167 (16.8)* | *2/83 (2.4)* | ***6.96 (1.70, 28.51)*** |
| Oedema peripheral | *20/167 (12)* | *2/83 (2.4)* | **4.97 (1.19, 20.76)** |
| Fatigue | *61/167 (36.5)* | *7/83 (8.4)* | **4.33 (2.07, 9.05)** |
| Myalgia | *24/167 (14.4)* | *2/83 (2.4)* | ***5.96 (1.44, 24.63)*** |
| Decreased appetite | *21/167 (12.6)* | *2/83 (2.4)* | **5.22 (1.25, 21.73)** |
| Grade 3/4 fatigue | *18/167 (10.8)* | *1/83 (1.2)* | ***8.95 (1.22, 65.87)*** |

Abbreviations: AEs = adverse events; Dxm = dexamethasone; n = number of participants with event; N = total participants in group; RR = relative risk; SAE = serious adverse events; TE = treatment emergent; TEAEs = treatment related adverse events.
Note: a = one patients had Grade 4 myopathy, the other two had AEs with unknown causality; b = patient had Grade 4 respiratory infection. Bolded values show statistical significance.
Source: Table 23, p57; Table 36, p73 all of the ADMYRE trial Summary of Clinical Safety. Table 49, p107; Table 58, pp133-137 of the *submission. Table 12.2.2.3bis of 12 CSR Safety Analysis (25AUG16) tables in CSR. Type-o errors were corrected for Grade 3/4 event numbers in nausea and fatigue. RR and OR estimates were calculated using RevMan 5.3 during evaluation.*

Pomalidomide + Dxm compared with Dxm: the NIMBUS trial

6.22 The summary of AEs for the NIMBUS trial is presented in Table 12. The safety analysis was conducted on patients who received at least one dose of trial medication. The submission stated that AEs were more likely to occur shortly after treatment initiation (within the first two cycles) and decreased in frequency thereafter. Almost all patients in each treatment group had a TEAE. There were 11 (4%) treatment-related deaths in the pomalidomide + Dxm arm and 7(5%) in the HI-Dxm arm (page 138 of NICE Committee papers [ID985]).

**Table 12: Summary of key AEs and Grade 3/4 AEs in the NIMBUS trial**

| | Pomalidomide + Dxm n with event/N (%) | HI-Dxm n with event/N (%) | RR (95% CI) |
|---|---|---|---|
| Any TEAE | 269/*300* (89.7) | 115/*150* (76.7) | ***1.17 (1.06, 1.29)*** |
| Grade ≥ 3 TEAEs | 202/300 (67.3) | 70/150 (46.7) | ***1.44 (1.20, 1.74)*** |
| Neutropenia | 154/300 (51.3) | 30/150 (20.0) | ***2.56 (1.83, 3.60)]*** |
| Leukopenia | 38/300 (12.7) | 8/150 (5.3) | **2.38 (1.14, 4.96)** |
| Muscle spasms | 46/300 (15.3) | 11/150 (7.3) | **2.09 (1.12, 3.92)** |
| Muscular weakness | 9/300 (3.0) | 19/150 (12.7) | **0.24 (0.11, 0.51)** |
| Cough | 60/300 (20.0) | 15/150 (10.0) | **2.00 (1.18, 3.40)** |
| Skin and subcutaneous tissue disorders | 94/300 (31.3) | 26/150 (17.3) | ***1.81 (1.23, 2.66)*** |
| Insomnia | 32/300 (10.7) | 32/150 (21.3) | **0.50 (0.32, 0.78)** |
| Grade 3/4 neutropenia | 145/300 (48.3) | 23/150 (15.3) | ***3.15 (2.13, 4.67)*** |
| Grade 3/4 leukopenia | 27/300 (9.0) | 5/150 (3.3) | ***2.70 (1.06, 6.87)*** |

Abbreviations: AE = adverse events; HI-Dxm = high-dose dexamethasone; Dxm = dexamethasone; n = number of participants with event; N = total participants in group; RR = relative risk; SAE = serious adverse events; TEAE = treatment emergent adverse events.
Note: Bolded values show statistical significance.
Source: Table 50, pp110-111; Table 51, pp113-114; Table 58, pp133-137 of the submission. *Estimated using RevMan 5.3 during evaluation. RR for neutropenia corrected during evaluation.*

Plitidepsin + Dxm vs. pomalidomide + Dxm Indirect Comparison of safety

6.23 The results of the indirect comparison of safety for AEs with significant rates between are presented in Table 13. There was a significant increase in the AE rates in diarrhoea, nausea, fatigue and muscular weakness in the plitidepsin + Dxm treatment arm. The submission stated that the higher toxicity profile of HI-Dxm (NMBUS trial) compared with Dxm (ADMYRE trial) affected the indirect analysis of AEs resulting in statistical anomalies. This could be interpreted as the common comparator arms not being comparable. This seems reasonable. Accordingly, the claim of non-inferior safety compared to pomalidomide + Dxm cannot be supported.

**Table 13: Key results of the indirect comparison for adverse events**

| | Plitidepsin + Dxm/ pomalidomide + Dxm n/N | Dxm/ HI-Dxm n/N | RR (95% CI) |
|---|---|---|---|
| **Diarrhoea** | | | |
| ADMYRE | 24/167 | 2/83 | **5.96** (1.44, 24.63) |
| NIMBUS | 66/300 | 28/150 | 1.18 (0.79, 1.75) |
| Indirect comparison: ADMYRE vs NIMBUS | | | **5.05** (1.16, 22.06) |
| **Nausea** | | | |
| ADMYRE | 62/167 | 9/83 | **3.42** (1.79, 6.54) |
| NIMBUS | 45/300 | 16/150 | 1.41 (0.82, 2.40) |
| Indirect comparison: ADMYRE vs NIMBUS | | | **2.43** (1.05, 5.63) |
| **Fatigue** | | | |
| ADMYRE | 61/167 | 7/83 | **4.33** (2.07, 9.05) |
| NIMBUS | 101/300 | 41/150 | 1.23 (0.91, 1.67) |
| Indirect comparison: ADMYRE vs NIMBUS | | | **3.52** (1.59, 7.82) |
| **Muscular weakness** | | | |
| ADMYRE | 16/167 | 2/83 | 3.98 (0.94, 16.89) |
| NIMBUS | 9/300 | 19/150 | **0.24** (0.11, 0.51) |
| Indirect comparison: ADMYRE vs NIMBUS | | | **16.58** (3.23, 85.09) |

Abbreviations: CI = confidence interval; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; n = number of participants with event; N = total number of participants in group; RR = relative risk.
Note: Bolded values show statistical significance.
Source: Table 58, pp133-137 of the submission. *Calculated during valuation.*

## *Benefits/harms*

6.24 A summary of the comparative benefits and harms for the comparison of plitidepsin + Dxm with Dxm is presented in Table 14.

**Table 14: Comparison using benefits and harms for plitidepsin + Dxm and Dxm**

| **Benefits** | | | | |
|---|---|---|---|---|
| PFS (median duration of follow up 17.1 mths in plitidepsin + Dxm and 20.7 mths in Dxm monotherapy) | | | | |
| **Event** | **Plitidepsin + Dxm** | **Dxm** | **Absolute Difference** | **HR (95% CI)** |
| IRC | | | | |
| Progressed, n/N (%) | 130/171 (76.0) | 61/84 (72.6) | | |
| Median PFS, months | 2.6 (1.9, 3.0) | 1.7 (1.1, 2.0) | 0.9 | **0.650** (0.477, 0.885) p-value = 0.0062 |
| % not progressed at 6 months (95% CI) | 20.0% (13.1, 26.9) | 10.0% (2.0, 18.0) | 10% | |
| OS (median duration of follow up 33.4 mths in plitidepsin + Dxm and 36.3 mths in Dxm monotherapy) | | | | |
| OS (ITT) | | | | |
| Deaths, n/N (%) | 123/171 (71.9) | 72/84 (85.7) | | |
| Median OS, months | 11.6 (9.2, 16.1) | 8.9 (6.0, 15.4) | *2.7* | 0.797 (0.596, 1.067) p-value = 0.1273 |
| % Alive at 6 months (95% CI) | 48.3% (40.4, 56.2) | 42.1% (31.3, 52.9) | 6.2% | |
| % Alive at 12 months (95% CI) | 30.8% (23.3, 38.3) | 21.0% (12.0, 30.1) | 9.8% | |
| OS, two-stage method crossover adj | | | | |
| Deaths, n/N (%) | 123/171 (71.9) | 72/84 (85.7) | | |
| Median OS, months | 11.6 (9.2, 16.1) | 6.7 (5.7, 9.7) | *4.9* | **0.667** (0.497, 0.895) p-value = 0.0069 |
| % Alive at 6 months (95% CI) | 48.3% (40.4, 56.2) | 32.9% (22.5, 43.2) | 15.4% | |
| % Alive at 12 months (95% CI) | 30.8% (23.3, 38.3) | 13.4% (5.5, 21.3) | 17.4% | |

| **ORR** | | | | | | |
|---|---|---|---|---|---|---|
| | **Plitidepsin + Dxm n/N (%)** | **Dxm n/N (%)** | **RR (95% CI)** | **Event rate/100 patients*** | | **RD (95% CI)** |
| | | | | **Plitidepsin + Dxm** | **Dxm** | |
| IRC - ITT | 17/171 (9.9) | 1/84 (1.2) | 8.35 (1.13, 61.70) | *9.9* | *1.2* | 0.09 (0.02, 0.15) |
| IA - ITT | 20/171 (11.7) | 1/84 (1.2) | 9.82 (1.34, 71.97) | *11.7* | *1.2* | *0.11 (0.04, 0.17)* |

| **Harms** | | | | | | |
|---|---|---|---|---|---|---|
| | **Plitidepsin + Dxm n/N** | **Dxm n/N** | **RR (95% CI)** | **Event rate/100 patients*** | | **RD (95% CI)** |
| | | | | **Plitidepsin + Dxm** | **Dxm** | |
| **Any Grade** | | | | | | |
| Nausea | 62/167 | 9/83 | 3.42 (1.79, 6.54) | *37.1* | *10.8* | *0.26 (0.15, 0.37)* |
| Fatigue | 61/167 | 7/83 | 4.33 (2.07, 9.05) | 36.5 | 8.4 | 0.28 (0.17, 0.39) |
| Vomiting | 28/167 | 2/83 | *6.96 (1.70, 28.51)* | *16.8* | *2.4* | *0.14 (0.07, 0.22)* |
| Diarrhoea | 24/167 | 2/83 | 5.96 (1.44, 24.63) | *14.4* | *2.4* | *0.12 (0.05, 0.20)* |
| Myalgia | 24/167 | 2/83 | *5.96 (1.44, 24.63)* | *14.4* | *2.4* | *0.12 (0.05, 0.20)* |
| Decreased appetite | 21/167 | 2/83 | 5.22 (1.25, 21.73) | *12.5* | *2.4* | *0.10 (0.03, 0.17)* |
| Oedema peripheral | 20/167 | 2/83 | 4.97 (1.19, 20.76) | *12.0* | *2.4* | *0.96 (0.03, 0.17)* |
| Grade 3/4 AE | | | | | | |
| Myalgia | 18/167 | *1/83* | *8.95 (1.22, 65.87)* | *10.8* | *1.2* | *0.10 (0.03, 0.16)* |

Abbreviations: adj = adjusted; AE = adverse events; CI = confidence interval; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; IA = investigator's assessment; IRC = independent review committee; ITT = intention to treat; n = number of participants with event; N = total number of participants in group; OS = overall survival; PD = progressed disease; PFS = progression free survival; RD = risk difference; RPSFT = Rank Preserving Structural Failure Time; RR = relative risk.

Note: * = the ADMYRE trial: PFS: Median duration of follow-up: 17.1 months (Plitidepsin + Dxm) and 20.7 months (Dxm); OS Median duration of follow up: 33.4 months (Plitidepsin + Dxm) and 36.3 months (Dxm).

Source: PFS: Table 31, p87; Table 32, p88; Table 33, p90; Table 35, p94; Table 37, p96; OS: Table 22, p74; Table 26, p81; Table 28, p83 of the submission. *Calculated during evaluation. ORR Table 39, p98 and Table 41, p100; Table 57, p131 of the submission. Calculated during evaluation; CI for risk difference calculated using Review Manger 5.3 software.* Harms: Table 49, p107; Table 58, pp133-137 of the *submission. Table 12.2.2.3bis of 12 CSR Safety Analysis (25AUG16) _tables in CSR. Type-o errors were corrected for Grade 3/4 event numberers in nausea, myalgia and fatigue. RR and OR estimates for vomiting and myalgia were calculated using RevMan 5.3 during evaluation.*

6.25 On the basis of direct evidence presented in the pivotal the ADMYRE trial, for every 100 patients treated with plitidepsin + Dxm in comparison to Dxm monotherapy and over a median duration of follow-up of 17.1 months (plitidepsin + Dxm arm) and 20.7 months (Dxm monotherapy arm):

- Approximately 10 additional patients remained progression-free at 6 months.
- After adjustment for crossover, approximately 15 more patients remained alive at 6 months and 17 more patients at 12 months
- Approximately 9 additional patients would have a response to treatment.
- Approximately 26 more patients would experience nausea.
- Approximately 28 more patients would experience fatigue.
- Approximately 14 more patients would have vomiting.
- Approximately 12 more patients would have diarrhoea.
- Approximately 12 more patients would experience myalgia (muscle pain) of which 10 patients would experience grade 3/4 (more severe) myalgia.
- Approximately 10 more patients would have decreased appetite.
- Approximately 9 more patients would have peripheral oedema (swelling of the legs/arms).

6.26 A summary of the comparative benefits and harms is not relevant for the comparison of plitidepsin with pomalidomide given the non-inferiority claim.

## *Clinical claim*

6.27 On the basis of the ITC, the submission presented a claim that plitidepsin in combination with Dxm was non-inferior in terms of effectiveness and safety compared with pomalidomide in combination with Dxm. The therapeutic conclusion presented in the submission was not adequately supported because:

- The indirect comparison of safety data between the ADMYRE trial and the NIMBUS trial showed a higher risk of AEs in the plitidepsin trial compared to pomalidomide. The ESC considered that despite the differences in occurrence of AEs between the Dxm arms of both trials, plitidepsin is associated with significant toxicity and likely greater toxicity than pomalidomide. The ESC considered the claim of non-inferior safety was not met.
- The populations across the two trials may be different with respect to their baseline disease characteristics.

- A non-inferiority margin was not proposed, the point estimates for the HRs from the indirect comparisons favoured pomalidomide and 95% confidence intervals were wide.

6.28 On the basis of the direct evidence from the ADMYRE trial, the submission claimed that plitidepsin in combination with Dxm is superior in terms of effectiveness and non-inferior in terms of safety compared with dexamethasone monotherapy. Evidence from the ADMYRE trial indicated a difference in median PFS of 0.9 months by IRC analysis or 1.8 months by IA analysis. The magnitude of this gain is of questionable significance in the context of other treatments for RRMM. The ESC agreed with the commentary, that the claim of superior efficacy of plitidepsin over Dxm in the fourth-line treatment setting was questionable, due to the magnitude of the gain in median PFS of 0.9 months in the IRC analysis or 1.8 months in the IA analysis.

6.29 The safety claim relative to Dxm was not supported by the pivotal trial (ADMYRE). The incidence of TEAEs, SAEs and Grade ≥ 3 TEAEs in the plitidepsin arm was higher than in the Dxm arm; the estimated risk of anaemia, diarrhoea, nausea, fatigue, oedema peripheral, decreased appetite, and muscular weakness was higher for plitidepsin + Dxm compared to Dxm. The ESC agreed with the commentary and considered the submission's claim of non-inferior safety compared to Dxm was not supported due to the higher incidence of adverse events reported in the plitidepsin + Dxm arm of the trial.

6.30 The ESC considered that the non-inferiority claims for efficacy and safety against pomalidomide were not well supported by the available information. In particular, ESC was concerned about an apparent increase in diarrhoea, nausea, fatigue and muscle weakness that appear increased with plitidepsin as compared with pomalidomide may have significant impact on quality of life.

6.31 The PBAC considered that the claim of non-inferior effectiveness compared to pomalidomide in the third-line setting was uncertain.

6.32 The PBAC considered that the claim of superior comparative effectiveness compared to Dxm in the fourth-line setting was reasonable for PFS but not for OS, with only a marginal increase in clinical benefit (increase in median PFS of 0.9 months) with plitidepsin.

6.33 The PBAC considered that the claim of non-inferior safety compared to Dxm was not adequately supported by the data and the claim non-inferior safety compared to pomalidomide could not be adequately assessed.

## *Economic analysis*

CMA

6.34 The CMA of plitidepsin + Dxm versus pomalidomide + Dxm in the third-line treatment setting was based on an indirect comparison. The proposed equi-effective

doses in the submission were 5 mg/m$^2$ IV of plitidepsin on Day 1 and 15 q4wk and 4 mg oral of pomalidomide on Days 1–21 q4wk, each in combination with 40 mg of Dxm orally on Day 1, 8, 15 and 22 q4wk. The equi-effective doses were sourced from the ADMYRE and the NIMBUS trials: actual dose exposure was assumed to be equivalent to the recommended dose for plitidepsin + Dxm and pomalidomide + Dxm. The ESC considered this approach was reasonable.

6.35 There is uncertainty surrounding the data used to establish the extent of exposure to pomalidomide in the NIMBUS trial due to inconsistency in the reported exposure across documents relied upon by the submission: NICE (2015) reported a median of 5 (range = 1-23) treatment cycles whilst the EMEA (2013) reported 3 (range = 1-16). The submission attributed the discrepancy to the probable different data cuts used in the two reports based on their publication dates. The submission relied on a median number of 3 treatment cycles for pomalidomide in establishing the equi-effective doses for the CMA, which was observed at an older data-cut, without justification of its choice. All else being equal, the use of 3 cycles for pomalidomide would result in a lower cost-minimising price for plitidepsin. The ESC noted the use of 3 treatment cycles for pomalidomide was conservative and considered this was appropriate.

6.36 The submission included additional costs and/or cost offsets associated with differences in the use of prophylactic medications, the mode of administration and management of AEs for plitidepsin + Dxm compared with pomalidomide + Dxm. This was reasonable, with the ESC noting it constituted a small proportion of the total cost in either arm.

6.37 The additional cost per treatment course was estimated as less than $10 million for administering plitidepsin intravenously and less than $10 million for prophylactic medications. The submission used three approaches to calculate the costs of AEs, noting that this was because of the difficulty in estimating the comparative safety profile of plitidepsin and pomalidomide: AE rates from the ADMYRE trial only; AEs in the ADMYRE or the NIMBUS trials; and AEs from the ITC. The approaches assumed that differences in AEs only result in a cost difference and not a relevant quality of life difference. This may not be reasonable particularly given the potential for some AEs to impact on quality of life (such as fatigue, peripheral oedema and febrile neutropenia).

6.38 For the base case evaluation, the submission used only the AEs rates from the ADMYRE trial under the assumption that the toxicity profile of pomalidomide + Dxm was no different to that of Dxm monotherapy. The evidence provided in Section 2 of the submission does not support this assumption. In addition, there were minor errors in the estimation of the AEs included and exclusion of some potentially relevant AEs. The impact of correcting these errors was tested in the Commentary.

6.39 The submission established the price of plitidepsin by cost minimising it to the published price of pomalidomide. This resulted in a price of $[redacted], which was

also applied in the CUA of plitidepsin + Dxm compared to Dxm monotherapy (fourth-line treatment setting) and the financial estimates. This price was sensitive to the approach used in estimating AEs included in the CMA and the differences in the AEs and their management in the CUA. The results of the CMA are presented in Table 15.

**Table 15: Results of the cost-minimisation analysis**

| Component | Plitidepsin + Dxm | Pomalidomide + Dxm |
|---|---|---|
| **Treatment costs** | | |
| Plitidepsin dose (mg/m$^2$) | 5 | |
| Plitidepsin dosing frequency per cycle | 2 | |
| Cost of plitidepsin per cycle | $[redacted] | |
| Pomalidomide dose (mg) | | 4 |
| Pomalidomide dosing frequency per cycle | | 21 |
| Cost of pomalidomide per cycle | | $10,547.29 |
| Dexamethasone dose [mg] (patients ≤75 years of age) | [redacted] | 40 |
| Dexamethasone dosing frequency per cycle (patients ≤75 years of age) | [redacted] | 4 |
| Dexamethasone dose [mg] (patients >75 years of age) | [redacted] | 20 |
| Dexamethasone dosing frequency per cycle (patients >75 years of age) | [redacted] | 4 |
| Cost of dexamethasone per cycle | $[redacted] | $21 |
| **Cost of prophylaxis medications** | | |
| Ondansetron 8 mg intravenous | $[redacted] | |
| Promethazine hydrochloride | $[redacted] | |
| Prochlorperazine mesylate | $[redacted] | |
| Aspirin | | $4.56 |
| **Administration costs** | | |
| Intravenous administration | $[redacted] | |
| **Treatment of Adverse events** | | |
| Cost of AEs | *$[redacted]* | *$11.99* |
| **Total cost of Therapy** | ***$[redacted]*** | ***$10,585*** |

Abbreviations: AEs = adverse events; Dxm = dexamethasone.
Note: *Italicised values are estimates calculated during the evaluation when the errors for entering AEs proportions were corrected.*
Source: Table 77, p.178-179 of the submission, Excel Worksheet 'Aplidin_EconomicModel_March2019', sheet AEs of the submission and *Table 12.2.2.3bis of 12 CSR Safety Analysis (25AUG16)_tables in CSR of the submission.*

CUA

6.40 A summary of the modelled and trial-based CUAs for the treatment of patients with RRMM who have received at least three prior treatments is presented in Table 16.

**Table 16: Summary of model structure and rationale**

| Component | Summary |
|---|---|
| Time horizon | 7 years in the model base case versus 5.9 years in the trial based analysis. |
| Outcomes | LYG and QALYs |
| Methods used to generate results | Cohort based state transition semi-Markov partitioned survival model. |
| Health states | Four: pre-progression on treatment, pre-progression off treatment, post-progression and death. |
| Utilities | The submission used a regression equation from a pomalidomide submission to NICE (March 2015) to estimate utility weights for the model. |
| Cycle length | One week |
| Transition probabilities | For the trial-based analysis:<br>Transition probabilities were derived from the KM curves of survival data from the ADMYRE trial. Proportion of patients in each health state at any point in time were estimated as:<br>• Pre-progression on treatment; based on the TTF curve.<br>• Pre-progression off treatment; based on PFS curve – TTF curve.<br>• Post-progression; based on OS curve – PFS curve.<br><br>For the modelled evaluation:<br>Transition probabilities were based on parametric extrapolations of the ADMYRE trial KM estimates of TTF, PFS and OS. The choice of parametric function was based on statistical goodness of fit tests (AIC and BIC) and the visual fit of the model to the data:<br>• TTF = generalised gamma<br>• PFS = generalised gamma, however the base case results were based on log-logistic for plitidepsin + Dxm arm and generalised gamma for the Dxm monotherapy arm.<br>• OS = generalised gamma (Plitidepsin + Dxm) and lognormal (Dxm)<br>The extrapolated estimates were applied over the entire time horizon. |

Abbreviations: AUC = area under a curve; Dxm = dexamethasone; KM = Kaplan Meir; LLD = low dose of dexamethasone; LYs = life years; MM = multiple myeloma; QALYs = quality adjusted life years; RRMM = refractory and/or relapsed multiple myeloma; OS = overall survival; PBAC = Pharmaceutical Benefit Advisory Committee; PBS = Pharmaceutical Benefit Listing; PFS = progression free survival; PSD = public summary document; TTF = time to failure

Source: Table 78, p.181 of the submission; Text, p.185-186, p.190, p.194 and p.199.

6.41 Extrapolations for the modelled analysis were informed by the ADMYRE trial data from the entire KM period. However, the submission applied the fitted survival curve from the start of the model time horizon. The available KM data should have been applied for the period in the model up to the time when there is uncertainty due to small number of patients remaining event-free (typically the median duration of follow-up), with the extrapolated data applied thereafter (PBAC Guidelines v4-5.pdf, p.148). Using the fitted survival function only did not favour plitidepsin. The ESC agreed with the Commentary but noted the effect of this on the ICER was modest.

6.42 The submission calculated utility weights as a sum of each regression coefficient (from the pomalidomide submission to NICE, 2015) multiplied by the proportion of patients with that event (e.g. SD or PD) in the ADMYRE trial (as inferred from the Text, p.196 of 290, NICE committee papers). There are issues with how the submission estimated the utility weights used in the model:

- The aim of applying the method was to estimate a utility value for each of the relevant health states, e.g. time without progression. However, in applying the regression equation, the submission applied the proportion of patients in each

of the mutually exclusive health states to the utility regression function, in effect deriving an average utility value rather than a health state specific utility value.

- The submission included the proportions of patients who have progressive disease as an input for calculating the utility for pre-progression health states, and vice versa. This was not consistent with the model structure.
- The ESC noted the submission allowed utility weights within a health state to differ based on treatment allocation. This approach was considered inappropriate, as the difference between treatments is captured through progression, and the assumption that patients would experience better quality of life when treated with the plitidepsin lacks face validity given the increased risk of toxicity.
- The submission did not provide any justification or evidence to support the nominated value for the red-blood cell (RBC) level used as input to estimate utility levels. During the evaluation, this was found to be a major driver of the utility values: the lower the RBC value, the lower the utility value and vice versa (e.g. a one-unit decrement of the RBC level leads to a utility decrement of 0.049). The ESC agreed with the commentary and questioned the inclusion of RBC level in the utilities; given RBC levels are not a surrogate measure for anaemia. The ESC considered the nominated RBC level of 4 used in the submission was unjustified, noting its substantial impact on the ICER. A change in the RBC level of 2 in either direction impacted the ICER substantially.

6.43 The ESC noted utility weights were not collected in the ADMYRE trial, instead the regression approach used in pomalidomide's NICE submission was adapted for use in the submission's economic model. The gaps between the health states are larger in the UK 3L algorithm and therefore the ICERs are smaller. The ESC considered this led to uncertainty in the ICER and use of Australian utility weights would probably increase the ICER.

6.44 The estimated utility values used in the model for the post-progression health state was higher compared to the utility values used for the pomalidomide submission to the PBAC for last-line therapy (Pomalidomide PSD, July 2014, paragraph 3.2): 0.681 vs. 0.470. The use of the pomalidomide submission utility values increased the ICER by nearly 40% (from $75,000-105,000 to $105,000-200,000).

6.45 The ESC considered a 5.9-year time horizon used in the trial-based evaluation may not have been appropriate, considering the evaluation relied on TTF and PFS data which were only available for up to 2 years within the ADMYRE trial; limiting the time-horizon to two years resulted in an ICER of more than $200,000 (using the published price). A five-year horizon increased the ICER to $$75,000-105,000.

6.46 The submission justified the 7-year time horizon based on the PBAC accepting a 5-year time horizon as reasonable for pomalidomide as a last-line therapy and the median OS presented for pomalidomide plus Dxm was 54 weeks (12.5 months)

(Pomalidomide PSD, July 2014, point 7.8) compared to 5.9 years' worth of the ADMYRE trial data. This was not reasonable considering the PBAC's previous advice regarding pomalidomide and that plitidepsin is a last-line therapy, with a median OS of 11.6 months (less than that of pomalidomide and Dxm in the same setting). The ESC considered a 5-year time horizon should be adopted in the model-based evaluation, consistent with the 5-year time horizon accepted by the PBAC as reasonable for pomalidomide. The ESC noted the time horizon was a key driver of the model, substantially impacting the ICER, with the 7-year time horizon adopted in the submission favouring plitidepsin + Dxm.

6.47 The submission used TTF in the model to estimate costs associated with the use of plitidepsin and dexamethasone. While the data underlying TTF could not be verified, a comparison with the median duration of treatment indicated that TTF may be underestimating treatment exposure; the median time on plitidepsin according to the TTF approach was 9 weeks as compared with 12.3 weeks as reported in the clinical study report provided with the submission. Thus the model may have underestimated treatment costs without adjusting the corresponding effect on treatment outcomes.

6.48 The key drivers of the model are presented in Table 17.

**Table 17: Key drivers of the model (based on published price)**

| Description | Method/Value | Impact<br>Trial based ICER: $[redacted]<br>Model based ICER: $[redacted] |
|---|---|---|
| Extrapolation | Extrapolations were applied from the start of the model time horizon. The application of extrapolation from the median follow-up of KM curve. | Moderate, favours Dxm monotherapy<br>ICER: $[redacted] (trial based) |
| Utilities | High values for model health states calculated by the submission using a regression model from the literature with inputs from the ADMYRE trial. | High, favours plitidepsin + Dxm. The ICER increased from $[redacted] to $[redacted] when utility values from the pomalidomide PBAC submission were used. |
| Time horizon | The trial-based evaluation adopts a 5.9 year time horizon, which was supported by 5.9 years of OS data in the ADMYRE trial. The model-based evaluation adopts a 7-year time horizon, which was supported by 5.9 years of OS data in the ADMYRE trial. | High, favours plitidepsin + Dxm. A 2-year time horizon, equivalent to the available number of years for TTF and PFS increased the ICER from $[redacted] to $[redacted] |
| Dose interruptions | Dose interruptions due to toxicity: a higher proportion favors plitidepsin + Dxm. | High, favours plitidepsin + Dxm<br>ICER: $[redacted] (model based) |

Abbreviations: Dxm = dexamethasone; OS = overall survival.
Source: Compiled during the evaluation from Excel spreadsheet 'Aplidin_EconomicModel_March2019'.

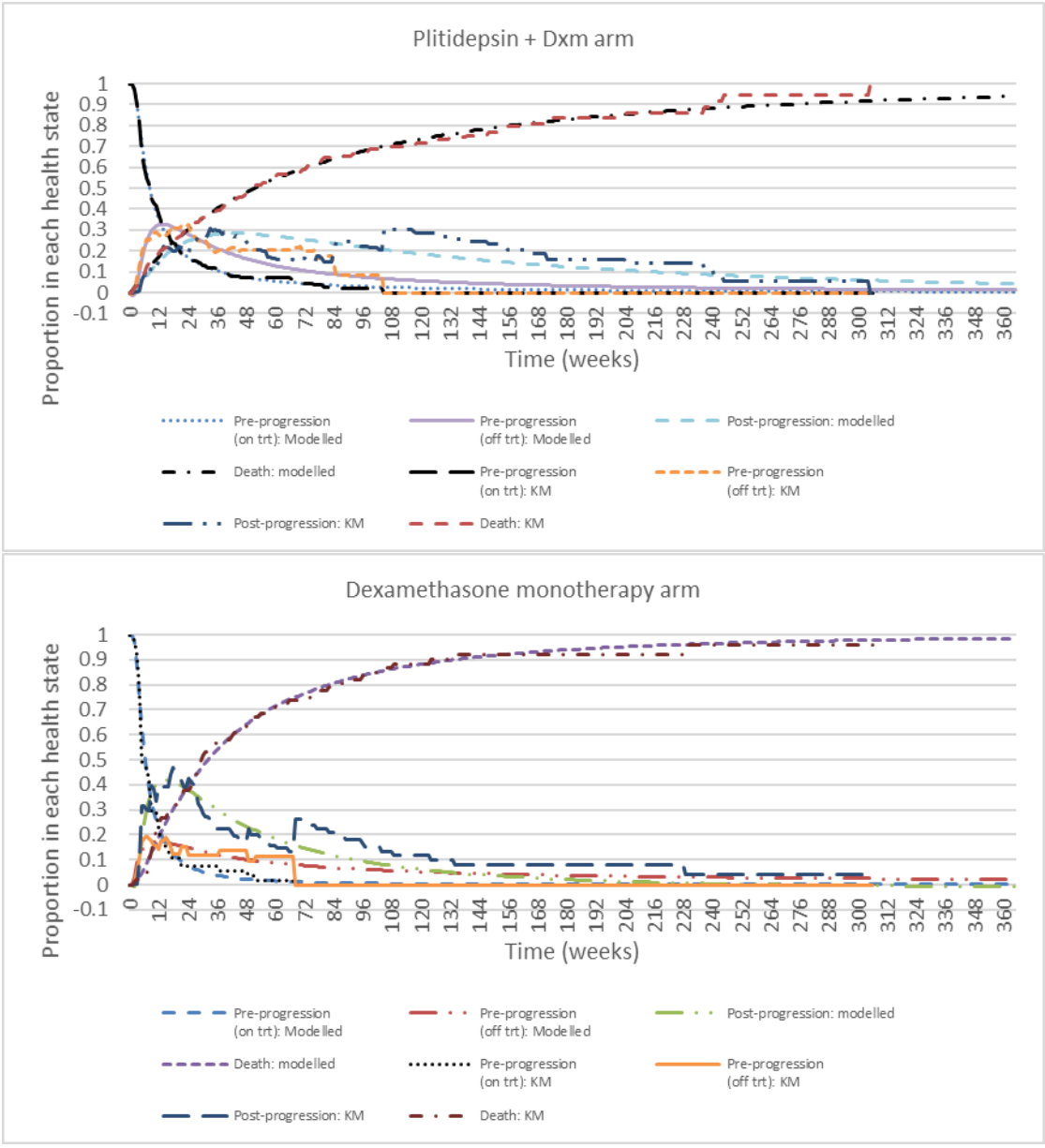
The redacted table shows ICERs in the range of $45,000 to over $200,000.

6.49 The Markov traces for the proportion of patients in each of the health states in both the trial based and modelled analyses for each treatment arm are presented in Figure 3. On inspection, the model is producing implausible results for some cycles: the proportion of patients in the 'pre-progression off treatment' health state has a negative value at cycle 1 for the trial-based evaluation and cycles 1 and 2 for the

modelled based evaluation. While the impact of these values is likely to be negligible, it raises uncertainty as to the overall robustness of the model construction.

6.50 Traces of the KM data (from the trial) vs. model results for PFS and OS were plotted for both treatment arms during the evaluation (Figure 4). The curves include the available KM data and extrapolated data for both treatment arms. Visual inspection indicates that the models were a reasonable fit to the KM data for OS, potentially but were less reliable in estimating PFS (underestimating during the KM period, and overestimating in the latter part of the curve).

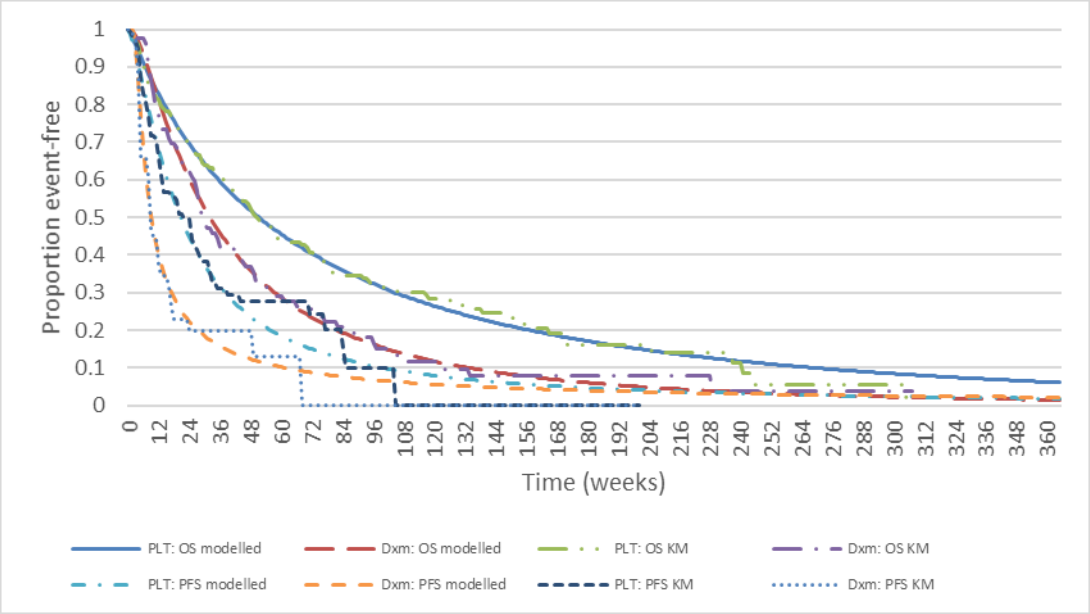
**Figure 3: Model trace for plitidepsin + Dxm arm (above) and Dxm monotherapy arm (below): trial vs model base evaluation**




Abbreviations: Dxm = dexamethasone; KM = Kaplan Meier; trt = treatment.

Source: Plotted during the evaluation from Excel spreadsheet 'Aplidin_EconomicModel_March2019' sheets 'PF PLIT' and 'PF DEX'.

**Figure 4: Trace of trial vs. modelled PFS and OS**




Abbreviations: Dxm = dexamethasone; KM = Kaplan Meir; PFS = progression-free survival; PLIT = plitidepsin + dexamethasone; OS = overall survival.
Source: Plotted during the evaluation from Excel spreadsheet 'Aplidin_EconomicModel_March2019' sheets 'PFS PLIT vs DEX' and 'OS PLIT vs DEX'.

6.51 The results of the economic evaluation are presented in Table 18; the submission referred to its trial based analysis as its base case (ICER of $75,000 to $105,000 per QALY). It should be noted that this is based on the price for plitidepsin calculated from the published price of pomalidomide. The use of the modelled data resulted in a minor improvement in the ICER. The submission did not present a stepped analysis. The base case utilised crossover adjusted OS data for the Dxm monotherapy arm. However, it was not possible to estimate an interim step for the analysis to utilise non-crossover adjusted OS as these were not provided by the submission.

**Table 18: Results of the economic evaluation**

| | Plitidepsin + Dxm | Dxm | Increment |
|---|---|---|---|
| **Trial data** | | | |
| Total cost ($) | $ [redacted] | $ [redacted] | $ [redacted] |
| | $ [redacted] | $ [redacted] | $ [redacted] |
| LYs | 1.589 | *1.060*[a] | *0.529* |
| QALYs | 1.080 | 0.694 | 0.387 |
| *Incremental cost per LYs gained* | | | $ [redacted] |
| Incremental cost per QALY gained | | | $ [redacted] |
| | | | $ [redacted] |
| **Modelled base case** | | | |
| Total cost ($) | $ [redacted] | $ [redacted] | $ [redacted] |
| | $ [redacted] | $ [redacted] | $ [redacted] |
| LYs | 1.669 | 1.044 | *0.625* |
| QALYs | 1.138 | 0.690 | 0.449 |
| *Incremental cost per LYs gained* | | | $ [redacted] |
| Incremental cost per QALY gained | | | $ [redacted] |
| | | | $ [redacted] |

Abbreviations: Dxm = dexamethasone; LYs = life years; QALY = quality adjusted life years

Note: [a]*Corrected from Excel spreadsheet 'Aplidin_EconomicModel_March2019' sheet 'Base case results' cell [D20]. Italicised were calculated during the evaluation.*

Italicised *estimates were calculated during the evaluation when the errors for entering AEs proportions were corrected. The resulting price of plitidepsin was $[redacted]. Since this does not materially alter the results, all the remaining analysis (results of the economic analysis) are as per the submission.*

Source: Table 108, p.218 of the submission.

6.52 The submission presented univariate sensitivity analyses, univariate scenario analyses and probabilistic sensitivity analyses. Selected univariate scenario analyses specified by the submission and additional analyses of relevance specified during the evaluation are presented in Table 19. These results show that the model was most sensitive to dose-interruptions, utility values and the time horizon.

**Table 19: Results of sensitivity analysis**

| Analyses | Incremental cost | Incremental QALY | ICER |
|---|---|---|---|
| **Sensitivity analysis for trial-based evaluation** | | | |
| **[a]Trial Base case** | **$** | **0.387** | **$** |
| Time horizon (base case 5.9 years) | | | |
| 1 year | $ | 0.042 | $ |
| 2 years | $ | 0.146 | $ |
| 3 years | $ | 0.248 | $ |
| 4 years | $ | 0.301 | $ |
| 5 years | $ | 0.331 | $ |
| Utilities: Recalculated using same input parameters but for health states to be mutually exclusive | $ | 0.329 | $ |
| Utilities: Change in value of placeholder for red-blood cells (base case 4) 2 | $ | 0.335 | $ |
| Utilities: Change in value of placeholder for red-blood cells (base case 4) 6 | $ | 0.439 | $ |
| Assume drug wastage for IV/SC treatments | $ | 0.387 | $ |
| Trial KM + extrapolated KM from median follow-up months (TTF and PFS: PLIT + Dxm: 17.1 months; Dxm: 20.7 months; OS: PLIT+ Dxm: 33.4 months, Dxm: 36.3 months) | $ | 0.511 | $ |
| **Sensitivity analysis for modelled evaluation** | | | |
| **[a]Modelled Base case** | **$** | **0.449** | **$** |
| Utilities (base case regression analysis on ADMYRE (NICE Pomalidomide) treatment modelled separately) | | | |
| Regression analysis on ADMYRE total trial population | $ | 0.399 | $ |
| Pomalidomide NICE submission | $ | 0.469 | $ |
| Pomalidomide PBAC submission | $ | 0.326 | $ |
| Carfilzomib NICE submission | $ | 0.397 | $ |
| Carfilzomib PBAC submission | $ | 0.402 | $ |
| Trial KM + extrapolated KM from median follow-up months[b] | $ | 0.511 | $ |
| BSA of 2.2 $m^{2}$[b] (base case 1.81 $m^{2}$) | $ | 0.448 | $ |

Abbreviation: Dxm = dexamethasone; ICER = incremental cost effectiveness ration; KM = Kaplan Meier; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life years; PBAC = Pharmaceutical Benefit Advisory Committee; PBS = Pharmaceutical benefit scheme; OS = overall survival; PFS = progression free survival; PLIT = plitidepsin; TTF = time to failure.
Note: Italicised was compiled during the evaluation using data that errors in the proportions of AEs has not be corrected.
[a]Sensitivity analyses were as presented in the submission.
[b]Sensitivity analysis was based on the corrected errors in the proportion of AEs.
Source: Table 109, p.220-221 of the submission. Compiled during evaluation from Excel spreadsheet 'Aplidin_EconomicModel_March2019' sheets 'Base case results', 'PF PLT', 'PF DEX', 'Utilities', 'Controls', 'PFS PLIT vs DEX', 'TTF PLIT vs DEX' and 'OS PLIT vs DEX'.

6.53 The ESC noted a multivariate sensitivity analysis using: (i) a time horizon of 5 years; and (ii) utility values assuming that health states are mutually exclusive. The ESC considered that this respecified analysis provided a more reasonable estimate of the ICER than the base case in the submission and could be considered the respecified base case if the claim of superior comparative effectiveness is accepted.

## *Drug cost/patient/treatment*

6.54 The cost per patient per course is presented in Table 20. These results show that the submission estimated a higher cost per patient per course for the trial-based use (assuming 3 cycles of treatment) compared with the CUA (assuming 4.28 cycles of treatment). This difference arose because the CUA incorporated the impact of treatment interruptions on the per cycle cost of care, resulting in a cost for the average patient of $[redacted] (essentially the same as in the trial based analysis, even though the number of cycles was higher than in the trial based analysis).

**Table 20: Drug cost per patient for proposed and comparator drugs**

| | Plitidepsin | | | | Pomalidomide | | |
|---|---|---|---|---|---|---|---|
| | **Trial dose and duration** | **CMA** | **CUA** | **Financial estimates** | **Trial dose and duration** | **CMA** | **Financial estimates** |
| Equi-effective dose (recommended) | 5 mg/m$^2$ | 5 mg/m$^2$ | 5 mg/m$^2$ | 5 mg/m$^2$ | 4 mg/day | 4 mg/day | 4 mg/day |
| Frequency/cycle | 2 | 2 | 2 | 2 | 21 | 21 | 21 |
| Median duration | 3 cycles | 3 cycles | *Mean 4.28 cycles* | 3 cycles | 3 cycles | 3 cycles | 3 cycles |
| Cost/patient/ cycle | $[redacted]a | $[redacted]b | $[redacted]c | $[redacted]d | $[redacted] (private) $[redacted] (public) | $[redacted] | $[redacted] (private) $[redacted] (public) |
| Cost/patient/ course | $[redacted] | $[redacted]b | $[redacted] | $[redacted]d | $[redacted]e Average for private/public | | *$[redacted]f Average for private/public* |

Abbreviations: CMA = cost minimisation analysis; CUA = cost utility analysis; NA = not applicable

Note: a = proposed DPMQ/DPMA private hospital price of plitidepsin b = *corrected during the evaluation for errors in AEs proportions.* c = cost of plitidepsin used in the CUA accounting for dose interruptions and using the BSA of 1.8m$^2$ to estimate value. d= this was presented in the submission as DPMQ/DPMA as private hospital price of plitidepsin in the model for Section 4, which is different from that presented in Sections 1 and 3. e = cost/patient/cycle * 3 cycles, without accounting for co-payment. *f = (cost/patent/cycle (private) * 3 cycles + cost/patent/cycle (public) * 3 cycles) / 2. g = used average cost of plitidepsin for private and public. Mean number of cycles estimated in the Excel Worksheet 'Aplidin_EconomicModel_March2019', sheet 'PF PLIT' cell AC.*

Source: Table 8, p25; Table 69, pp169-170; Table 70, p171; Table 77, pp178-179, Section 4 workbook, sheet 4b. Displaced -PUB of the utilisation-and-cost-model. Italicised values have been calculated

## *Estimated PBS usage & financial implications*

6.55 This submission was not considered by DUSC.

6.56 The submission presented an epidemiological approach to estimate the market size and financial implications of plitidepsin on the PBS. A market share approach was also presented to estimate the number of scripts for plitidepsin substituting for pomalidomide. This approach was reasonable. However, there was a large difference between the number of scripts estimated from each approach due to the epidemiological approach adopting a "whole-of-market" approach with respect to current third-line use, whereas the market share approach only considered current use of pomalidomide in the third-line setting. The ESC agreed with the commentary, considering the submission overestimated net plitidepsin use.

6.57 For the epidemiological approach, the submission used the clinical algorithm (presented in Section 1 of the submission) to estimate the number of patients to be treated with plitidepsin + Dxm in the third and fourth line settings. The submission also included 20 patients from the Aplidin (plitidepsin) Access Program.

6.58 The incidence patient population for plitidepsin was estimated based on the number of patients with MM each year who have previously received a PI and IMiD, who received pomalidomide and assuming 5% market growth with listing of plitidepsin. The assumed 5% growth to the market is not supported given the efficacy and safety profile of plitidepsin. The submission assumed uptake for plitidepsin of [redacted]% in Year 1 and gradually increasing to [redacted]% in Year 6. The approach taken to calculate yearly uptake could not be verified except for year 2. The submission's estimates for use among incidence patients are for the third-line setting only.

6.59 Prevalence of MM was calculated by estimating the 5-year prevalence pool using linear projections applied to historical data on patients receiving any MM scripts (DUSC Review 2017). To these estimates, the proportion of RRMM patients who have received two lines of therapy including both PI and IMiD and are refractory/intolerant (for third-line setting) and those who received at least 3 lines of therapy including PI and IMiD (for fourth-line setting) were applied. Estimates for the third and fourth line settings were combined as follows:

- Use in the third-line setting applied a proportion for those patients who would elect to receive any third-line treatment (81.9%). This proportion was derived as the ratio of all patients currently receiving third-line therapy to those in second-line therapy, and assuming 5% market growth due to the listing of plitidepsin. This approach establishes use for plitidepsin based on total current use in the third-line setting as the relevant patient pool and not just the use of pomalidomide (including pomalidomide, bortezomib, carfilzomib, lenalidomide and thalidomide). Thus, the submission has assumed that plitidepsin use will be drawn from all current therapies and not just pomalidomide, even though it has only presented indirect comparative evidence and cost-offsets against pomalidomide and the proposed restriction is for use following prior PI or IMiD use.
- Use in the fourth-line setting was estimated by applying the proportion of patients receiving fourth-line therapy or beyond (45%) to the estimated number of patients currently in the third-line setting. The proportion was derived as the ratio of all patients currently receiving fourth-line therapy or beyond to those in third-line therapy), and assuming 5% market growth due to the listing of plitidepsin.
- Estimated prevalence for third and fourth-line use were combined and applied to the assumed uptake rate for use of plitidepsin.

6.60 The submission did not report the estimated use of plitidepsin in the third and fourth-line settings separately. These have been calculated during the evaluation.

6.61 The submission presented a market-share approach based on the script volumes for pomalidomide, factoring in uptake of plitidepsin of [redacted]% in Year 1 to [redacted]% in Year 6. The estimated additional scripts were based on the assumption that 44.4% of patients on pomalidomide would receive subsequent therapy. These estimates can be considered as a separate validation of the estimates for use in the third-line setting, but were not named as such by the submission. The ESC considered that the uptake assumptions were uncertain.

6.62 The net cost of listing plitidepsin was based on the epidemiological approach and is presented in Table 21. Overall, the listing for plitidepsin is expected to result in an incremental cost to the PBS/RPBS of less than $10 million in Year 1, increasing to $10 - $20 million in Year 6.

6.63 The total financial implications to the PBS over 6 years of subsiding plitidepsin in the submission were $30 - $60 million: $10 - $20 million (30%) due to third-line therapy and $30 - $60 million (70%) due to fourth-line therapy. The apparent high net addition to government costs was due to the fourth-line setting where the magnitude of PFS gain with plitidepsin + Dxm compared to Dxm is of questionable significance in the context of other treatments available for RRMM. The additional financial costs to the PBS/RPBS in the third-line setting are largely due to the assumed 5% growth in the MM market due to the plitidepsin listing and the costs of prophylactic medications for plitidepsin. However, the submission included two of these prophylactic medications (promethazine hydrochloride and prochlorperazine mesylate) as reductions in scripts. Therefore, it appears that the costs for prophylactic agents associated with plitidepsin were underestimated in the submission.

6.64 In addition, for the third-line setting (where a CMA was conducted relative to pomalidomide), the submission estimated plitidepsin use based on total market size in the third-line setting but accounting for only pomalidomide substitution in that setting. In effect, the submission has underestimated the extent of likely substitution (assumed to be pomalidomide only) relative to the estimated number of patients (based on all current treatment use in the third-line setting).

**Table 21: Estimated use and financial implications**

| | *Year 1* | *Year 2* | *Year 3* | *Year 4* | *Year 5* | *Year 6* |
|---|---|---|---|---|---|---|
| ***Estimated extent of use*** | | | | | | |
| *Number of patients treated*<br>3rd line<br>4th line | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of scripts dispensed[a]<br>Epidemiological approach<br>Market-share approach<br>Market share scripts % of epidemiological approach | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated financial implications of plitidepsin** | | | | | | |
| 3rd line | | | | | | |
| Cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 4th line | | | | | | |
| Cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated financial implications for other medicines** | | | | | | |
| 3rd line | | | | | | |
| Cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 4th line | | | | | | |
| Cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less copayments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net financial implications** | | | | | | |
| Net cost to PBS/RPBS<br>3rd line<br>4th line<br>3rd and 4th lines | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net cost to MBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net cost to PBS/RPBS/MBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a] Assuming scripts per patient per treatment course as estimated by the submission.

The number of patients estimated for Year 1 during the evaluation was 1 patient less than the estimate presented for the submission due to rounding effect.

The financial implications of listing plitidepsin on the PBS were re-estimated during the evaluation according to line of treatment. Using the model from the submission, for 3rd-line treatment, the % of patients who have received both PI and IMiD (3+) and % of patients electing 4th line treatment were assumed to be 0%. The 20 grandfathered patients were included in this treatment setting. For 4th-line treatment, the % of patients who have received both PI and IMiD (2 only) and % of patients electing 3rd line treatment were assumed to be 0%.

The net cost to PBD/RPBS estimated for Year 3 during the evaluation is $15 more than presented in the submission because of rounding effect ($[redacted] vs $[redacted]).

Source: Table 120, p.233 of the submission; Excel worksheet 'Aplidin_utilisation-and-cost-model_March2019' of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $10 - $20 million per year.

6.65 The submission did not provide a sensitivity analysis for the financial estimates. Sensitivity analyses were conducted during the evaluation (Table 22) to test the:

- assumed market growth rate of 5% after plitidepsin is listed; the sensitivity analysis assumed no growth.
- use of median of 3 cycles per patient; the sensitivity analysis used the mean number of doses (4.28) calculated from the CUA, based on the trial data.

- The assumption of the number of cycles per patient has a large impact on the estimated net cost to PBS/RPBS.

6.66 At year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $30 - $60 million. The PBAC noted these costs were based on the published price of the comparator. The net cost to the PBS will reduce once the effective price of the pomalidomide is applied.

**Table 22: Sensitivity analysis**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Total |
|---|---|---|---|---|---|---|---|
| Base case | | | | | | | |
| Net PBS/RPBS | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |
| Estimated market growth rate | | | | | | | |
| 0% | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |
| Mean number of cycles | | | | | | | |
| 4.28[a] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Note: a = the mean number of cycles was based on total estimated cost of plitidepsin (in the trial based model in the CUA, Section 3) divided by the cost per cycle.
Source: Calculated during evaluation.

## *Quality Use of Medicines*

6.67 The submission provided a summary of safety concerns and planned pharmacovigilance actions for plitidepsin. The submission provided pharmacovigilance activities that generally aimed at characterising their incidence, monitoring their associated risks and taking appropriate actions when necessary.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 7 PBAC Outcome

7.1 The PBAC did not recommend the listing of plitidepsin in patients who are refractory to a PI and an IMiD (third-line) or in patients who have received at least three prior treatment regimens including both a PI and an IMiD (fourth-line setting). The PBAC

considered that, for the comparison of plitidepsin+Dxm versus Dxm alone, the magnitude of the clinical benefit in terms of PFS (median increase of 0.9 months) was marginal and the OS gain was uncertain given it was statistically significant only when adjusted for cross-over. The PBAC considered that the revised ICER for plitidepsin versus Dxm, based on the PBAC's preferred assumptions, was high. The PBAC considered that for the comparison against pomalidomide+Dxm, the claim of non-inferior efficacy was uncertain and the claim of non-inferior safety was not adequately supported.

7.2 The PBAC considered there may be a clinical place for plitidepsin as last-line treatment in RRMM; however, its use offers a clinically meaningful effect in only a small and undefinable subgroup of patients, with a significant toxicity profile. The PBAC noted that patients treated with plitidepsin in the ADMYRE trial experienced a significant increase in AEs, particularly diarrhoea, nausea, fatigue and muscle weakness when compared to patients treated with pomalidomide in the NIMBUS trial. The PBAC noted the sponsor's claim in the pre-PBAC response that plitidepsin's "toxicity profile did not significantly impact the patient's health or quality of life" (pre-PBAC response, page 1), but considered this claim could not be supported, with no quality of life data presented in the submission.

7.3 The submission nominated pomalidomide+Dxm as the third-line comparator and Dxm as the fourth-line comparator. The PBAC considered both comparators were appropriate, however, it noted that in practice, patients cycle through multiple therapies as they progress and treatment options will include all appropriate PBS-listed agents, clinical trials and compassionate access programs for novel agents. Considering agents are often 'recycled' in MM if a patient's initial response was favourable, particularly the PIs and IMiDs, it is unclear what standard of care in 3$^{rd}$ line versus 2$^{nd}$ line would be, with this likely to change in the near future as more treatment options become available. Given that patients are likely to cycle through treatments, the PBAC considered that plitidepsin was likely to displace, rather than replace, pomalidomide. For this reason the PBAC considered that the comparison against Dxm alone was the most relevant to determining the cost effectiveness of plitidepsin, while noting that the comparison with pomalidomide provided a useful reference point.

7.4 The PBAC noted that the evidence for plitidepsin+Dxm versus Dxm was based on a phase III, randomised, multicentre, open-label study (ADMYRE). The PBAC noted the submission presented two analyses from the ADMYRE trial for PFS, ORR, DOR and TTFST. The PBAC considered use of the Independent Review Committee (IRC) analysis to be the most appropriate.

7.5 The PBAC noted the ADMYRE trial showed a statistically significant improvement in PFS (HR=0.650; 95% CI 0.477, 0.885) with an increase in median PFS of 0.9 months, but considered the magnitude of clinical benefit was marginal. The PBAC noted the OS benefit was only statistically significant when adjusted for crossover (HR=0.676; 95% CI 0.500, 0.913). The PBAC also noted the modest 22% ORR and that patients

had an increase in the median time until subsequent therapy or death of 2.3 months in the plitidepsin arm compared to Dxm.

7.6 Overall, the Committee considered plitidepsin resulted in an incremental benefit versus Dxm in only a small subset of patients who experienced a prolonged response. The PBAC noted that there was no way to target treatment with plitidepsin to those patients who are most likely to respond.

7.7 The PBAC noted there were no head-to-head studies comparing plitidepsin with pomalidomide and the submission presented two trials, the ADMYRE trial and the NIMBUS trial, as the basis of an indirect comparison of plitidepsin + Dxm and pomalidomide + Dxm. The PBAC noted that both trials allowed for crossover but despite this, considered the risk of bias was low. The PBAC considered the submission's claim of non-inferior efficacy of plitidepsin + Dxm compared to pomalidomide + Dxm in the third-line setting was uncertain as a non-inferiority margin was not proposed, the point estimates for the HRs from the indirect comparisons favoured pomalidomide and the 95% confidence intervals were wide. Further, as per Paragraph 7.2, the higher toxicity profile of HI-Dxm (NIMBUS trial) compared to Dxm (ADMYRE trial) brought into question the comparability of the common comparator arms, and the PBAC considered the non-inferior safety claim of plitidepsin + Dxm versus pomalidomide + Dxm could not be adequately assessed.

7.8 The PBAC noted both trial based and modelled analyses comparing plitidepsin + Dxm to Dxm monotherapy were presented.

7.9 The PBAC noted the submission did not nominate an effective price for plitidepsin but instead relied on the price based on the CMA with pomalidomide.

7.10 The PBAC noted that the ESC had identified a number of issues regarding the inputs used in the modelled analysis versus Dxm including:

- the method used to estimate utility weights, including the application of the regression equation and the use of treatment-specific utility weights;
- the time-horizon of 7 years used in the submission was not appropriate;
- the data underlying the TTF could not be verified as it was not an outcome of the ADMYRE trial and may have underestimated treatment exposure; and
- that it was not possible to estimate the interim steps used to calculate the crossover adjusted OS data for the Dxm monotherapy arm, as these were not provided by the submission.

7.11 Furthermore, the PBAC considered that the costs of adverse events, as well as their impact on quality of life, should have been included in the analysis.

7.12 The PBAC noted the estimated financial impact of listing plitidepsin was overestimated because it was based on the published price of pomalidomide. The PBAC also noted that there were a number of issues with calculating the estimated

use of plitidepsin (refer to Paragraphs 6.56 - 6.61), including issues with assumed uptake rates. The submission estimated an uptake rate of [redacted]% in Year 1, increasing to [redacted]% in Year 6, based on the assumption that 44.4% of patients on pomalidomide would receive subsequent therapy with plitidepsin. The PBAC considered these uptake rates were uncertain and likely overestimated the extent of plitidepsin use due to plitidepsin's additional toxicity as well as a clinically meaningful effect observed in only a small and undefinable subgroup of patients.

7.13 The PBAC considered that any future analysis should account for the issues raised in paragraph 7.10 and 7.12, and the resulting ICER would need to be <$40,000/QALY to account for the substantial toxicity and minor additional benefit of plitidepsin. The PBAC further considered that the benefit observed in the ADMYRE trial may be smaller in the PBS population due to their poor prognosis and reduced tolerability of plitidepsin.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Rejected

## Context of Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## Sponsor's Comments

The sponsor had no comment.