Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Plitidepsin

Proprietary Product Name: Aplidin

Sponsor: Specialised Therapeutics Pharma Pty Ltd

May 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BM	Bone marrow
BP	Blood pressure
BSA	Body surface area
BTZ	Bortezomib
CI	Confidence interval
C_{max}	Maximum plasma concentration
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
DBP	Diastolic blood pressure
DL	Dose level
DLT	Dose-limiting toxicity
DR	Duration of response
DXM	Dexamethasone
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	Haemoglobin

Abbreviation	Meaning
HR	Hazard ratio
IA	Investigator's assessment
IDMC	Independent Data Monitoring Committee
IMiDS	Immunomodulatory agents
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous
L	Litre
LBS	Literature-based submission
LVEF	Left ventricular ejection fraction
mg	Milligram
mL	Millilitre
MM	Multiple myeloma
MR	Minimal response
NHL	Non-Hodgkin's lymphoma
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
Q4W	Every 4 weeks
Q2W	Every 2 weeks
PD	Progressive disease/disease progression
PFS	Progression-free survival
PI	Product information
PK	Pharmacokinetics
PR	Partial response

Abbreviation	Meaning
PS	Performance status
QoL	Quality of Life
RCT	Randomised controlled trial
RD	Recommended dose
SBP	Systolic blood pressure
sCR	Stringent complete response
SCT	Stem cell transplantation
SD	Stable disease
SMQ	Standardised MedDRA queries
SOC	System Organ Class
TGA	Therapeutic Goods Administration
U	Unit
ULN	Upper limit normal
US	United States
VGPR	Very good partial response
V_{ss}	Volume of distribution at steady state
µg	Microgram
³	At or greater than
£	At or lesser than
>	Greater than
<	Less than
versus	versus

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 December 2018
Date of entry onto ARTG:	12 December 2018
ARTG number:	291661
Black Triangle Scheme	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Plitidepsin
Product name:	Aplidin
Sponsor's name and address:	Specialised Therapeutics Pharma Australia Pty Ltd PO Box 2299 Kew Victoria 3101 Australia
Dose form:	Powder for Injection and solvent
Strength:	2 mg; after reconstitution, each mL of concentrate contains 0.5 mg of plitidepsin
Container:	Glass vial containing lyophilised powder (2 mg plitidepsin) and glass ampoule containing the diluent (4 mL).
Pack size:	One (1) vial and one (1) ampoule per carton
Approved therapeutic use:	*Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator. Aplidin may be used after two prior lines of therapy if refractory and/or intolerant to both a proteasome inhibitor and an immunomodulator.*
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Aplidin is 5 mg/m^2 according to Body Surface Area (BSA).

Product background

This AusPAR describes the application by the sponsor to register a new chemical entity, plitidepsin (Aplidin), to be used in combination with dexamethasone (DXM) for the treatment of multiple myeloma (MM) in patients who have received at least two prior therapies. The proposed dose is 5 mg/m^2 IV as a 3 h infusion. The infusion must be performed through a pump device over 3 h (fixed rate) on Day 1 and 15 and then every four weeks (Q4W). Plitidepsin is a synthetically manufactured cyclic depsipeptide.

The sponsor has proposed the following indication:

> *Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both a proteasome inhibitor and an immunomodulator.*

Background on condition being treated

Multiple myeloma is characterised by the neoplastic proliferation of clonal plasma cells in the bone marrow and extramedullary sites, which usually produce a monoclonal immunoglobulin. Typical manifestations of the disease include monoclonal proteins in blood and urine, organ dysfunction, lytic bone lesions and immunodeficiency. This often results in extensive skeletal destruction with osteolytic lesions, osteopaenia, and/or pathologic fractures. Other clinical characteristics include hypercalcaemia, renal impairment, anaemia and an increased risk of infections.

Multiple myeloma is the second most common haematological malignancy accounting for approximately 1% of neoplastic diseases and 13% of haematological cancers. The median age at diagnosis is around 70 years and many patients are older than 75 years.[1] The overall median survival is 5 to 6 years from the diagnosis of MM, although the outcome varies largely depending on biological characteristics, such as cytogenetics and age.

Despite the much improved survival outcome since the introduction of novel therapeutic agents including the immunomodulatory drugs (IMiDs) and proteasome inhibitors, MM remains an incurable disease. However, the expansion of effective treatment options over the last two decades, has converted what was once a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long-term control, often for 7 years or more. However, almost all patients will relapse after an initial response.

Various definitions for relapsed and refractory disease exist; however, new definitions have recently appeared in the literature, primarily by the International Myeloma Working Group (IMWG).[2]

Relapsed disease: Relapsed myeloma is defined as previously treated myeloma, which after a period of being off-therapy, requires salvage therapy but does not meet criteria for 'primary refractory 'or 'relapsed-and-refractory 'categories, as outlined below.

Refractory disease: Refractory myeloma is defined as disease that is non-responsive while on therapy or progresses within 60 days of last therapy.

Relapsed and refractory myeloma is defined as relapse of disease in patients who achieve minimal response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy.

Primary refractory myeloma refers to refractory disease in patients who have never achieved an MR with any therapy, and includes 2 sub-categories:

[1] Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.
[2] International Myeloma Working Group, see http://imwg.myeloma.org/

- Patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression.
- Primary refractory progressive disease (PD).

Treatment options for patients with relapsed or refractory MM include hematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include a risk stratification of myeloma (that is, high, intermediate or standard risk disease), prior treatments used, and the duration of response to these treatments.

Plitidepsin

Plitidepsin is a cyclic depsipeptide originally isolated from a Mediterranean marine tunicate, *Aplidium albicans*. The plitidepsin medicinal agent used in the submitted clinical trials and proposed for approval is manufactured by total synthesis.

Plitidepsin is stated to interact with a protein (eEF1A2) that has oncogenic properties and is involved in triggering oxidative stress in cells that can ultimately lead to cell death (apoptosis). It is believed that oxidative stress induces the sustained activation of c- Jun N-terminal kinase (JNK) and p38MAPK and finally apoptosis. The elongation factor 1A2 (eEF1A2) has been recently considered the target for plitidepsin. In vitro studies have investigated antiproliferative activity against a broad spectrum of tumour types, particularly against MM, leukaemia, lymphoma, pancreas, non-small cell lung cancer (NSCLC) and breast. In vivo studies showed anti-tumour effect of plitidepsin in xenograft models of MM (as a single agent or in combination with DXM) and non- Hodgkin lymphoma (NHL).

Regulatory status

Australian regulatory status

This is the first accepted application for plitidepsin in Australia.

International regulatory status

Aplidin has not yet been authorised as a medicinal product in any country.

European Medicines Agency

Aplidin was designated as an orphan medicinal product by the European Medicines Agency (EMA) on 16 November 2004 in the following condition '*Treatment of multiple myeloma* '.[3]
In September 2016, an application for marketing authorisation for plitidepsin was submitted to the EMA through centralised procedure. The sponsor applied for the following indication:

> *'Aplidin is indicated in combination with dexamethasone for the treatment of relapsed and refractory multiple myeloma (MM) in adult patients who have received at least three prior regimens including bortezomib, and either lenalidomide or thalidomide.'*

[3] For further details, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000165.jsp&mid=WC0b01ac058001d12b.

On 14 December 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Aplidin, intended for the treatment of MM.[4]

The sponsor subsequently requested a re-examination of the initial opinion. After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorisation on 22 March 2018.

The publically available information from the EMA states the following main concerns that led to the refusal:[5]

> *'At the time of the initial review, the CHMP was concerned that the data from the main study showed only a modest increase of around one month in the time patients given Aplidin lived without their disease getting worse, compared with those treated with dexamethasone alone. In addition, improvement in overall survival (how long patients lived overall) was not sufficiently demonstrated. Regarding safety, severe side effects were reported more frequently with the combination of Aplidin and dexamethasone than with dexamethasone alone. Based on the above, the CHMP was of the opinion that the benefits of Aplidin did not outweigh its risks and recommended that it be refused marketing authorisation. After re-examination, the Committee remained of the same opinion. The CHMP therefore confirmed its recommendation that the marketing authorisation be refused'.*

The sponsor has provided the TGA with key EMA evaluation, decision documentation and European Union (EU) sponsor responses. Furthermore, Specialised Therapeutics Pharma has provided the TGA with a response to the evaluation reports and the CHMP outcome, beginning with a chronological list of events for the EMA evaluation of Aplidin. For the purpose of this overview, the following points are briefly noted:

- '*Specialised Therapeutics Pharma strongly believes that there is a clinical need for Aplidin in the refractory/relapsed setting in Australia. This opinion is reinforced by leading Australian haematologists who participated in an Advisory Board Meeting held on 26 June 2017. Key feedback from these experts included the ability to be able to provide their MM patients with a medicine from a different class of drug, that is, with a different mechanism of action, to those already administered*'.
- *Specialised Therapeutics Pharma* states that '*for a number of reasons, this treatment could occur earlier or later in the course of an individual patient's illness. Thus, rather than stating that the drug should be indicated after particular lines of therapy, the number of prior therapies should not be the defining factor. The patient's individual situation should define the options, that is, 'when there are no available or suitable alternative therapies'. This could mean exhausting available drugs or the patient being in a condition in which the remaining approved drugs are not appropriate or safe. This would ultimately be a clinical judgment*'.
- '*A clear advantage of Aplidin is the favourable safety profile in terms of haematological toxicity'. 'Note also that a proportion of patients in this stage of their disease may have limited marrow reserve or other comorbidities and may not tolerate currently approved therapies. While the P+DXM group overall had an increment in progressive free survival (PFS) and OS, 48% of patients with clinical benefit (that is, best response standard deviation (SD) or better) also demonstrated durable responses (PFS of 4.6 months and OS of 18.4 months)*'.

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004354/WC500240754.pdf
[5] For further details, see: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004354/WC500240754.pdf.

- '*The benefit in OS is underestimated due to the cross-over and it should not be simply disregarded as a 'null 'or 'unfavourable' outcome. There was some positive effect, expressed by the HR (0.797, log-rank p value = 0.1261) and the confidence interval range (0.596-1.067), albeit not reaching a pre-defined statistical boundary. This effect should not be discarded especially in patients who have exhausted all the treatment options*'.
- *The sponsor considers that an additional factor in understanding the PFS outcome was the variation in progression criteria by International Myeloma Working Group (IMWG) over time. The sponsor's analysis of this variation included 'a preplanned sensitivity analysis done in the All Randomized Patients 'dataset with 'confirmation of PD by IRC, which showed a more substantial increase in median PFS'.*
- The sponsor argues that '*Some of the toxicities are more apparent in numbers than in severity. The most common ones cited fatigue (10.2%), myalgia (4.2%), nausea (3.6%), vomiting (1.8%) and diarrhea (1.2%) may be managed. Myelotoxicity was relatively mild and, partially explained by pre-existing haematology abnormalities. The more serious toxicities were unusual in frequency and can be identified in product labelling to provide guidance for monitoring and management*'.

Swiss Medic

The sponsor stated that an application for Aplidin is currently under evaluation with Swiss Medic. As of March 2018, the sponsor stated that a final decision was expected between December 2018 and March 2019.[6]

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2017
First round evaluation completed	4 May 2018
Sponsor provides responses on questions raised in first round evaluation	7 June 2018
Second round evaluation completed	2 July 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 July 2018
Sponsor's pre-Advisory Committee response	13 July 2018

[6] The Swissmedic application has been withdrawn

Description	Date
Advisory Committee meeting	2 August 2018
Registration decision (Outcome)	10 December 2018
Completion of administrative activities and registration on ARTG	12 December 2018
Number of working days from submission dossier acceptance to registration decision*	239

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Plitidepsin is to be presented as a powder for injection that must be reconstituted with the supplied diluent before dilution in 0.9 % sodium chloride (NaCl) or 5 % glucose solution for IV infusion as a micellar injection. One pack size is proposed and will contain one (1) each of the powder and diluent.

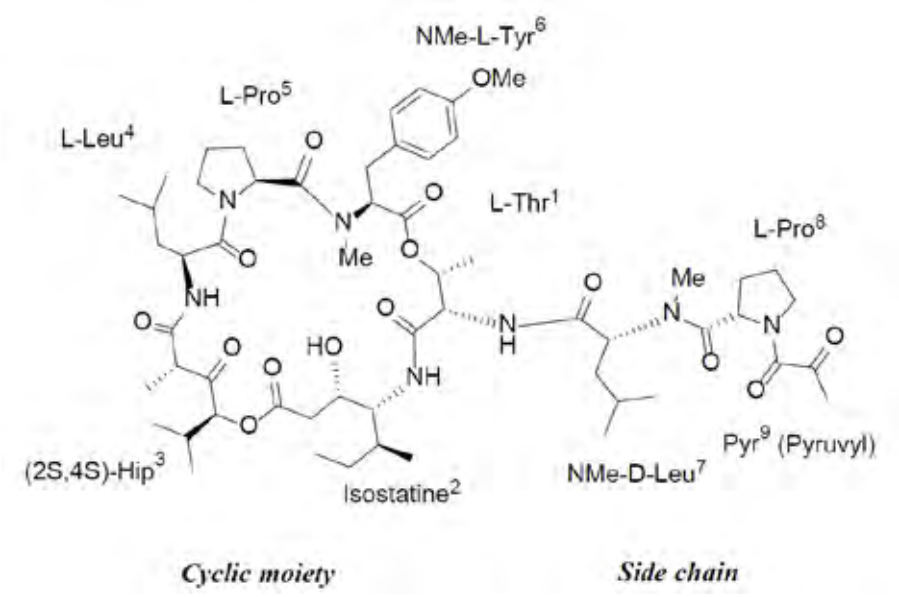
Drug substance

Structure

Plitidepsin is a cyclic depsipeptide,[7] originally isolated from Mediterranean tunicates (*Aplidium albicans*) and has the following structure as shown in Figure 1.

[7] A depsipeptide is a peptide in which one or more amide groups are replaced by an ester group. Plitidepsin has two (2) ester bonds joining the (2*S*,4*S*)-Hip/Isostatine and NMe-L-Tyr/L-Thr groups.

Figure 1: Chemical structure of plitidepsin



Structure of plitidepsin with identification of the peptide units (superscript numbers refer to company numbering).

Plitidepsin is prepared by a synthetic process beginning with appropriately protected amino acids/peptides, ensuring that the appropriate stereochemistry is obtained. It is isolated as white to pale yellow powder.

As the drug substance is in solution at the time of drug product manufacture and administration particle size and polymorphism of the drug substance is not critical however, solubility is a key factor. It is practically insoluble in aqueous media over the physiological pH range and slightly soluble to soluble in various polar organic solvents such as acetic acid, acetone, acetonitrile, dichloromethane, ethyl acetate and 2-propanol.

The Australian Register of Therapeutic Goods (ARTG) already includes several peptides that consist of a cyclic peptide core, such as caspofungin, anidulafungin and pasireotide, however only romidepsin contains an ester linkage in the cyclic peptide core similar to a 'depsipeptide'.

The proposed specification, which controls identity, purity, related substances and other chemical and physical properties of the drug substance have been set based on the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use principles and is acceptable.

Stability data have been generated and demonstrate that plitidepsin is sensitive to photo degradation and hydrolysis (alkali and acidic). The drug substance is stored protected from light and moisture under refrigerated conditions.

Drug product

Formulation

The product is to be supplied as a composite pack consisting of:

- A clear glass vial with bromobutyl stopper containing 2 mg of plitidepsin and mannitol (bulking agent).
- A clear glass ampoule containing 4 mL of the solution for reconstitution (the 'diluent'), which is comprised of PEG-35 castor oil, ethanol and water for injections.

The powder is to be reconstituted with the provided diluent to give a concentrated solution containing 0.5 mg plitidepsin/mL. The concentrate is further diluted with NaCl (0.9 %) or glucose (5 %) solutions prior to administration as described in the draft PI (5 mg/m^2 BSA in 250 or 500 mL depending on venous access).

Each diluent vial contains 0.6 mL (630 mg) of PEG-35 castor oil, also known as polyethylene glycol (35) castor oil and by the tradename Cremophor, which is known to cause hypersensitivity reactions, and 0.6 mL (474 mg) ethanol. Multiple vials/ampoules are required to reach the required dose (5 mg/m^2 BSA) therefore; PEG-35 castor oil and ethanol in each delivered dose will likely be in gram quantities.

Note that these excipients are included in other antineoplastic products in comparable quantities. The safety of these quantities in Aplidin has been considered as part of the non-clinical and clinical studies. The function of PEG-35 is to aid in the solubilisation of plitidepsin in the diluted solution by forming micelles, into which the water-insoluble and lipophilic plitidepsin can partition.

Manufacture

The powder is manufactured by dissolution of plitidepsin and mannitol in an aqueous-organic solvent followed by sterile filtration, filling into vials and lyophilisation to give the solvent-free powder. The diluent components are mixed, filled into ampoules and then sterilised using moist heat. The formulation of the commercial product is the same as that used during the clinical trials.

Two sites are responsible for the manufacture of the powder and essentially the same process is used at both sites. Data have been submitted that demonstrate that the quality is the same.

Specifications

The proposed specifications, which control identity, purity, uniformity of dose units/extractable volume and other physical, chemical and microbiological properties relevant to the product have been set in line with ICH guidelines and are acceptable. Appropriate validation data have been submitted in support of the test procedures.

Compatibility

Compatibility of the diluted solutions with the infusion bags, infusion sets, in-line filters and venous access systems (for example, catheters) stated in the draft PI have been demonstrated over the stated in use storage period.

Stability

Stability data have been generated under stressed, accelerated and real time conditions to characterise the stability profile of the product. The recommended shelf life is 48 months when stored at 5°C, protected from light.

No preservatives are included and the draft PI recommends immediate use.

Stability of the micelles in the diluted solutions has been demonstrated under in-use conditions. However, use of an in line filter is recommended during administration to ensure removal of sub visible particulates that may form during the preparation of the solution prior to infusion.

Biopharmaceutics

Because the product for administration contains micelles the plitidepsin injection is not considered to be a simple solution. No studies have been reviewed by the TGA. Justifications for the absence of the below studies have been provided.

- *Studies into the fate and persistence of micelles*: Based on the finding that plitidepsin has a high affinity to plasma proteins (refer nonclinical assessment) and high lipophilicity it is considered unlikely that plitidepsin would remain inside the micelles once injected IV and, because of the affinity to proteins and lipid structures, that in vivo precipitation is unlikely. For these reasons no further investigation into micelle fate has been performed by the company.
- *Biopharmaceutic data*: These data are largely provided in the nonclinical and clinical sections instead. The provided data characterised the plasma and blood kinetics (including toxicokinetics), distribution, metabolism and excretion of plitidepsin using both in vitro and in vivo test systems (refer to the nonclinical and clinical reports for further information).

Conclusion

The TGA's Advisory Committee on Medicines (ACM) is invited to comment on any aspect of the submission.

From a quality perspective, there are several relatively straightforward issues that remain outstanding however, once these are resolved, approval for registration of plitidepsin 2 mg powder for injection can be recommended from a quality perspective.

IV. Nonclinical findings

Introduction

The quality of the nonclinical dosser was mostly good. The scope of the nonclinical program was consistent with the relevant TGA adopted guideline for the nonclinical evaluation of anticancer pharmaceuticals.[8] All pivotal safety related studies were conducted according to Good Laboratory Practice (GLP).

Pharmacology

Primary pharmacology

Plitidepsin is a cyclic depsipeptide (a peptide in which one or more amide groups are replaced with the corresponding ester). The molecule was originally isolated from a sea squirt (*Aplidium albicans*), but is now obtained by total synthesis. The mechanism of action and nonclinical efficacy of plitidepsin was investigated in published literature and studies submitted by the sponsor.

The drug targets eukaryotic Elongation Factor 1A2 (eEF1A2), one of two isoforms of eukaryotic Elongation Factor 1 alpha (eEF1A). eEF1A is an important component of the translation machinery, and is the second most abundant protein (1 to –3% of total protein content) after actin in a cell. Its guanosine triphosphate (GTP) bound form delivers the aminoacylated transfer ribonucleic acid (tRNA) to the A site of the ribosome for decoding

[8] ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

of mRNA by codon-anticodon interactions.[9] The two isoforms display a pattern of expression that is mutually exclusive in normal mammalian tissues. The A1 isoform (eEF1A1) is expressed widely, while the expression of eEF1A2 appears to be restricted to brain, heart, pancreatic acinar and islet cells, endocrine cells of the gut and skeletal muscle. eEF1A2 has been shown to be overexpressed in several solid tumours, and also in mouse plasmacytomas and in human MM cells.[10]

Plitidepsin interacts and forms different complexes with eEF1A2 in two subcellular regions: first bound to the inner side of the plasma membrane and then free in the cytoplasm of tumour cells.[11] The interaction with eEF1A2 is linked to the induction of early oxidative stress via depletion of glutathione, which induces the sustained activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases (p38/MAPK), cell cycle disruption (G1 or G2 arrest) and finally apoptosis.[12][13]

In vitro, plitidepsin was shown to bind to eEF1A2 with high affinity (K_D, 79 nM) and induce apoptosis in various human cancer cell lines, with certain MM, leukaemia, lymphoma, pancreas, non-small cell lung cancer and breast cancer cell lines shown to be particularly sensitive. Anti-proliferative activity by plitidepsin against MM cell lines was demonstrated at nanomolar or sub nanomolar drug concentrations (for example, 50% inhibitory concentration (IC_{50}) of 0.114 nM against MMXF L363 cells; 3.87 nM against 5T33MM cells[14]; 4.1 to 8.2 nM against four cell lines[13]; 2.6 to 3.3 nM against four cell lines and 16.6 to 50.3 nM against three others).

As well as directly inducing tumour cell apoptosis, anti-tumour effects of plitidepsin are also seen to involve an effect on the tumour microenvironment (for example, induction of apoptosis of nurse-like cells [monocyte-derived cells that support leukaemia cell survival[15]) and inhibition of angiogenesis (for example, via inhibition of vascular endothelial growth factor [VEGF] secretion[16]).

In vivo anti-tumour activity with plitidepsin was demonstrated in mice bearing human MM xenografts. Intraperitoneal (IP) administration for 5 consecutive days significantly inhibited MM1S tumour growth (by approximately 80% at 140 µg/kg/day[13]), and inhibited 5T33 tumour growth as well as angiogenesis (90 µg/kg/day[14]).

[9] Browne G.J. and Proud C.G. (2002) Regulation of peptide-chain elongation in mammalian cells. *Euro. J. Biochem.* 2002; 269: 5360–5368.
[10] Li Z., Chen-Feng Q, et al (2010) Eef1a2 promotes cell growth, inhibits apoptosis and activates JAK/STAT and AKT signaling in mouse plasmacytomas. *PLoS One* 5: 2010; e10755.
[11] Garcia C., Losada A., et al. (2014) Interaction of plitidepsin with eEF1A in living tumor cells. In 26th AACR-NCI-EORTC Symposium on Molecular Targets and Cancer Theraputics Barcelona, Sapin (ed AACR) *Euro. J. Cancer* 2014; 50 (6 suppl): 345.
[12] González-Santiago L., et al (2006) Aplidin induces JNK-dependent apoptosis in human breast cancer cells via alteration of glutathione homeostasis, Rac1 GTPase activation, and MKP-1 phosphatase downregulation. *Cell Death Differ.* 2006; 13: 1968–1981
[13] Mitsiades C.S., et al (2008) Aplidin, a marine organism-derived compound with potent antimyeloma activity *in vitro* and *in vivo. Cancer Res.* 2008; 68: 5216–5225.
[14] Caers J., et al (2008) Antitumour and antiangiogenic effects of Aplidin in the 5TMM syngeneic models of multiple myeloma. *Br. J. Cancer* 2008; 98: 1966–1974
[15] Morande P.E., et al (2012) The cytotoxic activity of Aplidin in chronic lymphocytic leukemia (CLL) is mediated by a direct effect on leukemic cells and an indirect effect on monocyte-derived cells. *Invest. New Drugs* 2012; 30**:** 1830–1840
[16] Broggini M., et al. (2003) Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4. *Leukemia* 2003*;* 17**:** 52–59

Resistance

Resistance to plitidepsin was linked to reduced eEF1A2 expression (shown in experiments with HeLa cells), overexpression of P glycoprotein (shown by Tognon et al. (2005);[17] in a human ovarian cancer cell line), and impaired or absent functional mitochondria (as a source of reactive oxygen species).[18] Consistent with the involvement of JNK and p38 activation in plitidepsin-induced apoptosis, cell lines deficient in these proteins showed reduced sensitivity to the drug.[19,20]

The anti-proliferative activity of plitidepsin in human cell lines showing low sensitivity or resistance to established anti-MM agents was investigated in vitro.[13] Treatment with plitidepsin restored sensitivity to DXM in a DXM resistant MM cell line, and cell lines resistant to melphalan (RPMI-8226/LR5), mitoxantrone (RPMI-8226/MR20) and doxorubicin (RPMI-8226/Dox40) were shown to be responsive to plitidepsin.

Pharmacodynamic interactions

In vitro experiments examining inhibition of MM cell viability revealed an additive effect of plitidepsin in combination with either bortezomib or melphalan, and a synergistic effect in combination with DXM, thalidomide or lenalidomide.[13] In vivo, inhibition of human MM xenograft growth in mice was synergistically enhanced with plitidepsin in combination with DXM or bortezomib; greater than additive inhibition of renal tumour xenograft growth with plitidepsin in combination with sorafenib was also shown.

Secondary pharmacodynamics

Screening assays identified five kinases (ephrin type-B receptor 4, fibroblast growth factor receptor 2, tunica interna endothelial cell kinase 2, tropomyosin-receptor-kinase A and tropomyosin-receptor kinase B), M_3 and M_4 muscarinic subtype receptors, the melanocortin 1 receptor, follicle-stimulating hormone (FSH) receptor and tachykinin receptor 3 as secondary targets for plitidepsin. These were inhibited with IC_{50} values around 450 nM to 17 times higher than the peak plasma concentration (C_{max}) of total plitidepsin in patients at the maximum recommended human dose,[21] and > 1000 times higher than the peak plasma concentration of unbound drug,[22] indicating limited clinical relevance.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and the respiratory systems; toxicity to nerve cells, bone marrow progenitors and hepatocytes was also examined in cell-based experiments.

Plitidepsin significantly reduced nerve growth factor-induced neurite outgrowth in PC12 cells[23] at all concentrations tested (5 to 50 nM; 72 h exposure), with the lowest concentration typical of that for anti-tumour activity. This neurotoxic effect was greater

[17] Tognon G., et al (2005) Induction of resistance to Aplidin in a human ovarian cancer cell line related to MDR expression. *Cancer Biol. Ther.* 2005; 4**:** 1325–1330
[18] Humeniuk R., et al (2007) Aplidin synergizes with cytosine arabinoside: functional relevance of mitochondria in Aplidin-induced cytotoxicity. *Leukemia* 2007; 21**:** 2399–2405
[19] Cuadrado A., et al (2004). JNK activation is critical for Aplidin-induced apoptosis. *Oncogene* 2004; 23**:** 4673–4680
[20] Losada A., et al (2004) Establishment and characterisation of a human carcinoma cell line with acquired resistance to Aplidin. *Br. J. Cancer* 2004; 91: 1405–1413
[21] Clinical C_{max} for total plitidepsin: 26.2 nM [from 29.1 ng/mL in Study APL-B-014-03 with 3 h infusion at 5 mg/m^2]
[22] Clinical C_{max} for unbound plitidepsin: 0.445 nM [1.7% free & 98.3% bound]
[23] PC12 is a cell line derived from a pheochromocytoma of the rat adrenal medulla.

than seen with doxorubicin, vincristine, vinorelbine or paclitaxel at the same concentrations.

No acute effects on CNS or respiratory function were observed in rats with IV administration at ≤0.5 mg/kg (less than the clinical dose on a body surface area basis; 3 mg/m^2 in rats compared to 5 mg/m^2 in patients]), while various clinical signs (including decreased grooming, piloerection, abnormal gait, decreased touch response, passivity, hypothermia and decreased locomotor activity) as well as decreased respiratory rate and tidal volume were observed at 1.5 mg/kg IV (equivalent to 9 mg/m^2; 1.8 times the clinical dose), which exceeded the maximum tolerated dose in the species.

Plitidepsin (1 μM; 38 times the clinical plasma C_{max} for total drug) produced no inhibition of the hERG potassium (K^+) channel in transfected mammalian cells and had no effect on action potential parameters in dog cardiac Purkinje fibres in vitro. Effects on cardiovascular parameters were observed in vivo in dogs. Increased heart rate with corresponding decreases in various components of the action potential (PR interval, QRS duration, RR interval and uncorrected QT interval) was observed at 30 μg/kg IV (0.6 mg/m^2). With dosing at 130 μg/kg IV (2.6 mg/m^2), plitidepsin caused transient marked hypotension (to 0.5 h post-dose) and ST-segment depression (to 2 h post-dose), with tachycardia later seen. QTc prolongation,[24] without arrhythmias, was observed 4 to 6 h post-dose. These effects appear to be secondary and/or compensatory to an initial, transient peripheral vasodilation. ST-segment depression was observed in the general repeat-dose toxicity studies in dogs at ≥ 75 μg/kg/day IV.

No cytotoxicity towards human hepatocytes was seen with plitidepsin in vitro (≤ 100 nM). In experiments with cultured human bone marrow cells, megakaryocytic and multi-lineage progenitors were found to be more sensitive to the anti-proliferative activity of plitidepsin than myeloid and erythroid progenitors (IC_{50} values of 150 nM compared to 360 to 530 nM for 24 h exposure); such an effect was seen, though, at concentrations notably higher than required for anti-tumour activity.

Pharmacokinetics

The plasma kinetics of plitidepsin by the IV route was investigated in mice, rats and dogs. Multi-compartmental kinetics was observed in all species, featuring a rapid initial decline and a slower, more prolonged elimination phase. The terminal half-life in plasma was long in laboratory animal species; 136 h in mice, 24 h in rats and 17 h in dogs (mean across studies) and s well as approximately 50 h in humans, associated with low to moderate systemic clearance. Peak and overall exposure (C_{max} and area under the plasma concentration versus time curve (AUC)) was dose-proportional in rats and dogs, and accumulation with repeat dosing (once every 2 weeks) was not seen.

Plasma protein binding by plitidepsin was high in humans (98.3%) and laboratory animal species (96.6% and 97.5% in rats and dogs, respectively). Binding in human plasma was mostly to albumin, with a lesser contribution by α_1-acid glycoprotein.

The volume of distribution was far larger than total body water (150 L/kg in mice, 180 to 420 L/kg in rats and approximately 98 L/kg in dogs; compared to 617 L in MM patients from the population PK analysis), indicating extensive tissue distribution. This included distribution into the blood cell fraction, with very high blood: plasma ratios evident in rats and dogs (concentration-dependent).

[24] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes.

Tissue distribution in rats after IV administration of radiolabelled plitidepsin was rapid and wide. Tissues with the highest concentrations of radioactivity included the spleen, liver, lung, kidney, thyroid and heart. Tissue C_{max} and AUC values for these were hundreds of times higher than for plasma, but more modest multiples of the blood C_{max} and AUC (1.7 to 5.8 and 2.9 to 11 times, respectively). Significant levels of radiolabelled (^{14}C)-plitidepsin derived radioactivity were still present in all tissues at 72 h post-dose. Penetration into the CNS was limited, and limited distribution to the testes (but not ovary) was also shown.

Metabolism of plitidepsin in human liver microsomes involved dealkylation at the (R)-N-(methyl)-leucine group, hydroxylation at the isopropyl group, a combination of these, and demethylation at the C-atom in the threonine group. Hepatic metabolism was shown to be NADPH-dependent and mostly mediated by cytochrome P450 isozyme CYP3A4, with smaller contributions by CYP2A6, 2E1 and 4A11. Metabolism in plasma was also evident, mediated by carboxyl esterase.

Of the four human metabolites of plitidepsin observed in vitro, only one was also seen in the rat and two in the dog. Metabolism was less extensive in incubations with liver microsomes from these species compared to humans. Limited in vivo data in humans indicated the formation of a wide array of metabolites, with no major individual circulating metabolite. In humans, unchanged drug accounted for 29% of total ^{14}C-plitidepsin-derived radioactivity exposure in plasma. This was comparable in male rats (23% of exposure reflecting unchanged drug), while unchanged plitidepsin accounted for much more of the radioactivity in plasma in female rats (74% of exposure). No in vivo metabolism data were presented for dogs.

Excretion of plitidepsin was predominately via the faeces (approximately 60% and 70% of the administered dose in rats and humans, respectively); urine was a minor route of excretion (4 to 6% and 6% of the administered dose in rats and humans, respectively). Biliary excretion was demonstrated in rats. In humans, urinary excretion was mostly as unchanged drug and faecal excretion was mainly as metabolites. No data on excretion were presented for dogs.

Overall, sufficient similarities in the pharmacokinetic profiles of plitidepsin in the pivotal laboratory animal species (rat and dog) and humans are seen to allow these animal species to serve as adequate models for human toxicity. The metabolic profile has not been well characterised in any species, but this is not considered to be a critical deficiency given that concerns for toxicity with this drug are chiefly attributable to the parent molecule.

Pharmacokinetic drug interactions

Plitidepsin did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 in experiments with human liver microsomes (≤ 100 μM). Inhibition of CYP3A4 was observed, but the K_i (1.25 μM (1388 ng/mL)) is very much higher than the therapeutic concentration and no relevant inhibition of this isozyme in patients is predicted. There was no induction of CYP1A2 or CYP3A4 activity in human hepatocytes incubated with plitidepsin (≤ 1000 ng/mL), nor increases in CYP1A2 or CYP3A4 mRNA (tested up to 100 ng/mL). Modest induction (approximately 3 fold) of CYP2B6 expression was observed with plitidepsin at 100 ng/mL (but not at 10 ng/mL).

Plitidepsin was shown to be a substrate of P-glycoprotein, but not of breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2), organic anion transporter protein (OATP) 1B1, OATP1B3, organic cation transporter (OCT1) or Multidrug and toxin extrusion protein 1(MATE1). The drug also inhibited P-glycoprotein (inhibitory constant (K_i) 114 nM), as well as OATP1B3 (IC_{50}, 0.32 μM), OATP1B1 (IC_{50}, 1.03 μM), Bile Salt Export Pump (BSEP) (IC_{50} 4.2 μM), MRP2 (by 38% at 5 μM) and BCRP (by 22% at 5 μM); there was no inhibition of OCT1, MATE1, OAT1, OAT3 or OCT2 (≤5 μM). With the K_i or IC_{50} values being >250 times higher than the plasma C_{max} for

unbound drug in patients, no in vivo interactions due to transporter inhibition by plitidepsin are expected in patients.

Toxicity

Acute toxicity

Single-dose toxicity studies with plitidepsin were conducted in mice, rats and dogs; all involved IV bolus administration. Maximum non-lethal doses were 0.625 mg/kg in mice, 0.57 mg/kg in rats and 0.13 mg/kg in dogs, equivalent to 1.875, 3.42 and 2.6 mg/m^2 BSA in the respective species[25], less than the clinical dose (5 mg/m^2). An array of clinical signs (including piloerection in rodents, vomiting and tremors in dogs and decreased activity in all species) and body weight loss were observed. A very high order of acute toxicity for plitidepsin is evident.

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats and dogs; all involved IV bolus administration. The pivotal studies, in rats and dogs, involved dosing once every 2 weeks (matching the clinical dosing frequency) for 12 cycles. Shorter studies involved dosing once every 2 weeks for 6 cycles (dogs), or once daily for 5 consecutive days for one (mouse, rat and dog) or three (rat and dog) cycles with a 2 week non-dosing period between cycles. The 5 day studies in rodents did not include comprehensive histopathological examination.

Relative exposure

Exposure ratios in the three studies involving fortnightly dosing have been calculated below based on animal: human plasma $AUC_{0-\infty}$ (Table 1). Exposure in animals was well below that of patients at the maximum recommended clinical dose of 5 mg/m^2 at all dose levels tested (specifically, 6 to 42 times lower).

Table 1: Relative exposure in selected repeat-dose toxicity studies

Species	Study details	Dose (µg/kg); Q2W IV	$AUC_{0-\infty}$^ (ng·h/mL)	Exposure ratio#
Rat (SD)	12 cycles [Study RTC70760]	100	6.15	0.024
		200	18.26	0.071
		400	34.12	0.13
Dog (Beagle)	6 cycles [Study 8293-094]	100	25.09	0.098
		130	32.12	0.13
		160	41.09	0.16
	12 cycles	50	11.27	0.044

[25] Calculated using mg/kg to mg/m^2 conversion factors of 3 for mice, 6 for rats and 20 for dogs.

Species	Study details	Dose (µg/kg); Q2W IV	$AUC_{0-\infty}$^ (ng·h/mL)	Exposure ratio#
	[Study 8293-095]	75	17.23	0.067
		100	27.18	0.11
Human (MM patients)	Study APL-B-014-03 [3 h infusion]	[5 mg/m^2]	256	–

= animal: human plasma $AUC_{0-\infty}$; ^ = data are for the sexes combined and the mean of all sampling occasions

No toxicokinetic data were obtained in the studies involving dosing for 5 consecutive days (1 or 3 cycles) but exposure well below that of patients is predicted to have been achieved based on data from other studies.

Major toxicities

The major target organs for toxicity were the pancreas, bone marrow, thymus, spleen, skeletal muscle, heart, gastrointestinal (GI) tract, liver and male reproductive tract, with effects on the kidney and nervous tissue also seen.

The pancreas was the primary target organ for toxicity in the dog, and a key one in rats. Most treated dogs in the pivotal 12 cycle study showed microscopic pancreatic changes, comprising acinar atrophy (mild to marked), acinar cell atrophy/necrosis and islet cell atrophy (up to moderate) at all dose levels (≥ 50 µg/kg every 2 weeks (Q2W)), and chronic inflammation at ≥ 75 µg/kg Q2W; reversibility was not seen after a 4-week treatment-free period. There were similar pancreatic findings in dogs in all other repeat-dose studies, and also after a single dose (≥ 100 µg/kg). In the 6 cycle study, treatment at 100 to 160 µg/kg Q2W produced pancreatic findings of the highest severity grade, with exocrine pancreas insufficiency linked to mortality in the study. Exocrine pancreas insufficiency in dogs was also evident from clinical signs (vomiting, body weight loss, decreased food consumption, soft faeces) and changes in clinical chemistry (including increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and creatine kinase, and decreased plasma trypsinogen). Minimal to mild single cell apoptosis/necrosis and acinar cell degranulation of the exocrine pancreas was observed at all doses (≥ 100 µg/kg Q2W) in rats in the 12-cycle study, associated with body weight loss and emaciation. Of note, the primary pharmacological target of plitidepsin, eEF1A2, is known to be expressed in pancreatic acinar cells and Islets of Langerhans.[26]

Anaemia (with reticulocytosis), leukopenia and thrombocytosis were observed in rats at ≥ 200 µg/kg in the pivotal 12 cycle study; recovery after a 4 week treatment-free period was seen, except for leukopaenia. In dogs, there was thrombocytopenia (100 µg/kg), slight anaemia (≥ 50 µg/kg) and slight leucocytosis (≥ 75 µg/kg; probably related to inflammatory injection site lesions) in the 12 cycle study, with similar findings in the 6 cycle study. The effects on red blood cell parameters persisted 4 weeks after the cessation of treatment. Plitidepsin produced bone marrow depletion in rats with treatment at 140 µg/kg/day for 5 days, ≥ 70 µg/kg/day for 5 days for 3 cycles, and in dogs at 40 µg/kg/day for 5 days and 30 µg/kg/day for 5 days for 3 cycles. Increased

[26] Uhlén (2015) Tissue expression of EEF1A2 — staining in pancreas — the human protein atlas. http://www.proteinatlas.org/ENSG00000101210-EEF1A2/tissue/pancreas

extramedullary haematopoiesis in the spleen (as a compensatory response for insufficient bone marrow haematopoiesis) was seen in rats at ≥ 200 µg/kg Q2W in the pivotal 12 cycle study.

Severe thymic atrophy was observed in dogs at all dose levels tested in the 6 and 12 cycle studies (50 to 160 µg/kg Q2W). Slight to moderate thymic lymphoid depletion was seen in rats at ≥ 200 µg/kg Q2W in the 12 cycle study; thymic lymphoid depletion was also seen in rats that received three cycles of treatment at 140 µg/kg/day for 5 days. Treatment with plitidepsin for 5 consecutive days produced necrosis and atrophy of the thymus in mice (500 µg/kg/day), rats (140 µg/kg/day) and dogs (≥ 20 µg/kg/day).

Treatment with plitidepsin produced mild to moderate lymphoid depletion in the spleen of dogs at all dose levels in the 12 cycle study (≥ 50 µg/kg Q2W). In the spleen of rats, there was lymphocyte necrosis (of the white and red pulp) in rats at 140 µg/kg/day for 5 days (1 cycle), and lymphoid depletion at ≥ 70 µg/kg/day for 5 days for 3 cycles.

Skeletal muscle myofibre degeneration was observed in rats (140 µg/kg/day for 5 days for 3 cycles) and dogs (≥ 100 µg/kg Q2W for 6 cycles), with additional findings of chronic inflammation and fatty infiltration in the respective species at these doses. Plitidepsin also produced cardiac muscle lesions, with cardiomyopathy seen in rats with treatment at ≥ 70 µg/kg/day for 5 days for 3 cycles and at 100 and 400 µg/kg Q2W in the 12 cycle study. In dogs, there was mild to moderate myocardial degeneration at ≥ 100 µg/kg Q2W and moderate fatty infiltration in heart at 160 µg/kg Q2W in the 6 cycle study.

The stomach mucosa was a target for toxicity in the rat, with crypt cell necrosis, focal glandular mucosal necrosis, inflammatory cell infiltrate, ulceration and oedema of the submucosa seen with treatment at 140 µg/kg/day for 5 days (1 and/or 3 cycles). GI toxicity in dogs was evident as vomiting in the 6 and 12 cycle studies (all dose levels), and additionally diarrhoea in the shorter studies. No treatment related histopathological lesions were observed in the GI tract of dogs in the 6 and 12 cycle studies, while mineralisation of the stomach mucosa, and crypt abscesses and mucosal haemorrhage of the small and larger intestines were observed in dogs in the 5 day study (mostly at 20 and 40 µg/kg/day).

In the rat liver, vacuolation of parenchymal cells occurred at 140 µg/kg/day for 5 days, hepatocyte degeneration and periportal oedema were observed at 140 µg/kg/day for 5 days for 3 cycles (not examined at lower doses in the study) and periportal fibrosis, bile duct proliferation and single cell necrosis (all graded slight in severity) were seen at 400 µg/kg Q2W in the 12 cycle study. Treatment related liver histopathological changes in dogs comprised centrilobular vacuolation (at 40 µg/kg/day for 5 days and ≥ 100 µg/kg Q2W for 6 cycles); periportal vacuolation, cholestasis and apoptotic necrosis (30 µg/kg/day for 5 days for 3 cycles); bile duct proliferation (at all doses in the 6 and 12 cycle studies; ≥ 100 or ≥ 50 µg/kg Q2W); vacuolation of biliary epithelial cells (≥ 100 µg/kg Q2W for 6 cycles) and clear cell change (160 µg/kg Q2W for 6 cycles; ≥ 50 µg/kg Q2W for 12 cycles).

The male reproductive tract was affected by plitidepsin treatment. Various degenerative changes in the testes (pyknotic spermatogonia and spermatocytes; loss of spermatocyte precursors; presence of multinucleated cells within the seminiferous tubules; vacuoles within seminiferous tubule cells; poorly developed, immature, or clumped spermatozoa within the seminiferous tubule lumens; tubular germinal cell degeneration) were observed in rats (140 µg/kg/day for 5 days for 1 or 3 cycles) and dogs (≥ 10 µg/kg/day for 5 days for 3 cycles and at ≥ 75 µg/kg every 2 weeks (Q2W) for 12 cycles). There were additional findings in the epididymides (immature spermatocytes and oligospermia in rats at ≥ 35 µg/kg/day; degenerate sperm in dogs at ≥ 10 µg/kg/day) and seminal vesicles (depletion of secretory material in rats at 140 µg/kg/day) in the 5 day 3 cycle studies.

Vacuolation of distal tubular cells was observed in the kidney of dogs treated with plitidepsin at all doses in the 6 and 12 cycle studies (≥ 100 or ≥ 50 µg/kg Q2W). Axonal swelling in the grey matter of the dentate nucleus in the brain and in the thoracolumbar spinal cord was found in dogs following dosing at 40 µg/kg/day for 5 days, axonal atrophy of the sciatic nerve at 30 µg/kg/day for 5 days for 3 cycles, and vacuolation of astrocytes in the grey matter of the brain and of the retina at 100 and 160 µg/kg Q2W for 6 cycles. There were no treatment related findings in these tissues in rats.

Genotoxicity

The genotoxic potential of plitidepsin was investigated in vitro. Studies were appropriately conducted and validated. Plitidepsin was negative in assays for mutagenicity in bacteria (Ames test). Genotoxicity was evident in the mouse lymphoma Tk assay in the absence and presence of metabolic activation, although only at concentrations producing marked cytotoxicity (≥ 80% reduction in relative total growth). The size distribution of mutant colonies (that is, an increase in the proportion of large colonies) indicated the genetic damage induced by plitidepsin involved mutagenicity (compared to clastogenicity).

Carcinogenicity

No carcinogenicity studies were submitted. This is acceptable under the relevant EU guidelines;[8,27] for an agent for the treatment advanced cancer.

Reproductive toxicity

Reproductive toxicity studies with plitidepsin covered fertility, early embryonic development and embryofetal development. The absence of a study on pre-/post-natal development is in accordance with ICH S9.[8] All studies were performed in rats and involved IV administration. Dosing was once daily in studies on fertility and early embryonic development, while the embryofetal development study involved dosing on one occasion only during gestation.

Relative exposure

Systemic exposure in animals in the reproductive toxicity studies was well below that of patients (see Table 2 below).

No data on placental transfer or excretion in milk were provided.

Table 2: Relative exposure in reproductive toxicity studies with plitidepsin

Species	Study details		Dose (µg/kg/day) IV	AUC^ (ng·h/mL)		Exposure ratio#	
				M	F	M	F
Rat (SD)	Fertility and early embryonic development	[Study 2716-001P; pilot]	25	35.5	4.0	0.14	0.02
			50	78.6	16.8	0.31	0.07
		[Study 2716-001; main]	5	7.1	0.8	0.028	0.003
			15	21.3	2.4	0.08	0.009
			30	42.6	4.8	0.17	0.019

[27] ICH S1A Need for carcinogenicity studies of pharmaceuticals

Species	Study details	Dose (µg/kg/day) IV	AUC^ (ng·h/mL)		Exposure ratio#	
			M	F	M	F
	Embryofetal development [Study RTCX0090]	600	43.5		0.17	
Human (MM patients)	Study APL-B-014-03	[5 mg/m^2]	256		–	

= animal plasma $AUC_{0-24\,h}$: human plasma $AUC_{0-\infty}$;^ = animal AUC values are extrapolated from data obtained in Study 2716-001P

Impairment of male and female fertility was observed in rats at 50 µg/kg/day. This occurred in conjunction with significant toxicity (as body weight loss and mortality in males, and marked inhibition of body weight gain in females). Inhibition of ovulation (reduced corpora lutea), with corresponding decreases in the number of implantations and live litter size, was seen at ≥ 30 µg/kg/day (a non-maternotoxic dose). As noted above, histopathological changes suggesting impairment of male fertility were observed in the general repeat-dose toxicity studies in rats and dogs.

The embryofetal development study involved testing of a single dose level (600 µg/kg IV) administered on a single occasion early in the period of organogenesis in the rat (gestation Day 10). Total embryofetal lethality (100% post-implantation loss) occurred in all animals. This dose was maternotoxic (producing body weight loss and clinical signs), but the maternotoxicity does not itself explain the finding. With no viable fetuses remaining, teratogenicity was not examined.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[28] This is not supported. While pharmacologically mediated, the finding of complete embryofetal lethality in rats at a subclinical exposure multiple warrants placement in Pregnancy Category D instead.[29] This reflects the strong expectation of irreversible damage to the human fetus with use of Aplidin during pregnancy, and is consistent with the inclusion of recommendations for the use of contraception in women of childbearing potential contained in the proposed PI document.

Local tolerance

The local tolerance of the clinical formulation following single intravenous and perivascular injection was examined in a specialised study rabbits. Mild thrombophlebitis, mild subcutaneous oedema and mild perivascular/subcutaneous haemorrhage were observed following IV administration. Mild to moderate acute inflammatory changes in the subcutaneous tissues, and mild to moderate oedema and haemorrhage were observed following perivascular administration. In the general repeat-dose toxicity studies, irritation at the IV injection site was commonly seen in rats and dogs. Microscopic

[28] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

[29] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

examination of injection sites revealed inflammation, oedema, necrosis, haemorrhage, ulceration, scab and fibrosis.

Immunotoxicity

No specific immunotoxicity studies were submitted.

Phototoxicity

Plitidepsin absorbs ultraviolet (UV) light (peak absorbance at 210 nm). The drug was shown to not be phototoxic in an adequately conducted in vitro assay using Balb/c 3T3 cells.

Paediatric use

Plitidepsin is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Impurities

Specified impurities in the drug substance and drug product do not exceed the qualification threshold applicable to organic impurities in peptides obtained by chemical synthesis described in European Pharmacopeia (Ph. Eur.) monograph 2034.

Nonclinical summary and conclusions

- The nonclinical submission was of satisfactory quality and adequate scope, consistent with the relevant TGA adopted guideline for the nonclinical evaluation of anticancer pharmaceuticals.[8] All pivotal safety related studies were GLP compliant.
- The pharmacological target of plitidepsin is eEF1A2, a protein overexpressed in various tumour cells, including some MM cells. In vitro, plitidepsin was shown to bind to eEF1A2 with high affinity (K_D, 79 nM), with the interaction inducing oxidative stress leading to apoptosis. Plitidepsin showed anti-proliferative activity against various MM cell lines in vitro at nanomolar or subnanomolar concentrations (IC_{50} values, 0.114 to 50.3 nM). In vivo anti-tumour activity was demonstrated in mice bearing human MM xenografts.
- The primary pharmacology studies lend support for the proposed indication.
- Enhanced anti-neoplastic activity was observed with plitidepsin in combination with other agents (bortezomib, melphalan, DXM, thalidomide, lenalidomide and sorafenib; in vitro in cancer cell lines and/or in vivo in mice).
- Screening assays identified a number of kinases and receptors as secondary pharmacological targets of plitidepsin, but no relevant inhibition/antagonism of these is predicted in patients based on comparison of the IC_{50} values and the clinical plasma C_{max}.
- Safety pharmacology studies showed limited effects on the CNS and respiratory system at and beyond the maximum tolerated dose in rats. Plitidepsin did not inhibit the hERG K^+ channel in vitro. Effects on the cardiovascular system, including tachycardia, transient hypotension, ST-segment depression and QTc prolongation, were observed in dogs after a single IV dose less than that of patients (based on body surface area). These effects appear to be secondary and/or compensatory to an initial, transient peripheral vasodilation.
- Neurotoxicity was observed with plitidepsin in vitro in experiments with PC12 cells at a concentration typical of that for anti-tumour activity (5 nM; no lower concentration tested). This was of greater magnitude than with doxorubicin, vincristine, vinorelbine or paclitaxel at the same concentration.

- Pharmacokinetic studies with plitidepsin revealed a long plasma half-life in laboratory animal species, as in humans. Plasma protein binding was high (98.3% in humans; similar in rats and dogs). Extensive tissue distribution was evident, including into blood cells. Limited penetration into the CNS was shown in rats. Hepatic metabolism of plitidepsin was shown to be mediated mostly by CYP3A4, with smaller contributions by CYP2A6, 2E1 and 4A11. There is also degradation in plasma, mediated by carboxyl esterase. Excretion of plitidepsin was predominately via the faeces in rats and humans. Biliary excretion was demonstrated in rats.
- Plitidepsin was shown to be a substrate of P-glycoprotein. Plitidepsin is a weak inhibitor of CYP3A4 and various transporters (P-glycoprotein, OATP1B3, OATP1B1, BSEP, MRP2 and BCRP); no relevant in vivo inhibition to give rise to pharmacokinetic drug interactions is predicted in patients based on comparison of IC_{50} values and the clinical plasma C_{max}.
- Plitidepsin showed a high order of acute toxicity in mice, rats and dogs after IV administration.
- Pivotal repeat-dose toxicity studies were conducted in rats and dogs, and involved IV administration once every 2 weeks for 12 cycles. Shorter studies, also by the IV route, involved dosing for 5 consecutive days for one (mice, rats and dogs) or three (rats and dogs) cycles, with a 2 week non-dosing period between cycles; or dosing once every 2 weeks for 6 cycles (dogs). The major target organs for toxicity were the pancreas, bone marrow, thymus, spleen, skeletal muscle, heart, GI tract, liver and male reproductive tract, with effects on the kidney and nervous tissue (brain, spinal cord, sciatic nerve and retina) also seen. Treatment with plitidepsin produced anaemia (rats and dogs), leukopenia and thrombocytosis (rats), and thrombocytopenia (dogs). Electrocardiogram (ECG) examination in dogs commonly revealed ST-segment depression.
- With systemic exposure levels (plasma AUC) achieved in animals below that of patients at all doses tested in the repeat dose studies, all findings are considered potentially clinically relevant.
- The pharmacological target, eEF1A2, has a limited expression pattern in normal tissues, appearing to be restricted to brain, heart, pancreatic acinar and islet cells, endocrine cells of the gut and skeletal muscle. Of these known eEF1A2 expressing tissues, the pancreas was the most prominent target for toxicity in animals.
- In vitro genotoxicity assays showed that plitidepsin causes DNA damage but only in conjunction with marked cytotoxicity. No carcinogenicity studies have been conducted; this is acceptable for a medicine indicated for advanced cancer.
- Adverse effects on reproduction and embryofetal development were observed in animals and occurred at subclinical exposure levels. Treatment with plitidepsin impaired male and female fertility in a specialised study in rats; sperm degeneration was observed in the general repeat-dose toxicity studies in rats and dogs. Complete embryofetal lethality occurred in rats with administration of plitidepsin on a single occasion during gestation.
- The strong expectation of embryofetal lethality with use of Aplidin by a pregnant woman warrants assignment of plitidepsin to Pregnancy Category D (rather than Category C as the sponsor proposes).
- Mild to moderate injection site reactions were observed in a local tolerance study in rabbits. Irritation at injection sites was also commonly observed in the general repeat-dose toxicity studies in rats and dogs.

There are no nonclinical objections to the registration of Aplidin provided a favourable risk/benefit balance is shown from clinical data, and that the draft PI document is amended as proposed. Details of the latter are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Information on the condition being treated

Multiple myeloma is a malignant plasma-cell disorder characterised by the production of a monoclonal protein from plasma cells in the bone marrow (BM). Typical manifestations of the disease include monoclonal proteins in blood and urine, organ dysfunction, lytic bone lesions and immunodeficiency. MM is the second most common haematological malignancy accounting for approximately 1% of neoplastic diseases and 13% of haematological cancers. The median age at diagnosis is around 70 years and many patients are older than 75 years. The overall median survival is 5 to 6 years from the diagnosis of MM, although the outcome varies largely depending on biological characteristics, such as cytogenetics and age.

Current treatment options

The standard treatment approach in younger patients or eligible older patients involve an induction regimen, which typically consists of a combination of a proteasome inhibitor and/or an immunomodulator and DXM, to reduce the tumour load before consolidation with high-dose chemotherapy and stem cell transplantation (SCT) support. In patients who are ineligible for transplantation consolidation due to age and/or comorbidities, similar induction regimens that may include alkylating agents are used, followed by consolidation with more cycles of the same or different regimens. Although recent developments in the treatment of MM have led to improvements in response rates and to increased survival, relapse is considered inevitable in almost all patients. It is found that relapse and progressive refractoriness to treatments is common in MM. In this relapsed and refractory setting, MM typically becomes more aggressive with successive relapses. Once the patient has had several relapses, survival is usually no longer than nine months.

There is no standard treatment for patients with relapsed and refractory disease. Treatment of relapsed and refractory MM depends on several factors, including previous treatments, duration of remissions with previous treatments, and patient factors such as the integrity of organs typically affected by MM such as renal disease, BM reserve and bone disease. At present, treatment options available include IMiDS; for example, thalidomide, lenalidomide, pomalidomide) and proteasome inhibitor agents (such as bortezomib, carfilzomib). Newer agents include monoclonal antibodies that target antigens expressed by malignant plasma cell such as SLAM-7 and Cd38 (daratumumab and elotuzumab), and panobinostat, a histone deacetylase inhibitor. These agents, given as a single agent or in combination with DXM or in triple combinations of an immunomodulatory plus a proteasome inhibitor plus DXM, have been shown to improve PFS and survival rates. Each of these agents is associated with a characteristic safety/toxicity profile that can impact the treatment selection and their use in combination.

Clinical rationale

The treatment of patients with relapsed and refractory MM when agents used in prior lines of therapy have failed is challenging. Treatment with drugs that have the same mechanism of action as those previously used can progressively induce resistance to members of the same family of drugs. Therefore there is a need for new drugs with different mechanisms of action.

With each subsequent treatment failure, PFS and survival get shorter in patients with relapsed and refractory MM (median survival of no more than nine months). Therefore, the sponsor is of the opinion that there is a need for new agents with innovative mechanism of action and a favourable toxicity profile (including lack of or mild myelosuppression) in the late stages of the disease, where patients have very limited bone marrow reserve. The sponsor considers that plitidepsin, with its different mechanism of action, may provide a positive benefit profile when combined with DXM or with other agents in combination regimens while avoiding overlapping toxicity.

Formulation development

Early clinical trials and preclinical development were carried out with the drug substance obtained from semi-synthesis, but this was soon replaced by plitidepsin manufactured by total synthesis. The sponsor has confirmed that the composition of the drug product Aplidin is the same throughout all the preclinical and clinical studies, and that the formulation used in the pivotal Phase III trial in this submission is the same as the proposed commercial formulation.

Guidance

- European Medicines Agency Guideline on the evaluation of anticancer medicinal products in man; December 2012.
- European Medicines Agency Points to consider on application with 1. Meta-analyses; 2. One pivotal study; 31 May 2001.

Evaluator's commentary on the background information

Evaluation of the background information did not raise any major concerns. The clinical rationale is sound. Currently approved drugs for relapsed and refractory MM in Australia include immunomodulatory agents (such as thalidomide, lenalidomide, pomalidomide) and proteasome inhibitor agents (such as bortezomib). Elotuzumab was approved by TGA in September 2016 for '*in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy*'[30]. Panobinostat was approved by TGA in March 2016 for '*in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma, who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.*'[31]

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information relevant to proposed indication:

[30] Product Information for elotuzumab, Sep 2016
[31] Product Information for Panobinostat, Mar 2016

- 1 pivotal efficacy/safety study (Study APL-C-001-09; also known as ADMYRE; a multicentre, open label Phase III study of Aplidin with DXM or DXM alone), with an addendum report on the final analysis of OS outcomes
- 1 other efficacy/safety study (Study APL-B-014-03; a multicentre, open label, exploratory, Phase IIa study; Aplidin alone or with DXM)
- 2 Phase I studies (Study APL-A-009-08; an open label, multicentre, dose-escalating, Phase I study; Aplidin with bortezomib and DXM; Study APL-A-012-13 open label, dose-ranging, Phase I study; Aplidin with bortezomib and DXM)
- 28 other Phase I and II studies in adult patients with other types of malignancies.

In this evaluation report, Study APL-C-001-09 (ADMYRE) will be evaluated as the pivotal efficacy/ safety study and Study APL-B-014-03 will be evaluated as supportive study. The two Phase I studies, which investigated plitidepsin in the same disease setting (relapsed and refractory MM) but combined with bortezomib and DXM, will be evaluated as providing supportive data. In addition, the sponsor has provided pooled integrated safety data (525 patients) comprising of data from the pivotal Phase III study (Study APL-C-001-09, ADMYRE) as well as 14 Phase II studies and 6 Phase I studies with plitidepsin in different indications.

Paediatric data

This submission does not include paediatric data. The sponsor is not using data in this submission to support the use of plitidepsin in a paediatric population. The sponsor has also stated that plitidepsin has waiver from having to present a Paediatric Investigation Plan in Europe.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with the EU guideline CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

Evaluator's commentary on the clinical dossier

Evaluation of the scope of the clinical dossier did not raise any concerns.

Pharmacokinetics

Studies providing pharmacokinetic data

The reference study for the pharmacokinetic (PK) of plitidepsin in the relapsed and refractory MM patient population is the Phase II Study APL-B-014-03 (n = 45), supported by PK findings of plitidepsin in combination with DXM in the Phase III Study APL-C-001-09 (n = 139), and those of plitidepsin in combination with bortezomib and DXM in the Phase I Study APL-A-012-13 (n = 17). The Phase I Study APL-A-009-08 (plitidepsin in combination with bortezomib and DXM) was submitted in this application dossier but its low sample size (n = 3) had precluded PK analysis.

Evaluator's conclusions on pharmacokinetics

PK analyses of plitidepsin in the target population of patients with relapsed and refractory MM showed that half-lives were 44.38 h in whole blood and 50.35 h in plasma. C_{max} was about 1.93 times higher in whole blood than in plasma and AUC was about 3.4 times

higher in whole blood than in plasma. There was limited accumulation after repeated cycles of plitidepsin.

Submitted PK studies in patients with other malignancies were also briefly read through for the purpose of this evaluation and did not trigger concerns. The PK aspects of the proposed PI have been evaluated and found to be acceptable.

Pharmacodynamics

Not applicable.

Dosage selection for the pivotal studies

Phase I and II studies

The plitidepsin dose regimen chosen to be used in the pivotal Phase III study (5 mg/m^2 as a 3 h IV infusion on Days 1 and 15 every four weeks [Q4W]) was based on data from previous Phase I and II studies. This dose regimen had been evaluated in the Phase I Study APL-A-001b-98 in patients with solid tumours or NHL, and was then evaluated in different Phase II studies in solid tumours or haematological malignancies. Results of these Phase II studies showed that this dose regimen of plitidepsin lacked clinically relevant bone marrow toxicity, thus making it a suitable candidate to treat heavily pre-treated MM patients who would usually have a poor bone marrow reserve. Other non-haematological toxicities were found to be generally mild/moderate with this dose regimen and included myalgia, muscular weakness, transient and reversible transaminase increases, fatigue, and nausea/vomiting, with similar incidence among studies. Therefore, this dose schedule was selected for the exploratory Phase II Study APL-B-014-03 in patients with MM and later for the Phase III Study APL-C-001-09 (ADMYRE). In the exploratory Phase II Study APL-B-014-03, evidence of anti-myeloma activity was found with plitidepsin when given at a dose of 5 mg/m^2 as a 3 h IV infusion every two weeks (Q2W), alone or combined with oral DXM, to pre-treated patients with relapsed/ refractory MM.

In this Phase II study, DXM was added to plitidepsin treatment in study patients not reaching an optimal response after three to four plitidepsin infusions. This was based on preclinical evidence and on the consideration that this has been a common practice in the clinical development of new drugs for MM. Results showed that the addition of DXM to plitidepsin in this subset of patients enhanced the clinical benefit of single agent plitidepsin, and produced a slight increase in muscular toxicity, but a mild decrease in transient and reversible hepatic toxicity. These findings suggested that, similar with other therapies indicated for MM, the addition of DXM to plitidepsin could be a viable approach in order to optimise this synergistic effect, and thus achieve a higher and potentially longer and durable disease control. The results of this exploratory Phase IIa clinical study was considered to be supportive of the conduct of further studies to evaluate the potential role of this dose regimen of plitidepsin in combination with low-dose DXM in the treatment of relapsed and refractory MM. This formed the basis for the use of plitidepsin (5 mg/m^2 as a 3 h IV infusion on Days 1 and 15 Q4W) with DXM in the pivotal Phase III trial.

The sponsor also provided justification for the use of DXM alone as a comparator in the Phase III Study APL-C-001-09 (ADMYRE trial). DXM is an active compound that has been widely used as a single agent as well as part of combination regimens for treatment of MM patients. At the time of designing Study APL-C-001-09, no standard treatment existed for the intended population (that is patients with relapsed and refractory MM) that could be

considered a gold-standard comparator, and treatment options were limited. These options included participation in clinical trials of newer agents; dose-reduced oral alkylating agents (cyclophosphamide or chlorambucil); steroids (DXM or prednisone alone at high, intermediate or low doses); or symptomatic control for pain with narcotics; bisphosphonates to reduce the risk of bone fractures and management of hypercalcaemia; and blood-derived product transfusions in frail patients with poor performance status.

Although no formal comparisons had been done, both alkylating agents and steroids could induce clinical responses in this disease setting. However, the toxicity profile of steroids, particularly the lack of nephrotoxicity and myelosuppression, was considered to be advantageous over alkylating agents in this particular disease setting. In addition, the sponsor was of the opinion that a placebo controlled trial would be difficult to be conducted in this population, as some patients may still benefit in terms of response or symptoms palliation from steroid based treatment provided that side effects are manageable.

The suitability of low-dose DXM as the comparator arm in the Phase III trial APL-C-001-09 was discussed during the protocol assistance with the EMA Scientific Advice Working Party (SAWP). The answer of the Committee for Medicinal Products for Human Use (CHMP) was that, as DXM had been an important part of MM treatment in the recent years, the proposed control arm was considered acceptable. Therefore, low dose DXM alone (40 mg orally on Day 1, 8, 15 and 22 Q4W) was used in Study APL-C-001-09 (ADMYRE trial) as a comparator arm.

Evaluator's conclusions on dose finding for the pivotal studies

The rationale for the dose selection and dosing regimen for the pivotal Phase III trial is sound. The choice of comparator of DXM is acceptable and is consistent with the treatment of advanced MM in clinical practice, and is hence not expected to adversely affect external validity of the pivotal study outcomes.

Efficacy

Studies providing efficacy data

Pivotal efficacy study for the intended indication is the Phase III Study APL-C-001-09 (ADMYRE trial), with the Phase II Study APL-B-014-03 submitted as supportive efficacy study. In addition, two Phase I studies, Studies APL-A-009-08 and APL-A-012-13, which investigated plitidepsin in the same disease setting (relapsed and refractory MM) but combined with bortezomib and DXM, were submitted as providing supportive efficacy data.

Evaluator's conclusions on efficacy

Overall, the study design, inclusion and exclusion criteria, and study endpoints of the pivotal Phase III study (Study D1050301) were appropriate and in line with the recommendations of the TGA adopted EMA guideline on the evaluation of anticancer medicinal products in man. The primary and secondary efficacy endpoints allowed assessment of the effect of plitidepsin on progression-free survival, best ORR, DR and OS. Baseline demographic and disease characteristics were comparable between treatment groups, and were consistent with the target patient population. The use of DXM as a comparator is appropriate.

Efficacy results were generally supportive of a positive treatment effect of plitidepsin plus DXM over DXM alone in patients with relapsed and refractory MM. Analysis of the primary

efficacy endpoint showed that there was a statistically significantly longer median PFS with plitidepsin plus DXM compared to DXM alone (2.6 months versus 1.7 months; log-rank p = 0.0054). There was a statistically significant reduction in the relative risk of progression or death by 35.0% in patients treated with plitidepsin plus DXM compared to patients treated with DXM alone (Hazard ratio (HR) = 0.650; p = 0.0062). Subgroup analyses of PFS showed results consistent with those in the overall population.

Analyses of the secondary efficacy endpoints showed that overall response rate (including minor response) was statistically significantly higher with plitidepsin plus DXM compared to DXM alone (22.8% versus 3.6%; p<0.0001). Excluding minor responses from the analyses of overall response rate also yielded a response rate that was statistically significantly higher with plitidepsin plus DXM compared to DXM alone (9.9% versus 1.2%, p = 0.0085).

However, there was no statistically significant difference in the median duration of response (as determined by the Independent Review Committee (IRC)) between plitidepsin and DXM versus DXM alone (3.7 months versus 1.8 months; p = 0.1015). Excluding minor responses in the analyses of duration of response showed a statistically significantly longer median duration of response (as determined by the IRC) with plitidepsin plus DXM versus DXM alone (12.0 months versus 1.8 months; p = 0.0092), but the sample size was very small (n = 1 in the DXM only group), thus rendering the analyses difficult to interpret.

The results of both the interim (immature data) and final (mature data) OS analyses showed that there was no statistically significant difference in median OS between Arm A (plitidepsin plus DXM) and Arm B (DXM only) (interim median OS: 11.3 months in Arm A versus 8.1 months in Arm B, log-rank p = 0.5649; final median OS: 11.6 months in Arm A versus 8.9 months in Arm B, log-rank p = 0.1261). However, post hoc sensitivity analyses done to mitigate the effect of crossover (44% of patients in Arm B crossed over to Arm A) in the final OS analyses results showed statistically significant reduction in the relative risk of death for patients treated in Arm A compared to Arm B (32.4% to 38.4% reduction; log-rank p = 0.0065 to 0.0103).

Efficacy results in Study APL-B-014-03 were generally consistent with results in the pivotal Phase III study. Median PFS was 3.8 months with plitidepsin plus DXM. In patients treated with plitidepsin plus DXM, overall response rate was 21.1%, and median duration of response was 4.1 months. Efficacy sections of the proposed PI have been evaluated and found to be appropriate.

Safety

Studies providing safety data

The safety data to support this submission for the use of plitidepsin with DXM in MM patients were drawn mainly from the pivotal study (Study APL-C-001-09), with supportive data from the Phase II Study APL-B-14-03. Other studies which provided safety data were the 2 Phase I Studies APL-A-009-08 and APL-A-012-13, conducted in MM study population but with the use of plitidepsin with bortezomib. In addition, the sponsor has provided a secondary safety dataset, comprising of pooled integrated safety data (525 patients) coming from one Phase III study with plitidepsin in MM (Study APL-C-001-09) as well as 14 Phase II studies and 6 Phase I studies with plitidepsin in different indications.

Safety data from the Phase III Study APL-C-001-09 were evaluated as providing pivotal safety data in the MM population, with supportive data from the Phase II Study APL-B-14-03. Safety data from Studies APL-A-009-08 and APL-A-012-13 and the pooled integrated

safety dataset were evaluated and were found to be consistent with the safety findings in the pivotal study, and did not raise any additional safety concerns.

Patient exposure

Up to 31 March 2016, a total of 1108 patients with various advanced malignancies had been treated with plitidepsin in the clinical development program of plitidepsin. This included 280 patients with relapsed and refractory MM (204 in Study APL-C-001-09; 51 in Study APL-B-014-03; 3 in Study APL-A-009-08; and 22 in Study APL-A-012-13).

In Study APL-C-001-09 (ADMYRE trial), the median duration of exposure to study treatment was 12.3 weeks in the plitidepsin plus DXM arm (8.3 weeks in the DXM control arm). The treated patients received a median (range) of 3 (1-33) cycles. Median dose intensity was 1.9 mg/m^2 /week, which was similar to the 2.0 mg/m^2 /week of plitidepsin combined with DXM in Study APL-B-014-03, and the 1.8 mg/m^2 /week in Study APL-A012-13 of plitidepsin (at the recommended dose level) combined with bortezomib and DXM (Table 3).

Overall, the study drug exposure is adequate to assess the safety profile of plitidepsin in patients with relapsed and refractory MM.

Table 3: Summary of overall duration of exposure to plitidepsin alone or in combination by study in patients with relapsed/refractory multiple myeloma

	Primary main data	Supportive primary data		
	APL-C-001-09 (ADMYRE) Arm A (P+DXM) (n=167)	APL-B-014-03 Total (n=51)	APL-B-014-03 P + DXM (n=19)	APL-A-012-13 P+DXM+BTZ (n=10)
Time on treatment (weeks)	12.3 (1.3-137.1)	15.0 (6.0-39.4)	NA	30.4 (5.7-81.3+)
Cycles per patient	3 (1-33)	2 (1-9)	3 (2-9)	3 (1-10+)[a]
Plitidepsin dose intensity (mg/m^2/week)	1.9 (1.1-2.7)	2.3 (1.3-2.6)	2.0 (1.6-2.5)	1.8 (1.1-2.1+)[a]

Data shown are median (range) for all treated patients.
Data for APL-A-009-08 (P+DXM+BTZ) were obtained from only three patients and cannot be summarised in this table. Patients received two, three and six cycles, respectively. Median dose intensity for plitidepsin was 1.1 (1.0-1.2) mg/m^2/week.
[a] Data at the recommended dose: plitidepsin 5.0 mg/m^2 plus BTZ 1.3 mg/m^2 plus DXM 40 mg/m^2.

+, patients ongoing treatment at cut-off; BTZ, bortezomib; DXM, dexamethasone; NA, not available; P, plitidepsin.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Pivotal and/or main efficacy study

In Arm A (plitidepsin plus DXM), the incidence of raised ALT was higher in Arm A versus Arm B (84.9% versus 20.3%), as was the incidence of raised AST (66.0% versus 24.4%) (Table 4). Most of these abnormalities in Arm A were Grade 1 or 2 in severity (Grade 3 ALT increased and AST increased: 12.6% and 8.3% respectively; Grade 4 ALT increased and AST increased: 1.9% and 0.6% respectively).

Table 4: Biochemical abnormalities during treatment. Worst grade per patient (Studies APL-C-001-09/ADMYRE trial)

	Arm A (P+DXM)										Arm B (DXM)									
	n[a]	NCI-CTCAE grade								Total		n[a]	NCI-CTCAE grade								Total	
		1		2		3		4					1		2		3		4			
		n	%	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%	n	%
ALP increased	158	40	25.3	6	3.8	2	1.3	1	0.6	49	31.0	77	9	11.7	1	1.3	.	.	.	.	10	13.0
ALT increased	159	72	45.3	40	25.2	20	12.6	3	1.9	135	84.9	79	16	20.3	.	.	.	.	.	.	16	20.3
AST increased	156	73	46.8	16	10.3	13	8.3	1	0.6	103	66.0	78	18	23.1	1	1.3	.	.	.	.	19	24.4
Bilirubin increased	159	11	6.9	4	2.5	3	1.9	.	.	18	11.3	79	4	5.1	3	3.8	.	.	.	.	7	8.9
CPK increased	155	18	11.6	20	12.9	13	8.4	18	11.6	69	44.5	70	1	1.4	2	2.9	.	.	.	.	3	4.3
Creatinine increased	160	97	60.6	32	20.0	2	1.3	1	0.6	132	82.5	79	46	58.2	21	26.6	2	2.5	1	1.3	70	88.6

Abnormalities that occurred after crossover have been excluded from this table. Denominator for percentages was patients with available laboratory tests.

[a] Patients with available laboratory tests.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; DXM, dexamethasone; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; P, plitidepsin.

In Arm A, Grade 3/4 ALT increase appeared on Day 14 (range: 1 to 35 days) after dosing and most cases (58.3%) returned to values ≤ 2.5 x ULN before Day 28, with a median duration of 6 days (range: 1 to 16 days). Grade 3/4 AST appeared on Day 18 (range: 1 to 35 days) after dosing; half of episodes returned to values ≤ 2.5 x upper limit of normal (ULN) before Day 28, with a median duration of 6.5 days (range: 1 to 28 days) The median values for peak counts of ALT or AST, over 32 cycles, showed no evidence of cumulative toxicity.

The incidence of ALT increase reported as a treatment related serious AEs (SAEs) in Arm A was low (4.2% (n = 7) versus 0% in Arm B) as was the incidence of AST increase reported as a treatment related SAE in Arm A (3.6% (n = 6) versus 0%). Incidences of ALT/AST increases in Arm A leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (1.2% (2/167), 6.6% (11/167), 7.2% [12/167) and 4.8% (8/167), respectively).

Only one patient was identified as meeting the criteria of Hy's law. This patient developed raised ALT of 35.0 x ULN and raised AST of 94.7 x ULN, with total bilirubin of 2.8 x ULN and alkaline phosphatase (ALP) of 0.7 x ULN. The patient had several confounding factors, such as hepatitis B, concomitant medication, and infection related to MM progression. In this patient, Grade 1 or 2 increases in transaminases were apparent from Cycle 1 and reported as adverse events (AEs). In Cycle 6, the AST and ALT elevations reached Grade 4. No symptoms of severe hepatic failure were observed. The study treatment was discontinued after Cycle 6 (dose was omitted in this cycle) due to pulmonary haemorrhage related to the progression of her MM, which finally resulted in the patient's demise.

Other studies

Study APL-B-014-03

In patients treated with single agent plitidepsin, the incidence of raised ALT was 92.2% and that of raised AST was 90.2% (Table 5). Most of these abnormalities were Grade 1 or 2 in severity (Grade 3 ALT increased and AST increased: 27.5% and 9.8%, respectively; Grade 4 ALT increased and AST increased: 0% and 2.0% respectively).

In patients treated with plitidepsin and DXM, the incidence of raised ALT was 89.5% and that of raised AST was 68.4% (Table 6). Most of these abnormalities were Grade 1 or 2 in severity (Grade 3 ALT increased and AST increased: 5.3% and 10.5%, respectively; no incidence of Grade 4 ALT or AST increased).

Table 5: Biochemistry (worst grade per patient): plitidepsin Study APL-B-014-03

	NCI-CTC grade								Total (n=51)	
	1		2		3		4			
	n	%	n	%	n	%	n	%	n	%
ALT increased	17	33.3	16	31.4	14	27.5	.	.	47	92.2
AP increased	15	29.4	4	7.8	1	2.0	.	.	20	39.2
AST increased	28	54.9	12	23.5	5	9.8	1	2.0	46	90.2
CPK increased (n=50)*	12	24.0	5	10.0	3	6.0	4	8.0	24	48.0
Creatinine increased	17	33.3	8	15.7	2	3.9	.	.	27	52.9
Total bilirubin increased	4	7.8	4	7.8	1	2.0	.	.	9	17.6

*Missing data for patient #218 (all cycles).
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table 6: Biochemistry (worst grade per patient): plitidepsin + dexamethasone Study APL-B-014-03

	NCI-CTC grade								Total (n=19)	
	1		2		3		4			
	n	%	n	%	n	%	n	%	n	%
ALT increased	10	52.6	6	31.6	1	5.3	.	.	17	89.5
AP increased	8	42.1	2	10.5	.	.	.	.	10	52.6
AST increased	9	47.4	2	10.5	2	10.5	.	.	13	68.4
CPK increased (n=18)*	2	11.1	.	.	1	5.6	3	16.7	6	33.3
Creatinine increased	7	36.8	4	21.1	1	5.3	.	.	12	63.2
Total bilirubin increased	2	10.5	1	5.3	.	.	.	.	3	15.8

*Missing data for patient #149 (all cycles).
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Renal function and renal toxicity

Pivotal and/or main efficacy studies

Evaluation of renal function laboratory parameters did not trigger any safety concerns. The incidence of laboratory creatinine increased was 82.5% in Arm A versus 88.6% in Arm B.

Other studies

Study APL-B-014-03

Evaluation of renal function laboratory parameters did not trigger any safety concerns.

Other clinical chemistry

Pivotal and/or main efficacy studies

In Arm A (plitidepsin plus DXM), the incidence of raised CPK was higher in Arm A versus Arm B (44.5% versus 4.3%). Most of these abnormalities in Arm A were Grade 1 or 2 in severity. Incidence of Grade 3 and 4 CPK increases in Arm A were 8.4% (versus 0% in Arm B) and 11.6% (versus 0% in Arm B), respectively. The median values for peak counts of CPK, over 32 cycles, showed no evidence of cumulative toxicity. Median CPK peak value, by cycle, in patients with Grade 3/4 abnormalities in Arm A showed that earlier cycles (up to Cycle 3) had higher median peak levels compared to later cycles. Median duration of CPK increases in patients treated with plitidepsin plus DXM (including those crossed over from Arm B to Arm A) was 20 days and median time to recovery in these patients was 28 days.

The incidence of CPK increase reported as a treatment related SAEs in Arm A was low (3.0% [n = 5] versus 0% in Arm B). One of these cases resulted in treatment discontinuation and patient's death; the cause of death was assessed by the investigator as related to Grade 4 myopathy but was considered by the sponsor to be derived from complications of Grade 4 rhabdomyolysis.

Incidences of CPK increase in Arm A leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (0.6% [1/167], 1.8% [13/167], 6.0% [10/167] and 10.8% [18/167], respectively.

Other studies

Study APL-B-014-03

In patients treated with single-agent plitidepsin, the incidence of CPK increased was 48.0% (Table 5). Most of these abnormalities were Grade 1 or 2 in severity.

In patients treated with plitidepsin and DXM, the incidence of CPK increased was 33.3% (6/18) (Table 6). The incidence of grades 3 and 4 CPK increased were 5.6% (n = 1) and 16.7% (n = 3), respectively.

Haematology and haematological toxicity

Pivotal and/or main efficacy study

The incidences of anaemia, neutropenia and thrombocytopenia were generally comparable between Arms A (plitidepsin plus DXM) and B (DXM only) (anaemia: 98.1% in Arm A versus 97.5% in Arm B; neutropenia: 47.5% versus 42.3%; thrombocytopenia: 59.4% versus 67.1%).

Other studies

Study APL-B-014-03

Evaluation of haematological laboratory parameters did not trigger any safety concerns.

Electrocardiograph findings and cardiovascular safety

Pivotal and/or main efficacy study

Electrocardiograph

In Arm A (plitidepsin plus DXM), ECG QT prolongation was reported as a treatment related AE in 9 patients (5.4%), reaching Grade 3 in one patient and one cycle. Two of these cases were reported as SAEs. One patient had Grade 3 ECG QT prolonged concomitantly with Grade 3 atrial fibrillation of unknown cause that required hospitalisation and treatment discontinuation after four cycles. This patient had received concomitant medication (levofloxacin and venlafaxine) that could prolong QT. The other patient had Grade 2 ECG QT prolonged in the first cycle that required hospitalisation and dose omission, delay and reduction. Concomitant medication (propafenone and amiodarone) was considered as the primary cause of QTc prolongation that extended patient hospitalisation.

No abnormal values or AEs related to ECG data were reported in Arm B (DXM only).

ECG QT prolonged was reported as treatment related AE in 3 patients after crossover (3/37; 8.1%), reaching Grade 1 in two patients and Grade 2 in one patient.

A QTc substudy was conducted at some of the sites participating in Study APL-C-001-09. The potential effects of a 5 mg/m^2 plitidepsin dose given as a 3 h IV infusion on the QTc interval duration was assessed based on ECG evaluation when patients were treated in Arm A with plitidepsin for the first time (Day 1 of Cycle 1). In order to detect any delayed drug effect on the QTc interval, these investigations were repeated at the second infusion of plitidepsin (Day 15 of Cycle 1), when the drug was expected to reach steady state. The QTc substudy was started with its implementation through protocol amendment Number 2 three years after the start of Study APL-C-001-09 and was not mandatory for all patients and was not conducted in some countries. Overall, only 7 patients eventually participated and 6 of them were evaluable for Day 1 measurements and 4 for Day 15 measurements. The limited sample size precluded ruling out an effect of plitidepsin on QT interval.

However, according to the sponsor, available data did not show any definite relevant effect of plitidepsin on the QT interval or any other ECG parameter.

Left ventricular ejection fraction (LVEF)

In Arm A (plitidepsin plus DXM), no incidence of ejection fraction decrease was reported as treatment related AE. In Arm A, ejection fraction decrease was reported as AE with unknown relationship in 3 patients (1.8%), being Grade 3 in two patients and Grade 2 in one patient. One patient with Grade 3 ejection fraction decrease (LVEF = 30%) had to discontinue treatment after 10 cycles. This patient had a low LVEF at baseline (48%; below normal value of 60% ±10, and reported as protocol deviation). This patient had myocardial infarction in the baseline medical history and received polaramine and mopral as premedication. Ejection fraction decrease was present at all follow-up visits done. The other patient with Grade 2 ejection fraction decrease required in Cycle 12 a cycle delay of 16 days.

In Arm B (DXM), no abnormal values or AEs related to LVEF data were reported.

One patient had Grade 1 ejection fraction abnormal reported as treatment related AE after crossover from Arm B to Arm A.

Vital signs and clinical examination findings

Pivotal and/or main efficacy study

Analyses of vital signs did not trigger any safety concerns.

Hypersensitivity events

Pivotal and/or main efficacy study

Incidence of hypersensitivity reactions reported as treatment related AE in Arm A was low (6.1% versus 0% in Arm B). Grade 1/2 treatment related hypersensitivity reactions were observed in 5 patients and Grade 3 in 3 patients. In addition, one patient had Grade 4 anaphylactic shock after crossover (first plitidepsin dose in Cycle 16) that led to cardiac arrest, with resolution after resuscitation manoeuvers. The sponsor concluded that although hypersensitivity reactions were infrequent provided that prophylactic medication according to protocol guidelines was implemented, it could be of potential seriousness. Hypersensitivity reactions have been claimed to be caused by the Polyoxyl 35 castor oil present in the formulation, but according to the sponsor, it is not currently possible to exclude plitidepsin as a contributor.

Serious skin reactions and infusion related events

Pivotal and/or main efficacy studies

With respect to skin and subcutaneous reactions ≥ Grade 3, only one patient in Arm A had Grade 3 rash (in the first cycle), which required reduction of plitidepsin dose.

The incidence of treatment related infusion related events in Arm A was low (3.6% versus 0% in Arm B) and the majority of them were ≤ Grade 2 and without effects on the study treatment. They consisted of Grade 1 catheter site pain (1/167 patients; 0.6%); Grade 1/2 catheter site phlebitis (2/167; 1.2%), Grade 1 infusion site reaction (1/167; 0.6%); and Grade 2 injection site extravasation (1/167; 0.6%). One event of Grade 3 thrombosis in device was reported (1/167; 0.6%) This event was the only infusion related event reported as treatment related SAE, as the patient required hospitalisation and the study treatment was discontinued.

Other safety parameters

Pivotal and/or main efficacy study

Musculoskeletal Disorders, CPK Increases and Rhabdomyolysis

The most common musculoskeletal disorders reported as treatment related AEs (or with unknown causality) in Arm A were myalgia (14.4% versus 2.4% in Arm B) and muscular weakness (9.6% versus 2.4%). Most of these were of Grades 1 or 2. The most commonly reported Grade 3/4 treatment related musculoskeletal disorder AE in Arm A was myalgia (Grade 3: 4.2%; Grade 4: 1.2%). Two events of Grade 3/4 rhabdomyolysis were reported as AEs (one treatment related and the other with unknown causality) in Arm A.

Analyses of CPK increases have been discussed above.

Cardiac disorders

In Study APL-C-001-09 (ADMYRE), the incidence of cardiac disorders reported as treatment related AEs (or with unknown causality) was 14.4% in Arm A versus 3.6% in Arm B. Most of these were of Grades 1 or 2. The most commonly reported treatment related cardiac disorders in Arm A was atrial fibrillation (4/167 patients, 2.4%; Table 7).

Table 7: Cardiac disorders reported as treatment-related AEs (including AEs with unknown relationship) (Studies APL-C-001-09/ ADMYRE)

MedDRA PT	Arm A (P+DXM)												Arm B (DXM)									
	NCI-CTCAE grade										Total		NCI-CTCAE grade								Total	
	1		2		3		4		5		(n=167)		1		2		3		4		(n=83)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Angina pectoris	.	.	1	0.6	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Atrial fibrillation	.	.	2	1.2	2	1.2	.	.	.	.	4	2.4	.	.	.	.	1	1.2	.	.	1	1.2
Atrial tachycardia	.	.	1	0.6	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Cardiac arrest	.	.	.	.	.	.	.	.	1	0.6	1	0.6	.	.	.	.	.	.	.	.	.	.
Cardiac failure	.	.	1	0.6	2	1.2	.	.	.	.	3	1.8	.	.	.	.	.	.	.	.	.	.
Cardiac failure chronic	.	.	1	0.6	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Cardiac failure congestive	.	.	.	.	1	0.6	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Left ventricular dysfunction	1	0.6	1	0.6	.	.	.	.	.	.	2	1.2	.	.	.	.	.	.	.	.	.	.
Left ventricular failure	1	0.6	.	.	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Mitral valve incompetence	1	0.6	.	.	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Myocardial infarction	.	.	1	0.6	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Palpitations	1	0.6	.	.	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Sinus tachycardia	1	0.6	1	0.6	.	.	.	.	.	.	2	1.2	1	1.2	.	.	.	.	.	.	1	1.2
Supraventricular tachycardia	1	0.6	.	.	.	.	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Systolic dysfunction	.	.	.	.	1	0.6	.	.	.	.	1	0.6	.	.	.	.	.	.	.	.	.	.
Tachycardia	2	1.2	.	.	.	.	.	.	.	.	2	1.2	.	.	.	.	.	.	.	.	.	.
Ventricular extrasystoles	.	.	.	.	.	.	.	.	.	.	.	.	1	1.2	.	.	.	.	.	.	1	1.2

Adverse events that occurred after crossover have been excluded from this table.
DXM, dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities v.16.0; NA, not available; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; P, plitidepsin; PT, preferred term; SOC, System Organ Class.

Analyses of ECG parameters have been discussed above.

Transaminases Elevations and Hepatobiliary Disorders

The incidence of hepatobiliary disorders reported as treatment related AEs (or with unknown causality) was low in Arm A (2.4% versus 0% in Arm B), and consisted of Grade 3 cholestasis, Grade 3 portal vein thrombosis, Grade 2 hepatocellular injury, and Grade 2 hepatomegaly (one patient each, 0.6%).

Analyses of laboratory liver parameters have been discussed above.

Other safety issues

Safety in special populations

To identify safety issues limited to or more frequently observed in specific subgroups of patients, incidence of treatment related (or with unknown relationship) AEs, treatment related (or with unknown relationship) SAEs, treatment related (or with unknown relationship) AEs leading to treatment discontinuation, and treatment related (or with

unknown relationship) AEs leading to death were summarised in subgroups in the integrated safety dataset. Intrinsic factors analysed included age, gender, Eastern Cooperative Oncology Group (ECOG) Performance status (PS)[32] score at baseline, and body mass index (BMI). Safety was also assessed by geographic region (that is study location) as an extrinsic factor. Results did not trigger any particular safety concerns.

Post marketing data

Not applicable for a new chemical entity.

Evaluator's conclusions on safety

Overall, safety analyses in the pivotal Phase III Study APL-C-001-09 showed that incidences of treatment related AEs and treatment related SAEs were higher with plitidepsin plus DXM compared to DXM alone (treatment related AEs: 86.2% versus 45.8%; treatment related SAEs: 28.1% versus 7.2%). The most commonly reported treatment related AEs with plitidepsin plus DXM were nausea (37.1% versus 10.8% with DXM alone) and fatigue (36.5% versus 8.4%) and majority of these were of severity Grades 1 or 2. The most commonly reported Grade ≥ 3 AEs related to plitidepsin plus DXM was fatigue (10.8% versus 1.2% with DXM alone). The most commonly reported treatment related SAEs with plitidepsin plus DXM were pneumonia (4.2% versus 0% with DXM alone), ALT increased (4.2% versus 0%) and AST increased (3.6% versus 0%).

The incidence of deaths during treatment or follow-up was lower with plitidepsin plus DXM compared to DXM alone (59.3% versus 68.7%). Most deaths were due to progression of the patient's underlying malignant disease and only one patient each in arm died on study due to treatment related AEs (Arm A: one patient died due to Grade 4 myopathy; Arm B: one patient died due to Grade 4 respiratory tract infection).

Treatment with plitidepsin plus DXM was associated with higher incidences of raised transaminases compared to DXM alone (raised ALT: 84.9% versus 20.3%; raised AST: 66.0% versus 24.4%). However, most of these abnormalities with plitidepsin plus DXM were Grade 1 or 2 in severity: incidences of Grade 3 ALT increased and AST increased were 12.6% and 8.3% respectively, while those of Grade 4 ALT increased and AST increased were 1.9% and 0.6% respectively. Incidences of ALT/AST increases with plitidepsin plus DXM leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (1.2% to 7.2%), as was the incidence of ALT/AST increases reported as a treatment related SAEs with plitidepsin plus DXM (4.2% for ALT increases and 3.6% for AST increases).

Transaminases increases with plitidepsin plus DXM appeared to be transient and reversible. In Arm A (plitidepsin plus DXM), Grade 3/4 ALT increase appeared on Day 14 (range: 1 to 35 days) after dosing and in most cases (58.3%) returned to values ≤ 2.5 x ULN before Day 28, with a median duration of 6 days (range: 1 to 16 days). Grade 3/4 AST appeared on Day 18 (range: 1 to 35 days) after dosing and about half of the episodes

[32] ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking h
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking h
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

returned to values ≤ 2.5 x ULN before Day 28, with a median duration of 6.5 days (range: 1 to 28 days). In addition, the median values for peak counts of ALT or AST, over 32 cycles, showed no evidence of cumulative toxicity. The incidence of hepatobiliary disorders reported as treatment related AEs with plitidepsin plus DXM was low (2.4%). Only one patient was identified as meeting the criteria of Hy's law. It is noted that monitoring of transaminases has been included in the proposed PI.

Treatment with plitidepsin plus DXM was associated with higher incidences of muscular AEs. The most common musculoskeletal disorders reported as treatment related AEs with plitidepsin plus DXM were myalgia (14.4% versus 2.4% in Arm B) and muscular weakness (9.6% versus 2.4%). Most of these were of Grades 1 or 2 in severity and the most commonly reported Grade 3/4 treatment related musculoskeletal disorders AEs with plitidepsin plus DXM was myalgia (Grade 3: 4.2%; Grade 4: 1.2%). The incidence of raised creatine phosphokinase (CPK) was higher with plitidepsin plus DXM compared to DXM alone (44.5% versus 4.3%). Most of these abnormalities with plitidepsin plus DXM were Grade 1 or 2 in severity: incidences of Grade 3 and 4 CPK increases in Arm A were 8.4 and 11.6%, respectively. Incidences of CPK increase in Arm A leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (0.6% to 10.8%) as was the incidence of CPK increase reported as a treatment related SAEs with plitidepsin plus DXM (3.0%). The median values for peak counts of CPK, over 32 cycles, showed no evidence of cumulative toxicity. CPK increases with plitidepsin plus DXM appeared to be transient: median duration of CPK increases in patients treated with plitidepsin plus DXM (including those crossed over from Arm B to Arm A) was 20 days and median time to recovery in these patients was 28 days. It is noted that monitoring of muscular toxicities has been included in the proposed PI.

The effect on muscles did not appear to extend significantly to cardiac muscles. There was no incidence of treatment related ejection fraction decrease reported in Arm A (plitidepsin plus DXM), and only one patient had Grade 1 ejection fraction abnormal reported as treatment related AE after crossover from Arm B to Arm A.

The incidence of hypersensitivity reactions reported as treatment related AE was low with plitidepsin plus DXM (6.1% versus 0% with DXM alone), as was the incidence of treatment related infusion related events (3.6% versus 0%).

The safety findings in the Phase II Study APL-B-014-03 were generally consistent with those of the pivotal study. Safety sections of the proposed PI have been evaluated and found to be appropriate.

First round benefit-risk assessment

The first round assessment of benefits are summarised below in Table 8.

Table 8: First round assessment of benefits

Benefits	Strengths and Uncertainties
Potential benefit is in the treatment of patients with relapsed and refractory MM. Treatment options for patients who have relapsed/ refractory MM are limited, and there is therefore a need for more treatment options for patients in this disease	Efficacy results were generally supportive of a positive treatment effect of plitidepsin plus DXM over DXM alone in patients with relapsed and refractory MM. There was a statistically significantly longer median progression free survival with plitidepsin plus DXM compared to DXM alone (2.6 months versus 1.7 months). This represented a statistically significant reduction in the relative risk of progression or death by 35.0%

Benefits	Strengths and Uncertainties
setting.	in patients treated with plitidepsin plus DXM compared to patients treated with DXM alone. It is noted, however, that the treatment effect of plitidepsin plus DXM over DXM alone was a median progression-free survival of 0.9 months (2.6 months versus 1.7 months). The clinical significance of this is uncertain. However, given the nature of the disease under treatment (advanced MM), it is anticipated that this is an issue that is best considered and weighed at the level of an individual patient with his/her treating physician. Although final analysis of median OS showed no statistically significant difference between treatment plitidepsin plus DXM versus treatment with DXM (11.6 months versus 8.9 months; log-rank p = 0.1261), this analysis did not take into account that 44% of patients in Arm B crossed over to Arm A. Post hoc analyses that excluded patients who crossed over showed statistically significant longer median OS with plitidepsin plus DXM compared to DXM alone (11.6 months versus 5.0 months, p = 0.0069; reduction in the relative risk of death of 38.4%, p = 0.0075). Overall response rate was statistically significantly higher with plitidepsin plus DXM compared to DXM alone (22.8% versus 3.6% when including minor responses; 9.9% versus 1.2% when excluding minor responses). The pivotal study did not assess quality of life data. This could potentially reduce the ability to have a comprehensive evaluation of the benefit/risk profile of plitidepsin. The adverse drug reactions of plitidepsin coupled with its mode of administration by IV infusion could potentially affect the patient's perception of their quality of life. Conversely, if the quality of life was perceived by patients to not have been reduced despite the adverse drug reactions and mode of administration, this could also aid in the evaluation of the benefit/risk profile of plitidepsin

First round assessment of risks

The first round assessment of risks are summarised below in Table 9.

Table 9: First round assessment of risks

Risks	Strengths and Uncertainties
The most commonly reported treatment related AEs with plitidepsin plus DXM were nausea (37.1% versus 10.8% with DXM alone) and fatigue (36.5% versus 8.4%) in the pivotal Phase III study.	The majority of the commonly reported treatment related AEs with plitidepsin plus DXM were of severity Grades 1 or 2. The incidence of treatment related SAEs were low and the most commonly reported treatment related SAEs with plitidepsin plus DXM were pneumonia (4.2% versus 0% with DXM alone), ALT increased (4.2% versus 0%) and AST increased (3.6% versus 0%). Incidence of death due to treatment related AEs with plitidepsin plus DXM was low (n = 1 in the pivotal Phase III study; due to Grade 4 myopathy).
Treatment with plitidepsin plus DXM was associated with higher incidences of raised transaminases compared to DXM alone.	In the pivotal Phase III study, treatment with plitidepsin plus DXM was associated with higher incidences of raised transaminases compared to DXM alone (raised ALT: 84.9% versus 20.3%; raised AST: 66.0% versus 24.4%). However, most of these abnormalities with plitidepsin plus DXM were Grade 1 or 2 in severity and did not lead to severe complications (incidences of ALT/AST increases with plitidepsin plus DXM leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (1.2% to 7.2%)). The incidence of ALT/AST increases reported as a treatment related SAEs with plitidepsin plus DXM was also low (4.2% for ALT increases and 3.6% for AST increases). In addition, transaminases increases with plitidepsin plus DXM appeared to be transient and reversible (Grade 3/4 ALT increase appeared on Day 14 (range: 1 to 35 days) after dosing and in most cases (58.3%) returned to values ≤ 2.5 x ULN before Day 28, with a median duration of 6 days; Grade 3/4 AST appeared on Day 18 (range: 1 to 35 days) after dosing and about half of the episodes returned to values ≤ 2.5 x ULN before Day 28, with a median duration of 6.5 days). The median values for peak counts of ALT or AST, over 32 cycles, showed no evidence of cumulative toxicity. Overall, the incidence of hepatobiliary disorders reported as treatment related AEs with plitidepsin plus DXM was low (2.4%).
Treatment with plitidepsin plus DXM was associated with higher incidences of muscular AEs and CPK increases.	In the pivotal Phase III study, treatment with plitidepsin plus DXM was associated with higher incidences of muscular AEs. The most common musculoskeletal disorders reported as treatment related AEs with plitidepsin plus DXM were myalgia (14.4% versus 2.4% with DXM alone) and muscular weakness (9.6% versus 2.4%). However,

Risks	Strengths and Uncertainties
	most of these were of Grades 1 or 2 in severity and the most commonly reported Grade 3/4 treatment related musculoskeletal disorders AEs with plitidepsin plus DXM was myalgia (Grade 3: 4.2%; Grade 4: 1.2%). The incidence of raised CPK was also higher with plitidepsin plus DXM compared to DXM alone 44.5% versus 4.3%). Most of these abnormalities with plitidepsin plus DXM were Grade 1 or 2 in severity and did not lead to severe complications (incidences of CPK increase leading to treatment discontinuation, cycle delay, dose omission or dose reduction were low (0.6% to 10.8%)). The incidence of CPK increase reported as a treatment related SAEs with plitidepsin plus DXM was low (3.0%). In addition, CPK increases with plitidepsin plus DXM appeared to be transient: median duration of CPK increases in patients treated with plitidepsin plus DXM (including those crossed over from Arm B to Arm A) was 20 days and median time to recovery in these patients was 28 days. The median values for peak counts of CPK, over 32 cycles, showed no evidence of cumulative toxicity.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance for the use of plitidepsin, in combination with DXM, for the treatment of patients with relapsed and refractory MM is positive.

There was a statistically significantly longer median progression-free survival with plitidepsin plus DXM compared to DXM alone (2.6 months versus 1.7 months). This represented a statistically significant reduction in the relative risk of progression or death by 35.0% in patients treated with plitidepsin plus DXM compared to patients treated with DXM alone. Analyses that excluded patients who crossed over from the DXM alone group to the plitidepsin plus DXM group showed that there was a statistically significant longer median OS with plitidepsin plus DXM compared to DXM alone (11.6 months versus 5.0 months; reduction in the relative risk of death of 38.4%).

The most commonly reported treatment related AEs with plitidepsin plus DXM were symptomatic: nausea and fatigue. The majority of these were of severity Grades 1 or 2. The incidence of treatment related SAEs and deaths were low. Although the treatment with plitidepsin plus DXM was associated with higher incidences of raised transaminases, most of these abnormalities were of Grade 1 or 2 in severity and did not lead to severe complications. In addition, transaminases increases with plitidepsin plus DXM appeared to be transient and reversible. This adverse reaction can also be monitored with routine laboratory assessments. It is noted that monitoring of transaminases has been included in the proposed PI.

Treatment with plitidepsin plus DXM was also associated with higher incidences of muscular AEs and CPK increases. The most common musculoskeletal disorders reported as treatment related AE with plitidepsin plus DXM was symptom of myalgia and most of

these AEs were of Grades 1 or 2 in severity. Most of the incidences of raised CPK were also of Grade 1 or 2 in severity and did not lead to severe complications. In addition, CPK increases with plitidepsin plus DXM appeared to be transient. This adverse reaction can also be monitored with routine laboratory assessments. Monitoring of muscular toxicities has been included in the proposed PI.

It is noted that the treatment effect of plitidepsin plus DXM over DXM alone was a median PFS of 0.9 months (2.6 months versus 1.7 months). Given the disease setting of advanced MM where treatment options are limited and survival rates low, the clinical significance of this when weighed against the potential adverse effects is best addressed at the level of an individual patient with his/her treating physician.

First round recommendation regarding authorisation

It is recommended that the application for the registration of plitidepsin for the treatment of patients with relapsed and refractory MM in combination with DXM be approved. This is subject to compliance with the following:

- Incorporation of suggested changes to proposed PI and consumer medicine information (CMI). The details of the proposed amendments are beyond the scope of this AusPAR.

Clinical questions

No questions were raised.

Second round evaluation

No second round evaluation was conducted as no clinical questions were raised.

VI. Pharmacovigilance findings

- The sponsor has submitted EU Risk Management Plan (RMP) version 2.0 (dated 6 July 2017; data lock point (DLP) 31 March 2016) and Australian Specific Annex (ASA) version 1.1 (dated 18 July 2017) in support of this application. In their response to TGA's request for further information, the sponsor has submitted an updated ASA (version 1.2 dated 26 February 2018). The EU-RMP version remains the same as initially submitted.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 10.

Table 10: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	Al
Important identified risks	Myopathies, including rhabdomyolysis	ü	–	ü	–
	Severe hypersensitivity	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	Al
	reactions				
	Liver enzymes increased	ü	–	ü	–
Important potential risks	Cardiac effects and QT prolongation	ü	ü	ü	–
	Off-label use in malignancies other than MM (in adults and children)	ü	–	ü	–
	Use in pregnancy/reproductive toxicity and development toxicities*	ü	–	ü	–
Missing information	Use in patients with severe renal impairment*	ü	–	ü	–
	Safety in Asian patients*	ü	–	–	–
	Long-term safety	ü	–	–	–
	Use in very elderly patients	ü	–	–	–
	Use in lactation	ü	–	ü	
	Use in patients with hepatic impairment	ü	–	ü	
	Drug interaction with potent CYP3A4 inhibitors	ü	ü	ü	–

*Recommended by the RMP Evaluator and agreed to by the sponsor.

- There are two additional pharmacovigilance activities which are planned (QT Study and a drug interaction study with plitidepsin plus DXM and a strong CYP3A4 inhibitor such as itraconazole). There is no Australian involvement at this stage, but the results are considered to be generalisable to the Australian population.
- There are no additional risk minimisation activities.

New and outstanding recommendations after the second round evaluation

The sponsor has updated the CMI satisfactorily. The sponsor has also added the wording regarding the black triangle scheme. However, the wording states '*See the end of the section on Side Effects for how to report side effect*' but wording has not been added on how to report side effects. Wording for black triangle scheme should also include the following: '*You can report side effects to your doctor, or directly at www.tga.gov.au/reporting-problems*'.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- The Aplidin EU-Risk Management Plan (RMP) (version 2.0, dated 6 July 2017, data lock point 31 March 2016), with Australian Specific Annex (version 1.2, dated 26 February 2018), included with submission PM-2017-02669-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Aplidin (plitidepsin) is to be included in the Black Triangle Scheme. The PI and CMI for APLIDIN must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval is not currently recommended from a quality perspective and outstanding issues remain at the time of writing this overview.

The second round evaluation of chemical, pharmaceutical and biopharmaceutical aspects included the following comment:

> *'Approval is not recommended from a pharmaceutical chemistry and biopharmaceutics perspective at this stage for the following reasons. If the sponsor was to satisfactory address the outstanding matters then approval could be recommended.*
>
> – The 2016 GMP clearance for [information redacted]
>
> – The specifications for control of mannitol and tert-butanol should be updated as outlined.[33]'

In addition to the outstanding issues identified above, the second round report raised a number of issues for the TGA Delegate's attention:

- The EU guidance on bioavailability and bioequivalence and the TGA's guidance on Biopharmaceutic Studies state that micellar forming products are considered 'complex' solutions due to the introduction of an additional micellar compartment or 'lipophilic phase'. This position is also stated in more detail in the EMA's Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems. The proposed drug product is *not* considered to be a simple aqueous solution and, upon dilution, forms polyethylene glycol micelles to aid solubilisation of the drug substance. The sponsor was asked to submit a justification for why no biopharmaceutical data were submitted and the sponsor's response discusses pharmacokinetic findings from non-clinical and clinical studies. While the sponsor's justification is appropriate from a pharmaceutical

[33] These issues were resolved prior to recommendation for approval.

chemistry perspective it should nevertheless be referred to the Delegate for consideration.

The Delegate is happy to accept the pharmaceutical chemistry advice on this issue. Given the potential for additional information to be available since the sponsor's response, the presence of any additional information or justification from the sponsor has also been requested.

- Persistence and fate of the micelles in vivo is discussed as this has the potential to affect the availability of the drug substance. In summary, in vitro data collected to date demonstrates that plitidepsin has a high affinity for plasma proteins, red blood cells and has high lipophilicity. The sponsor states that these findings correlate with the pharmacokinetic findings of plitidepsin studies following IV administration, whereby it is was found to be dose-proportional and time independent and was found to have kinetics suggestive of a wide distribution and a slow elimination. The sponsor states that these results suggest that plitidepsin is not retained in micelles after infusion. For that reason, no further studies were executed in order to determine the persistence of micelles in vivo, as this was considered non relevant. While the sponsor's justification is appropriate from a pharmaceutical chemistry perspective it should nevertheless be referred to the Delegate for consideration.

The Delegate is happy to accept the pharmaceutical chemistry advice on this issue. Given the potential for additional information to be available since the sponsor's response, the presence of any additional information or justification from the sponsor has also been requested.

- Inclusion of PEG-35 in the formulation, which is known to cause hypersensitivity reactions. The expected minimum dose (7 mg plitidepsin) is 2.2 g.

Question for sponsor: Please provide the most recent clinical data regarding the rates of hypersensitivity reactions across all patients exposed to plitidepsin.

The Delegate commented that in the pivotal study, all patients in the plitidepsin plus DXM arm received prophylactic medication 20 to 30 min before infusion of plitidepsin. This included: Ondansetron 8 mg IV or equivalent (granisetron 3 mg IV preferred when available); Diphenhydramine hydrochloride 25 mg IV or equivalent, and; Ranitidine 50 mg IV or equivalent. All patients also received DXM. The draft PI document for plitidepsin reflects the pre-medication advice as per the pivotal study. The PI also states '*If dexamethasone treatment is discontinued due to toxicity, dexamethasone at a lower dose (8 mg) must be given as premedication for plitidepsin treatment*.' Information regarding infusion reactions is provided under Section 4.2 and information regarding 'injection site reactions and hypersensitivity reactions 'is provided in 4.4 [of the PI]. Aspects of this information may require amendment following the advisory committee's advice regarding the risk/benefit balance of plitidepsin.

- Stability of the micelles in the diluted solutions has been demonstrated under in-use conditions. However, use of an in line filter is recommended during administration to ensure removal of sub visible particulates that may form during the preparation of the solution prior to infusion.'

The Delegate is happy to accept the pharmaceutical chemistry advice on this issue. The draft PI document for plitidepsin includes information regarding the use of an in-line filter under the section titled 'Instructions for Administration'.

- The suitability of name 'Aplidin 'was raised by the quality evaluator.

The Delegate commented that in following advice from the Trade Name Committee, the Delegate had no reason to object to the Tradename 'Aplidin 'at this stage.

Question for sponsor: Is there any additional data, biopharmaceutical data or justification available to address the issues of the 'lipophilic phase' of plitidepsin and the persistence and fate of the micelles *in vivo*?

Recommendation for sponsor: Please address the outstanding quality issues identified by the quality evaluator.[34]

Nonclinical

Overall, there were no nonclinical objections to the registration of plitidepsin (Aplidin) '*provided a favourable risk/benefit balance is shown from clinical data and that the draft Product Information document is amended as directed*'. Subsequent PI changes were negotiated with the sponsor and an updated PI document submitted on 24 June 2018. The nonclinical evaluator considered this response and on 25 June 2018, the nonclinical evaluator stated the following:

> *The sponsor has updated the Product Information document as requested, and the PI is now considered to be acceptable from a nonclinical perspective*.

The nonclinical evaluator noted the strong expectation of embryofetal lethality with use of Aplidin by a pregnant woman. The evaluator recommended that this warrants assignment of plitidepsin to Pregnancy Category D (rather than Category C as the sponsor proposes).[28,29] The sponsor subsequently accepted this recommendation.

Clinical

As well as the clinical data summarised under *Scope of the clinical dossier* above, the submission also included a pooled integrated safety data analysis comprising of data from the pivotal Phase III study (Study APL-C-001-09/ADMYRE trial) as well as 14 Phase II studies and 6 Phase I studies with plitidepsin in different indications.

The submitted data was evaluated using TGA adopted EMA Guidelines including the '*Guideline on the evaluation anticancer medicinal products in man, December 2012, Points to consider on application with1. Meta-analyses; 2. One pivotal study* 'and '*CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice*. The clinical evaluation report considered Study APL-C-001-09 (ADMYRE) as the pivotal efficacy/ safety study and Study APL-B-014-03 was evaluated as a supportive study. The two Phase I studies which investigated plitidepsin in the same disease setting (relapsed and refractory MM) but combined with bortezomib and DXM were evaluated as providing supportive data.

Clinical evaluator's recommendation

The clinical evaluator concluded that the benefit-risk balance for the use of plitidepsin, in combination with DXM, for the treatment of patients with relapsed and refractory MM is positive and recommended that the application for the registration of plitidepsin be approved. This is subject to compliance with the incorporation of suggested changes to proposed PI and CMI.

Pharmacokinetics (PK)

An overview of the clinical studies with PK assessment data is shown in Table 11. Of these studies, the Phase III Study APL-C-001-09 (n = 139) provided key data regarding the PK profile of plitidepsin in combination with DXM in patients with MM. Supportive studies in

[34] Clarification: At the time of the Delegate's recommendation for approval, all outstanding quality issues identified by the quality evaluator were addressed.

this population group included the Phase I Study APL-A-012-13 (n = 17) investigating plitidepsin in combination with bortezomib and DXM; in addition to the Phase II Study APL-B-014-03 (n = 17) in MM with or without DXM.

Table 11: Clinical Studies with PK data

Study	Population	Doses (mg/m²)	Plitidepsin infusion length (hour)	Number of patients [a] Full PK Profiles	Number of patients [a] Limited PK Sampling	Matrix	Included in Pop-PK
Phase I Studies In Patients With Solid and Haematological Tumours							
APL-A-001a-98	Solid tumours, NHL	0.13 to 4.50	24	34	-	B & P	No
APL-A-001b-98	Solid tumours, NHL	3.00 to 6.00	3	26	-	B	No
APL-A-002-98	Solid tumours, NHL	0.13 to 3.60	1	46	-	B & P	No
APL-A-003-98	Solid tumours, NHL	0.20 to 8.00	24	48	-	B & P	No
APL-A-004-98	Solid tumours, NHL	0.08 – 1.50	1	37	-	B & P	No
APL-A-013-13 [b]	Solid tumours	7 mg (FD) [c]	3	6	-	B & P	No
Phase I Study in Special Populations							
APL-A-005-02 [d]	Children with solid tumours	4.00 to 6.00	3	34	-	P	No
Phase I Combination Studies							
APL-A-006-05	Solid tumours, lymphoma, with carboplatin	1.80 – 3.00	1	20	-	P	No
APL-A-010-08	Solid tumours, lymphomas, with gemcitabine or sorafenib	1.80 – 3.00	1	32	-	B	No
APL-A-011-08	Solid tumours, with docetaxel or bevacizumab	2.80 – 4.80	3	13	-	B	No
APL-A-012-13	Multiple myeloma, with bortezomib	4.00 – 5.00	3	17	-	B	No
Phase II Studies in Patients with Solid Tumours							
APL-B-001-01	Renal cancer, colorectal cancer	5.00 to 7.00	24	-	43	B	No
APL-B-002-02	Medullary thyroid carcinoma	4.25 to 5.00	3	-	16	B	No
APL-B-005-02	Carcinoma of the urothelium	5.00	3	-	20	P	Yes
APL-B-006-02	SCLC	2.00 to 3.20	1	-	15	P	Yes
APL-B-007-02	Melanoma	5.00	3	-	37	P	Yes
APL-B-011-02	Prostate cancer	5.00	3	8	-	B & P	Yes
APL-B-016-05 [e]	Melanoma, with or without dacarbazine	1.80 – 3.20	1	67	-	B	No
Phase II Studies in Patients with Haematological Tumours and Multiple Myeloma							
APL-B-013-02	NHL	3.20	1	24	-	B	Yes
APL-B-014-03	MM, with or without DXM	5.00	3	45	-	B & P	Yes
APL-B-015-04	ALL	3.20	1	17	-	B & P	Yes
Phase III Study in Patients with Multiple Myeloma							
APL-C-001-09	MM, with DXM	5.00	-	-	139	B	Yes

These clinical studies are summarised in Appendix 1.

[a] Number of patients with PK assessment of plitidepsin.

[b] Human mass-balance study using ^{14}C-radiolabelled plitidepsin.

[c] Only the first infusion of Cycle 1, corresponding to the radiolabelled dose. Subsequent infusions were administered as a 5 mg/m² over 3 hours.

[d] Paediatric study.

[e] Phase I/II study with two arms in phase II stage: in Arm A, patients were treated with plitidepsin 3.2 mg/m² as a 1-hour infusion on Days 1, 8 and 15 every four weeks. In Arm B, 36 patients were treated with plitidepsin 2.4 mg/m² as a 1-hour infusion on Days 1, 8 and 15 followed by dacarbazine 800 mg/m² as a 1-hour infusion on Day 1 every four weeks.

ALL, acute lymphoblastic leukaemia; B, whole blood; FD, flat dose; NHL, non-Hodgkin's lymphoma; P, plasma; PK, pharmacokinetic; Pop-PK, population pharmacokinetic analysis; SCLC, small cell lung cancer.

Key findings of the pharmacokinetic data include:

- PK analyses of plitidepsin in the target population of patients with relapsed and refractory MM showed that half-lives were 44.38 h in whole blood and 50.35 h in plasma.
- C_{max} was about 1.93 times higher in whole blood than in plasma and AUC was about 3.4 times higher in whole blood than in plasma.

- There was limited accumulation after repeated cycles of plitidepsin.
- The inter-patient variability for plasma clearance (CL) and central volume of distribution (V1) is moderate to high (45.7% and 61.1%, respectively).
- In vitro preclinical studies have shown plitidepsin is likely to be substrate of P-gp.
- Studies with human microsomes indicate CYP3A4 is the predominant CYP enzyme responsible for the hepatic metabolism of plitidepsin. In addition, Studies with plasma esterases demonstrated that plitidepsin experiences a moderate clearance by these plasma enzymes.
- The sponsor states that following a single-dose administration of ^{14}C-labeled plitidepsin, a majority of the radioactivity excreted up to 20 days was recovered in the faeces (70% of the dose). Smaller amounts were recovered up to 10 days in the urine (6% of the dose), where most of the radioactivity recovered in urine was unchanged drug (75%). Taken together, these findings reflect a moderate metabolism of plitidepsin in vivo.
- The sponsor states that a small fraction of plitidepsin dose is excreted in the urine as unchanged drug, indicating minimal impact of renal impairment on the overall excretion of plitidepsin. In addition, the PK parameters of plitidepsin are not dependent on the creatinine clearance of patients with mild (creatinine clearance 60 to < 90 mL/min) or moderate (creatinine clearance < 60 mL/min) renal impairment. Dose adjustment is not recommended by the sponsor.
- A formal clinical study to evaluate the impact of hepatic impairment on the PK of plitidepsin was not performed.
- No formal drug-drug interaction studies have been conducted.

The clinical evaluator concluded that the submitted PK studies in patients with other malignancies did not trigger concerns and concluded that the PK aspects of the proposed PI was evaluated and found to be acceptable. In my view, the lack of formal drug-drug interaction studies is a limitation of the pharmacology data currently available.

Question for sponsor: Are any formal drug-drug interaction studies planned for plitidepsin?

Population pharmacokinetics (PopPK)

A separate evaluation of the population pharmacokinetic (popPK) data was completed. Key conclusions of the final evaluation:

- Overall, the conclusions of the report are supported by the analysis and no significant issues arose that contradict the sponsor's findings.
- Plitidepsin pharmacokinetics was found to be significantly altered by disease status (relapsed and refractory MM versus non relapsed and refractory MM) and the assay method used to measure plitidepsin concentrations. Other patient characteristics, including body size, were not found to impact plitidepsin pharmacokinetics.
  - Plitidepsin clearance (CL) and central volume (V1) were found to be significantly impacted by disease status (relapsed and refractory MM versus non relapsed and refractory MM).
  - The assay method ('Medeval' versus 'Mario Megri' Techniques) had a significant impact on plitidepsin plasma and blood concentrations.
  - No other statistically important covariates were identified.

- Binding of plitidepsin to blood cells is not expected to significantly impact plitidepsin concentrations at the dose recommended for the Australian Product Information (5 mg/m^2 every 2 weeks).
- Based on the median exposure predicted from the final model, plitidepsin would not be expected to accumulate in either plasma or blood in most patients with repeated dosing of 5 mg/m^2 every 2 weeks.
- No changes to the text of the draft Plitidepsin PI were proposed.

Overall, the PopPK evaluation concluded that there were no significant issues found that would affect the main findings.

Pharmacodynamics (PD)

The clinical evaluation report did not consider the pharmacodynamics of plitidepsin. Key findings of the clinical data include:

- Plitidepsin exposure (plasma AUC) predicts part but not all (63%) of the overall plitidepsin effect on PFS, and a minor part (2%) of the overall response rate (ORR), with 5 mg/m^2 administered by IV route during 3 h infusion in relapsed and refractory MM patients.
- The impact of plitidepsin exposure on transient transaminase elevation was assessed through the development of PK/PD model for ALT, as an indicator of hepatocyte leakage. This model indicated that a reduction of haematocrit is associated with an increase in plitidepsin plasma concentration, which in turn increases the ALT elevation. Stochastic simulation projects that the incidence of Grade ≥ 3 ALT elevation following plitidepsin 5 mg/m^2 on a biweekly basis is 33.4%, which is approximately 27% higher than the incidence of this toxicity in patients with haemoglobin ≥ 10 g/dL. This finding appears to conflict with the finding of the population PK analysis which indicated that binding of plitidepsin to blood cells is not expected to significantly impact plitidepsin concentrations.
- A pooled dataset was used for univariate and multivariate logistic regression analysis for CPK toxicity. Plitidepsin increased the risk of having grade ≥ 3 CPK elevation in relapsed and refractory MM patients up to 18.2% (95% confidence interval (CI): 13.2-24.5%).
- The effects of plitidepsin on the QTc interval were evaluated in a multicentre, single arm, uncontrolled QTc substudy, nested at the Phase III clinical Study APL-C-001-09 (ADMYRE). Evaluable ECG data was available for seven patients only and no patient had a QTc exceeding 500 ms or an increase from baseline in QTc exceeding 60 ms at any point. This data is not sufficient to rule out an effect of plitidepsin on QT interval.

Efficacy

The pivotal efficacy study submitted by the sponsor was Study APL-C-001-09 (ADMYRE). Supportive studies included the Phase II Study APL-B-014-03 and two Phase I studies, Study APL-A-009-08 and Study APL-A-012-13, which investigated plitidepsin in the same disease setting (relapsed and refractory MM) but combined with bortezomib and DXM.

Pivotal Study APL-C-001-09 (ADMYRE)

The pivotal Study APL-C-001-09 (ADMYRE) was described in detail in the clinical evaluation report. This was a Phase III multi-centre, prospective, randomised, open label study of plitidepsin in combination with DXM (Arm A, n = 167) versus DXM alone (Arm B, n = 83); in patients with relapsed and refractory MM. A total of 255 adults were randomised and 250 treated across both arms. Eligible subjects were diagnosed with MM

based on IMWG diagnostic criteria, which are relapsed or relapsed and refractory after at least three, but not more than six, prior therapeutic regimes for MM. Of note, the previous regimes must have included bortezomib containing and lenalidomide containing regimens (or thalidomide, where lenalidomide was not available), unless unable to tolerate either of them. Prior regimes also included induction therapy and stem cell transplantation in candidate patients, which were considered as only one regimen. All patients were required to meet an ECOG PS of ≤ 2 and life expectancy of ≥ 3 months.

Median time from first diagnosis to first study drug administration was 73.0 and 70.1 months in Arms A and B, respectively. The majority of patients had secretory MM at baseline (89.9% and 97.6 %, respectively). The proportion of patients with relapsed MM, refractory MM, and relapsed and refractory MM were comparable between treatment arms (relapsed: 19.9% in Arm A versus 17.9% in Arm B; refractory: 41.5% versus 46.4%; relapsed and refractory: 32.2% versus 27.4%). Median number of lines of previous systemic treatment was 4 in both groups.

In both arms, DXM 40mg was given orally on Days 1, 8, 15 and 22 every four weeks (Q4W). In Arm A, plitidepsin 5 mg/m^2 was also given by IV infusion over three h (fixed rate) on Days 1 and 15 Q4W.

The primary objective of the study was to compare the efficacy of plitidepsin plus DXM versus DXM alone, as measured by progression-free survival (PFS), in patients with relapsed and refractory MM. Secondary objectives included: to evaluate tumour response according to the International Myeloma Working Group (IMWG) criteria; to assess duration of response (DR) and OS; to assess efficacy in patients who underwent crossover from DXM alone to plitidepsin plus DXM combination; to characterise and compare the safety profile of both arms in this population.

Primary efficacy analysis based on the blinded IRC assessment of all randomised patients showed that there was a statistically significantly longer median PFS with plitidepsin plus DXM (2.6 months; 95% CI: 1.9 to 3.0 months) compared to DXM alone (1.7 months; 95% CI: 1.1 to 2.0 months) (log-rank p = 0.0054) (Table 12). The relative risk of progression or death was reduced by 35.0% in patients treated with plitidepsin plus DXM compared to patients treated with DXM alone (HR = 0.650; 95% CI: 0.477-0.885, p = 0.0062).

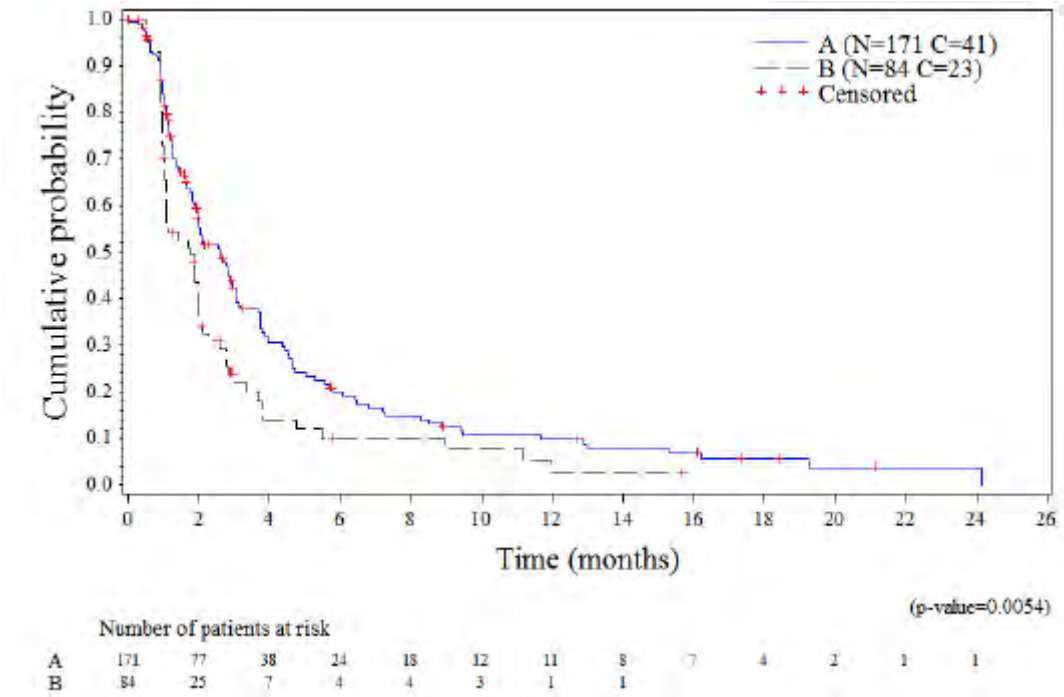
Table 12: Progression-free survival: Independent Review Committee-All Randomised Patients (primary analysis) (Study APL-C-001-09/ADMYRE)

	Arm A (P+DXM)	Arm B (DXM)	Parameter	p-value
n	171	84	-	-
Number of events	130 (76.0%)	61 (72.6%)	-	-
Censored	41 (24.0%)	23 (27.4%)	-	-
Median	2.6	1.7	Log-rank: 7.746	LR:0.0054
(95% CI)	(1.9-3.0)	(1.1-2.0)	HR *: 0.650 95%CI (0.477-0.885)	HR *:0.0062
PFS at 6 months	20.0%	10.0%	Diff: 10.0%	0.0618
(95% CI)	(13.1-26.9%)	(2.0-18.0%)		

Data shown are n of randomised patients (%) except for median (months) and PFS at 6 months.
* HR: Arm A compared to Arm B. HR and p-value as determined by Cox regression.
CI, confidence interval; Diff, difference between Arm A and Arm B; DXM, dexamethasone; HR, hazard ratio; LR, unstratified log-rank test; P, plitidepsin; PFS, progression-free survival.

The Kaplan-Meier curves for PFS showed separation between the 2 arms before Month 2 of treatment in favour of the plitidepsin plus DXM arm, with separation over the course of the study (see Figure 2).

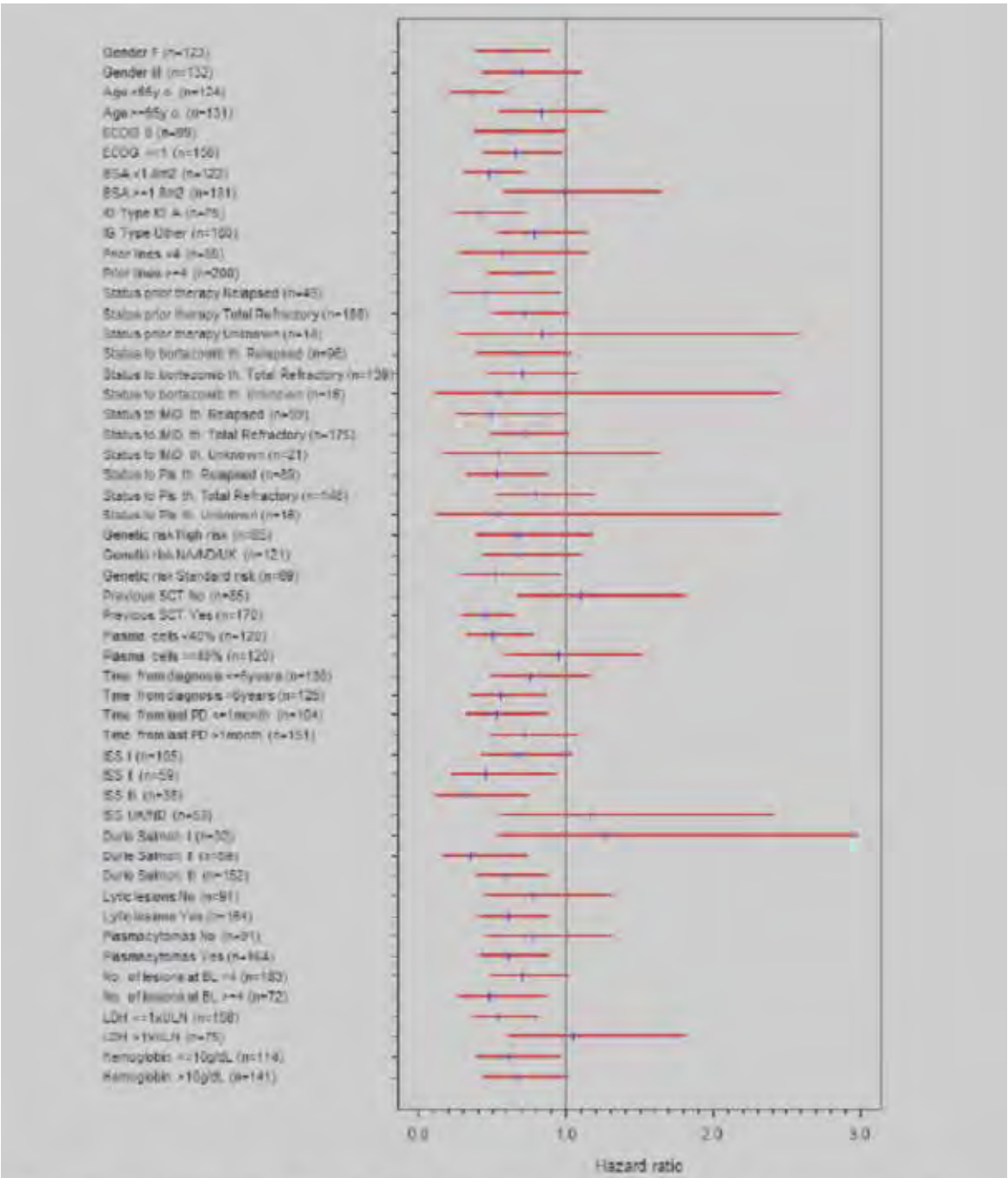
Figure 2: Kaplan-Meier plot of progression-free survival (Independent Review Committee–All Randomised Patients: primary analysis) (Study APL-C-001-09/ ADMYRE)



The sponsor considered that an additional factor in understanding the PFS outcome was the variation in progression criteria by International Myeloma Working Group (IMWG) over time. The sponsor considered as to whether a single assessment was sufficient, or if a second, confirmatory assessment was required to conclude progression. The analysis of this variation included 'a pre-planned sensitivity analysis done in the All Randomized Patients 'dataset with confirmation of PD by IRC, which showed a more substantial increase in median PFS. An updated analysis was undertaken, resulting in lower levels of censoring (38.6% and 40.5% of patients in Arm A and B, respectively) and showing a median PFS of 3.8 months (95% CI, 2.9-5.6 months) in Arm A and 1.9 months (95% CI, 1.1 to 2.7 months) in Arm B (HR = 0.611; 95% CI, 0.434 to 0.860).

Pre-planned subgroup analyses of progression free survival by subgroup, based on the Independent Review Committee assessment in All Randomised Patients were completed (see Figure 3 below). The sponsor's interpretation of this data is that '*PFS benefit of plitidepsin plus DXM was consistent across a series of pre-planned subgroup analyses, demonstrating a consistent treatment effect in favour of Arm A (plitidepsin plus DXM) across clinically relevant subgroups…, then suggesting that this treatment effect was robust and widely achieved in the whole population*.' However, key patient characteristics that influenced PFS and demonstrated no statistical difference were identified in this analysis. This includes including: age; body surface area; < 4 prior lines of therapy; patients who have not undergone SCT; plasma cells ≥ 40%; patients without lyctic lesions or plasmacytosis and; patients with LDH > 1 x ULN. For a full list, please see Figure 3 below.

Figure 3: Forest plot of progression-free survival by subgroup, based on the Independent Review Committee assessment in All Randomised Patients



The central vertical line denotes a HR of 1. Each black mark denotes an individual HR and the horizontal red lines their 95% CI. HR <1 indicates lower risk of the event in Arm A (plitidepsin plus DXM) relative to Arm B (DXM). Results reach statistical significance (at a 5% significance level) if the red line does not cross the vertical line.
BL, baseline; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; F, female; IMiD, immunomodulatory drugs; ISS, International Staging System; LDH, lactate dehydrogenase; M, male; NA, not available; ND, not done; PD; progressive disease; PI, proteasome inhibitors; SCT, stem cell transplantation; th., therapy; UK, unknown; y.o., years old.

Question for sponsor: The multivariate analysis of PFS presented on page 106/3709 of the APL-C-001-09 Clinical Study Report investigated a parameter titled '≥ 65 years better than < 65 years '. The results of this multivariate analysis indicate that the HR was 0.642 with statistical significance. Could you [the sponsor] please clarify the calculation of this result and how this compares to the data presented in Figure 3 above indicating that the PFS difference for patients ≥ 65 years did not reach statistical significance.

The results of secondary efficacy analyses are described in the clinical evaluation report. Key results include:

- ORR (including MR) was statistically significantly higher in the plitidepsin plus DXM arm (22.8%; 95% CI, 16.8 to 29.8%) than in the DXM arm (3.6%; 95% CI, 0.7 to 10.1%) ($p < 0.0001$). ORR (excluding MR) was also statistically significantly higher in the plitidepsin plus DXM arm than in the DXM arm (9.9% versus 1.2%, $p = 0.0085$).
- Median duration of response as determined by the IRC in responding patients was 3.7 months (95% CI, 2.7 to 10.5 months) in Arm A (plitidepsin plus DXM) versus 1.8 months (95% CI, 1.8 to 5.5 months) in Arm B (DXM), but the difference was not statistically significant ($p = 0.1015$).
- The results of the first (interim) OS analysis (presented in the study report), performed concomitantly with the final PFS analysis (data cut-off date of 20 November 2015), showed that the difference in median OS between Arm A (plitidepsin plus DXM) and Arm B (DXM only) was not statistically significant (11.3 months [95% CI, 8.7 to 16.1 months] in Arm A versus 8.1 months [95% CI, 6.0 to 18.4 months] in Arm B; log-rank $p = 0.5649$). The HR showed a 9.1% reduction in the relative risk of death for patients treated in Arm A (plitidepsin plus DXM) (HR = 0.909; $p = 0.5654$).

It was anticipated that the potential for this trial to detect statistically significant differences in OS between the two treatment arms would be hampered by the protocol-defined crossover of patients from Arm B to Arm A. Pre-planned sensitivity analyses were therefore done to improve the characterisation of the actual impact of crossover in those patients who switched from DXM (Arm B) to plitidepsin plus DXM (Arm A). The first pre-planned sensitivity analysis excluded the patients who crossed over and the second pre-planned sensitivity analysis censored survival at the time of crossover. Results of these 2 analyses confirmed an effect of crossover on OS results, showing a greater reduction in the relative risk of death for patients treated in Arm A compared to the main analysis. The exclusion of the 37 patients who crossed over from Arm B to Arm A resulted in a 38.6% reduction in the relative risk of death for patients treated in Arm A (plitidepsin plus DXM) (HR = 0.614; $p = 0.0112$). Censoring of patients who crossed over resulted in a 17.1% reduction in the relative risk of death for patients treated in Arm A (plitidepsin plus DXM) (HR = 0.829; $p = 0.3333$).

The final OS analysis was presented in the addendum report with data cut –off of 19 May 2017. This analysis was based on 195 death events (that is 76.5% of the 255 randomised patients). The final OS analysis showed that the difference in median OS between Arm A (plitidepsin plus DXM) and Arm B (DXM only) was not statistically significant (11.6 months [95% CI, 9.2 to 16.1 months] in Arm A versus 8.9 months (95% CI, 6.0 to 15.4 months) in Arm B; log-rank $p = 0.1261$). The HR showed a 20.3% reduction in the relative risk of death for patients treated in Arm A (plitidepsin plus DXM) (HR = 0.797; $p = 0.1273$).

Additional Delegate comments regarding the pivotal study:

- The median age was 64 and 65 years in Arms A and B, respectively. The median age is not representative of the general myeloma population in Australia, or the sub population who are identified as relapsed/ refractory MM after at least three therapies. Considering the higher median age at first diagnosis in Australia together with the median time from diagnosis for study subjects within the study at 73.0 and 70.1 months in Arm A and B respectively; it is reasonable to consider that the age of the study population is a source of bias limiting generalisability of the findings. Further to this, PFS subgroup analysis based on age ≥ 65years demonstrated no statistically significant difference in PFS between the two arms.

- The choice of comparator must be interpreted with caution. In recent years, a number of new therapies have been introduced which has changed clinical practice and therapeutic options in this setting. Currently, only a subset of patients with relapsed or relapsed and refractory MM would be treated with DXM alone. The TGA advisory committee's advice and opinion on how to interpret this efficacy data in light of choice of comparator has been requested. In particular, advice has been requested on how this efficacy data can be generalised to the Australian public.
- There was missing information on cytogenetic risk. Overall, 57.9% of patients in Arm A and 57.3% of patients in Arm B did not have information on cytogenic risk grouping at baseline (Study APL-C-001-09/ADMYRE Clinical Study Report).
  - Progression-free survival by subgroup analysis of cytogenic risk demonstrated no statistically significant difference for patients with high risk cytogenics, or patients with unknown/not done/unavailable data. A statistically significant difference in PFS could only be demonstrated for patients with standard risk cytogenics (n = 69).
  - This is particularly important in an application where the benefit risk equation is marginal and toxicities are noted.
- The sponsor did not provide a clear definition of 'relapsed or relapsed and refractory multiple myeloma'. The clinical evaluator also noted that throughout the submitted dossier, a variety of terms were used interchangeably: relapsed and refractory; relapsed and/or refractory; relapsed or relapsed and refractory. In the EMA Rapporteur Meeting for Aplidin on 27 June 2016, the sponsor, in responding to queries on the definitions, stated that '*Relapsed MM was defined as previously treated myeloma that progressed and required the initiation of salvage therapy but did not meet the criteria for either 'refractory 'or 'relapsed and refractory 'myeloma categories. Total refractory MM included two categories of refractory myeloma: Refractory MM was defined as disease that was non-responsive in patients who had never achieved a MR or better, with any therapy. It included patients who never achieved MR or better, in whom there was no significant change in monoclonal protein (M-protein), and no evidence of clinical progression, as well as primary, refractory PD where patients met criteria for true PD. Relapsed and refractory MM was defined as disease that was non-responsive while on salvage therapy, or progressed within 60 days of the last therapy in patients who had achieved 'minor response 'or better at some point previously before progressing*'.
- It is noted that the study did not assess quality of life data. This may have contributed to the understanding of the patient experience and also the benefit/risk profile of plitidepsin. The adverse drug reactions of plitidepsin coupled with its mode of administration by IV infusion could potentially affect the patient's perception of their quality of life. Conversely, if the quality of life was perceived by patients to not have been reduced despite the adverse drug reactions and mode of administration, this could also aid in the evaluation of the benefit/risk profile of plitidepsin. The open label non-blinded structure of the trial may have also impacted on the interpretation of quality of life data.

Question for ACM: What is the Committee's impression of the choice of comparator selected for the pivotal study? How might this impact on the generalisability of these results to the Australian public with relapsed and refractory MM?

Supportive efficacy studies

Three supportive efficacy studies were submitted. These were:

1. Study APL-B-014-03, a Phase IIa multicentre, open label, exploratory study of plitidepsin 5 mg/m^2 administered as a 3 h IV infusion Q2W, alone or in combination with DXM in patients with relapsed and refractory MM (n = 53).
2. Study APL-A-009-08, a multicentre, open label, dose escalating Phase I trial of plitidepsin in combination with bortezomib and DXM in patients with relapsed and refractory MM (n = 3).
3. Study APL-A-012-013, open label, dose-ranging, uncontrolled, Phase I clinical trial conducted to determine the recommended dose (RD) of a combination of plitidepsin administered as a 3 h IV infusion on Days 1 and 15, bortezomib administered as a subcutaneous (SC) injection on Days 1, 4, 8 and 11, and DXM administered orally on Days 1, 8, 15 and 22, Q4W to adult patients with relapsed and refractory MM (n = 22).

The results of these studies are described in the clinical evaluation report. Overall, the small sample sizes, heterogeneity in plitidepsin administration and differences combination therapies must be noted when interpreting this data. Of the 53 patients enrolled in Study APL-B-014-03, 51 received treatment with single-agent plitidepsin and 19 patients had DXM added to treatment following a protocol amendment. Median PFS was 2.3 months with plitidepsin alone and 3.8 months with plitidepsin plus DXM. The increased median PFS with the plitidepsin plus DXM combination in comparison with single agent plitidepsin was statistically significant (log rank p = 0.0058). The sponsor acknowledged that this finding could be biased by several factors, such as the possibility of DXM addition after the amendment in patients with suboptimal response to plitidepsin, and slight differences between populations in the number and type of agents received before inclusion into the study, and that this precluded any formal comparison of values.

Safety

The safety dataset for the use of plitidepsin with DXM in MM patients was drawn mainly from the Phase III pivotal study (Study APL-C-001-09), with supportive data from the Phase II Study APL-B-14-03. Other studies which provided safety data were the 2 Phase I Studies APL-A-009-08 and APL-A-012-13, conducted in MM study population but with the use of plitidepsin with bortezomib. In addition, the sponsor provided a secondary safety dataset, comprising of pooled integrated safety data (527 patients, 356 with haematological malignancies and 171 with solid tumours), with data from the Phase III study with plitidepsin in MM (Study APL-C-001-09) as well as 14 Phase II studies and 6 Phase I studies with plitidepsin in different indications. Key findings from this data are discussed in this overview.

Overall, the major toxicities of plitidepsin plus DXM combination consist of GI disorders (nausea, vomiting, diarrhoea), general disorders (fatigue), metabolic/nutritional disorders (decreased appetite), musculoskeletal disorders (myalgia, muscular weakness), haematological and biochemical (CPK, ALT or AST) laboratory abnormalities. The clinical evaluator emphasised the results of the Phase III pivotal Study APL-C-001-09.

Key findings from the safety dataset from the pivotal Study APL-C-001-09 include the following:

- A greater frequency of Grade ≥ 3 AE's regardless of relationship with the study treatment was noted in patients treated with plitidepsin plus DXM (arm A) compared to DXM alone (Arm B) (83.2% in Arm A versus 63.9% in Arm B) (Table 13 below).
- AE's leading to treatment discontinuation (regardless of relationship with the study treatment) was higher in patients treated with plitidepsin plus DXM (Arm A) compared to DXM alone (Arm B) (25.1% in Arm A versus 14.5% in Arm B) (Table 13 below).

- The rate of patients with AEs that led to patient's death (regardless of relationship with the study treatment) was 13.2% in Arm A and 6.0% in Arm B. The rate of treatment related deaths was 0.6% in Arm A (1/167 patients) and 1.2% in Arm B (1/83 patients).
  - The treatment related death in Arm A was due to rhabdomyolysis (Study APL-C-001-09 ADMYRE).
  - Two patients in Arm A died due to causes with unknown relationship with the study treatment (Escherichia sepsis, and cardiac arrest).
- The percentage of patients with at least one treatment related AE was higher in Arm A (plitidepsin plus DXM; 86.2%) than in Arm B (DXM; 45.8%). The most commonly reported treatment related AEs in Arm A were nausea (37.1% versus 10.8% in Arm B) and fatigue (36.5% versus 8.4%). The majority of these commonly reported treatment related AEs in Arm A were of severity Grades 1 or 2. The incidence of Grade ≥ 3 treatment related nausea in Arm A was 3.6% (versus 1.2% in Arm B). The incidence of Grade ≥ 3 treatment related fatigue in Arm A was 10.8% (versus 1.2% in Arm B).

Types of Adverse Events:

- In Arm A, the most common AE's (all grades, regardless of relationship with the study treatment) were general disorders (fatigue 53.9% versus 37.3% in Arm B), GI disorders (nausea 49.1% versus 22.9% in Arm B, and diarrhoea 35.9% versus 9.6%), blood and lymphatic system disorders (anaemia 44.3% versus 43.4% in Arm B).
- In Arm B (DXM), the most common AEs (all grades) regardless of relationship with the study treatment were blood and lymphatic system disorders (anaemia, 43.4%), general disorders (fatigue, 37.3%), musculoskeletal and connective tissue disorders (bone pain 27.7% in Arm B versus 6.6% in Arm A) and GI disorders (nausea, 22.9%).
- The most common Grade ≥ 3 AEs regardless of relationship with the study treatment in Arm A were anaemia (n = 59, 35.3%), blood CPK increase (n = 26, 15.6%), and fatigue (n = 20, 12.0%). In Arm B this was found to be anaemia (n = 35, 42.2%), fatigue (n = 9, 10.8%), thrombocytopenia (n = 8, 9.6%), and back pain (n = 6, 7.2%).
- A subgroup analysis by age was completed across three age groups, 18-64 years (n = 106), 65-74 (n = 68), 75-85 (n = 30). Overall, this analysis demonstrated a higher rate of AEs in patients aged ≥ 65 compared to patients aged < 64. More specifically, this trend was evident for the rates of Grade ≥ 3 treatment related AE's, treatment related SAE's, treatment related Grade ≥ 3 SAE's, treatment related AE's leading to treatment discontinuation, death, death within 30 days of last dose and death within 60 days of first plitidepsin dose.

Table 13: Summary of AEs regardless of relationship with the study treatment (Study APL-C-001-09/ ADMYRE)

	Arm A (P+DXM)		Arm B (DXM)	
	n	%	n	%
n	167		83	
AEs regardless of relationship	166	99.4	81	97.6
Grade ≥3 AEs regardless of relationship	139	83.2	53	63.9
AEs regardless of relationship leading to treatment discontinuation	42	25.1	12	14.5
AEs regardless of relationship leading to death	22	13.2	5	6.0

Data shown are n (%) of treated patients.
AE, adverse event; DXM, dexamethasone; P, plitidepsin; q4wk, every four weeks.

The Integrated Safety Analysis (ISA) was presented which combined all Phase III and II plitidepsin data. Additional findings include:

- In patients with haematological malignancies, the most common AE's (by System Organ Class) regardless of relationship with the study treatment in all dose groups

were reported from GI disorders (72.5%) or n = 258/356) general disorders and administration site conditions (78.7% n = 280/356), and musculoskeletal and connective tissue disorders (62.1% or n = 221/356).

  - In the plitidepsin plus DXM group, the most common AEs regardless of relationship with the study treatment were fatigue (54.4%), nausea (48.0%), anaemia (46.6%), diarrhoea (33.8%), vomiting (26.5%), pyrexia (22.5%), and decreased appetite (20.6%).

- In patients with haematological malignancies, 29.8% (n = 106/356) of patients experienced Grade 3 or 4 severity AEs related to 'Blood and lymphatic system disorders '(regardless of cause).
- In patients with haematological malignancies, 21.9% (n = 78/356) of patients experienced Grade 3 or 4 severity AEs related to 'infections and infestations '(regardless of cause). A total of 2.5% (n = 9/356) experienced Grade 5 severity 'infections and infestations '(regardless of cause).
- The rate of treatment related AEs (including those of unknown relationship) in patients with haematological malignancies was 82.6% (n = 294/356). The rate of Grade ≥ 3 (including those of unknown relationship) AEs was 44.1% (n = 157/356) (see Table 14 below).
- Overall, 10.7% (n = 38/356) of treatment related AEs lead to treatment discontinuation (See Table 14 below).
- A total of 2.0% (n = 7/356) of treatment related AEs lead to death (see Table 14 below).

Table 14: Summary of treatment related AEs (including AEs with unknown relationship) (Integrated Safety Analysis, Phase III and II data)

		Group A (P+DXM) APL-C-001-09		Group B (P) D1,15 q4wk		Group C (P) D1,8,15 q4wk		Overall phase II P single-agent (B+C)		Overall (A+B+C)	
		n	%	n	%	n	%	n	%	n	%
Haematological	**n**	204		63		89		152		356	
	Treatment-related AEs [a]	175	85.8	55	87.3	64	71.9	119	78.3	294	82.6
	Grade ≥3 treatment-related AEs [a]	109	53.4	26	41.3	22	24.7	48	31.6	157	44.1
	Treatment-related AEs leading to treatment discontinuation [a]	22	10.8	8	12.7	8	9.0	16	10.5	38	10.7
	Treatment-related AEs leading to death [a]	3	1.5	2	3.2	2	2.2	4	2.6	7	2.0
Solid tumours	**n**			132		39		171		171	
	Treatment-related AEs [a]			107	81.1	35	89.7	142	83.0	142	83.0
	Grade ≥3 treatment-related AEs [a]			44	33.3	17	43.6	61	35.7	61	35.7
	Treatment-related AEs leading to treatment discontinuation [a]			26	19.7	13	33.3	39	22.8	39	22.8
	Treatment-related AEs leading to death [a]			2	1.5	1	2.6	3	1.8	3	1.8
Total	**n**	204		195		128		323		527	
	Treatment-related AEs [a]	175	85.8	162	83.1	99	77.3	261	80.8	436	82.7
	Grade ≥3 treatment-related AEs [a]	109	53.4	70	35.9	39	30.5	109	33.7	218	41.4
	Treatment-related AEs leading to treatment discontinuation [a]	22	10.8	34	17.4	21	16.4	55	17.0	77	14.6
	Treatment-related AEs leading to death [a]	3	1.5	4	2.1	3	2.3	7	2.2	10[b]	1.9

Data shown are n (%) of treated patients.
[a] Including AEs with unknown relationship.
[b] Two of these 10 patients with AEs leading to death had treatment-related AEs: grade 4 myopathy in patient [redacted] (Group A, APL-C-001-09, ADMYRE), and grade 5 multi-organ failure in patient [redacted] (Group C, APL-B-006-02). The other eight patients had AEs with unknown causality. The first two cases are further explained in Section 3.1.5.2 and Section 3.2.
Group A: plitidepsin 5 mg/m^2 as a 3-hour i.v. infusion on D1 and 15 q4wk plus DXM 40 mg orally on D1, 8, 15 and 22, q4wk. Includes analysis from 167 patients who were treated in Arm A, and 37 patients who crossed over from Arm B (DXM) to Arm A (plitidepsin plus DXM) (only data from cycles with the combination are included in this analysis). All 204 patients had relapsed/refractory MM.
Group B: plitidepsin fortnightly schedule (D1 and 15, q4wk). Haematological malignancies included relapsed/refractory MM (n=51) and myelofibrosis (n=12). Solid tumours included bladder (n=21), exocrine pancreas (n=19), head and neck (n=10), melanoma (n=37), MTC (n=16), NSCLC (n=21), and prostate (n=8).
Group C: plitidepsin weekly schedule (D1, 8 and 15, q4wk). Haematological malignancies included leukaemia (n=17), NHL (indolent, n=8), and NHL (aggressive, n=64). Solid tumours included melanoma (n=20) and SCLC (n=19).
AE, adverse event; D, day; DXM, dexamethasone; MM, multiple myeloma; MTC, medullary thyroid carcinoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; P, plitidepsin; q4wk, every four weeks; SCLC, small cell lung cancer.

In patients with haematological malignancies treated with plitidepsin plus DXM, the most common treatment related AEs were reported from GI disorders (52.9% of patients), general disorders and administration site conditions (48.5%), investigations (42.2%), and musculoskeletal and connective tissue disorders SOCs (27.9%). By Medical Dictionary for Regulatory Activities (MedRA) Preferred Term, the most common treatment related AEs were nausea (36.3%), fatigue (34.8%), blood CPK increased (17.6%), vomiting (16.2%), diarrhoea (15.2%), ALT increased (15.2%), myalgia (12.7%), and decreased appetite (12.7%). The rate of treatment related Serious Adverse Events (SAE's) was 28.1% (n = 47/167) in this group, with 20.4% grade ≥ 3 SAE's, 6.0% leading to treatment discontinuation and 1.8% leading to death. The most common treatment related SAE's were ALT increase (3.9%), pneumonia (3.4%), and AST increase and CPK increase (3.4% each).

A subgroup analysis by age was completed for the Integrated Safety Analysis (Phase III and II data). Overall, the incidence of severe AE's and SAE's was lower in patients aged ≤ 64 years compared to patients aged ≥ 65 years across all three dose groups analysed. This trend was present for both groups of patients (treated with plitidepsin in combination with DXM versus all patients exposed to plitidepsin). Specifically, a higher rate of AEs in patients aged > 65 compared to patients aged < 64. More specifically, this trend was evident for the rates of Grade > 3 treatment related AE's, treatment related SAE's, treatment related grade > 3 SAE's, treatment related AE's leading to treatment discontinuation, death, death within 30 days of last dose and death within 60 days of first plitidepsin dose.

Hypersensitivity reactions

A total of five hypersensitivity reactions occurred in the pivotal study in the plitidepsin + DXM arm. Grade 1/2 was observed in five patients and Grade 3 in three patients (6.1%) (Study APL-C-001-09/ADMYRE). Of these five events, three were referred to as 'drug hypersensitivity ', one of which was Grade 2 severity and considered treatment related (Study APL-C-001-09/ADMYRE). Two hypersensitivity reactions were considered treatment related and was classed as Grade 2 severity and one as Grade 3 severity (Study APL-C-001-09/ADMYRE).

Of these events, one patient had Grade 4 anaphylactic shock concomitant with Grade 4 cardiac arrest that were reported as SAEs and caused treatment discontinuation. This patient was administered the first dose of plitidepsin after crossing over from Arm B (DXM) to Arm A (plitidepsin plus DXM) during Cycle 16. Another patient had Grade 3 infusion related reaction with Grade 3 hypoxia, required hospitalisation, and led to treatment discontinuation. With respect to skin and subcutaneous reactions, one patient in Arm A had Grade 3 rash in the first cycle that required reduction of plitidepsin dose.

Overall, the rate of hypersensitivity reactions in the pivotal study appears to be approximately 3.9%. The hypersensitivity events reported across all patients exposed to plitidepsin was also presented (see Table 15). Overall, this data indicates a rate of hypersensitivity reactions of approximately 8%, noting that varied dose regimes are utilised. The sponsor reports that 11 patients (11/527 = 2.1%) required hospitalisation for the events shown in Table 15. The sponsor states that no patients have been reported to have a fatal outcome.

Table 15: Hypersensitivity reported as treatment related AE (including AEs with unknown relationship) (Integrated Safety Analysis, Phase III and II data, total patients)

MedDRA PT	Group A (P+DXM) APL-C-001-09				Group B (P) D1,15 q4wk				Group C (P) D1,8,15 q4wk				Overall phase II P single-agent (B+C)				Overall (A+B+C)			
	NCI-CTCAE grade				NCI-CTCAE grade				NCI-CTCAE grade				NCI-CTCAE grade				NCI-CTCAE grade			
	1/2		3/4		1/2		3/4		1/2		3/4		1/2		3/4		1/2		3/4	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
n	204				195				128				323				527			
Anaphylactic shock			1	0.5			1	0.5							1	0.3			2[a]	0.4
Drug hypersensitivity	1	0.5															1	0.2		
Flushing	1	0.5			8	4.1			1	0.8			9	2.8			10	1.9		
Hypersensitivity	1	0.5	1	0.5	14	7.2	4	2.1	3	2.3	2	1.6	17	5.3	6	1.9	18[b]	3.4	7[c]	1.3
Infusion-related reaction	2	1.0	1	0.5	1	0.5							1	0.3			3	0.6	1[d]	0.2

Data shown are n (%) of treated patients.
[a] Two events of grade 3/4 anaphylactic shock reported as treatment-related SAEs: one in Group A and one in Group B.
[b] Two grade 1/2 hypersensitivity events were reported as treatment-related SAEs: one in Group B and one in Group C.
[c] Six grade 3/4 hypersensitivity events were reported as treatment-related SAEs: four in Group B and two in Group C.
[d] One event of grade 3/4 infusion-related reaction was reported as treatment-related SAE in Group A.
Group A: plitidepsin 5 mg/m^2 as a 3-hour i.v. infusion on D1 and 15 q4wk plus DXM 40 mg orally on D1, 8, 15 and 22, q4wk. Includes analysis from 167 patients who were treated in Arm A, and 37 patients who crossed over from Arm B (DXM) to Arm A (plitidepsin plus DXM) (only data from cycles with the combination are included in this analysis). All 204 patients had relapsed/refractory MM.
Group B: plitidepsin fortnightly schedule (D1 and 15, q4wk). Haematological malignancies included relapsed/refractory MM (n=51) and myelofibrosis (n=12). Solid tumours included bladder (n=21), exocrine pancreas (n=19), head and neck (n=10), melanoma (n=37), MTC (n=16), NSCLC (n=21), and prostate (n=8).
Group C: plitidepsin weekly schedule (D1, 8 and 15, q4wk). Haematological malignancies included leukaemia (n=17), NHL (indolent, n=8), and NHL (aggressive, n=64). Solid tumours included melanoma (n=20) and SCLC (n=19).
ALT, alanine aminotransferase; CPK, creatine phosphokinase; D, day; DXM, dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities v.18.0; MM, multiple myeloma; MTC, medullary thyroid carcinoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; P, plitidepsin; PT, preferred term; q4wk, every four weeks; SAE, serious adverse event; SCLC, small cell lung cancer.

Rates of infusion related events in the pivotal study were approximately 3% (6/204).

Question for sponsor: Please provide the most recent clinical data regarding the rates of hypersensitivity reactions across all patients exposed to plitidepsin, including severity and outcome.

Question for sponsor: Please clarify why the patient who suffered anaphylactic shock and cardiac arrest was not reported as a Grade 5 SAE?

Question for sponsor: Please clarify why the patient with an infusion related reaction involving hypoxia requiring hospitalisation was classified as Grade 3? This appears to be a life-threatening AE related to an infusion reaction.

Question for sponsor: Please clarify why a total of 8 AEs related to hypersensitivity are recorded in Table 15 above, however in the sponsor's Clinical Summary only 5 cases were reported for the pivotal study.

The cardiac effects of plitidepsin are unclear. Fifty-seven patients with normal LVEF at baseline had abnormal values during treatment, 33 of them being treated in Study APL-C-001-09 (ADMYRE). Within the pivotal study, 17.2% of patients with normal ECG interpretation at baseline had abnormal results during the study. Limitations of the safety data include the in sufficient data regarding the effect of plitidepsin on QT interval. The Risk Management Plan (RMP) evaluation notes that two additional studies are planned, one of which was a QT study. However, it appears that these studies have been included in the current dossier.

Question for sponsor: Are further studies planned to investigate the potential cardiac effects of plitidepsin?

Risk management plan

There were no objections to the registration of plitidepsin (Aplidin) from an RMP perspective. However, two minor issues remained outstanding after the second round

evaluation. These are that the correct accompanying statement (see below) must be included in the CMI next to the black triangle symbol. In addition, the black triangle symbol and statement should be placed at the very top of the first page of the CMI.

> *This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. You can report side effects to your doctor, or directly at* www.tga.gov.au/reporting-problems*.*

The Delegate requested that the sponsor amend these two aspects of the CMI.

Recommendation for sponsor: Please include the correct accompanying statement in the CMI next to the black triangle symbol. In addition, the black triangle symbol and statement should be placed at the very top of the first page of the CMI.

The RMP evaluator also noted that there are two additional pharmacovigilance activities planned (QT Study and a drug interaction study with plitidepsin plus DXM and a strong CYP3A4 inhibitor such as itraconazole). There is no Australian involvement at this stage, but the results are considered to be generalisable to the Australian population.[35]

Recommended conditions of registration

The RMP evaluator recommends the following conditions of registration:

> *The Aplidin EU-Risk Management Plan (RMP) (version 2.0, dated 6 July 2017, data lock point 31 March 2016), with Australian Specific Annex (version 1.2, dated 26 February 2018), included with submission PM-2017-02669-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

As Aplidin is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Aplidin (plitidepsin) is to be included in the Black Triangle Scheme. The PI and CMI for Aplidin must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

[35] All outstanding RMP issues had been addressed at the time of approval.

Risk-benefit analysis

Delegate's considerations

Efficacy

The pivotal Study APL-C-001-09 (ADMYRE) was a Phase III multicentre, prospective, randomised, open label study of plitidepsin in combination with DXM (Arm A) versus DXM alone (Arm B). This study enrolled patients with MM who are relapsed (total of 19.9% in Arm A versus 17.9% in Arm B), refractory (Arm A 41.5% versus Arm B 46.4%) or relapsed and refractory (32.2% Arm A versus 27.4% Arm B); after at least three, but not more than six, prior therapeutic regimes for MM. Of note, the previous regimes must have included bortezomib-containing and lenalidomide-containing regimens (or thalidomide, where lenalidomide was not available), unless unable to tolerate either of them. The median number of lines of previous systemic treatment was 4 in both groups.

Primary efficacy analysis based on the blinded IRC assessment of all randomised patients showed that there was a statistically significantly longer median PFS with plitidepsin plus DXM of 2.6 months (95% CI: 1.9-3.0 months) compared to the median PFS in the DXM alone arm of 1.7 months (95% CI: 1.1 to 2.0 months) (log-rank p = 0.0054). The relative risk of progression or death was reduced by 35.0% in patients treated with plitidepsin plus DXM compared to patients treated with DXM alone (hazard ratio (HR) = 0.650; 95% CI: 0.477 to 0.885, p = 0.0062). The sponsor has argued that the progression criteria by the International Myeloma Working Group (IMWG) have varied over time, thus impacting the ability to understand this primary efficacy endpoint. The sponsor considered as to whether a single assessment was sufficient, or if a second, confirmatory assessment was required to conclude progression. A second (pre-planned) sensitivity analysis on all randomised patients with confirmation of disease progression by IRC showed a more substantial increase in median PFS. This analysis resulted in lower levels of censoring and demonstrated a median difference in PFS of 1.9 months, with a median PFS of 3.8 months (95% CI, 2.9 to 5.6 months) in Arm A and 1.9 months (95% CI, 1.1 to 2.7 months) in Arm B (HR = 0.611; 95% CI, 0.434 to 0.860).

The secondary efficacy endpoint of ORR was statistically significantly higher in the plitidepsin plus DXM arm, regardless of whether MR was included or excluded from the analysis (ORR excluding MR in Arm A was 9.9% versus 1.2% in Arm B, p = 0.0085). Other secondary endpoints including median DOR and OS indicated a positive numerical trend in favour of the plitidepsin plus DXM arm; however the difference did not reach statistical significance. The sponsor has stated that the benefit in OS is underestimated due to the cross-over and it should not be simply disregarded as a 'null 'or 'unfavourable 'outcome. There was some positive effect, expressed by the HR (0.797, log-rank p value = 0.1261) and the CI range (0.596 to 1.067), albeit not reaching a pre-defined statistical boundary.

Although the Delegate agrees with the sponsor that the pivotal study meet its primary endpoint and a *statistically* significant difference in PFS was demonstrated in favour of the plitidepsin plus DXM arm, the Delegate would appreciate the advisory committee's advice on interpreting the *clinical* magnitude of this difference in the Australian setting. It is the Delegate's opinion that this modest improvement in PFS must be interpreted in the context of this heavily pre-treated group of patients; however other factors must also be discussed when interpreting this data.

Firstly, the choice of comparator must be carefully considered in the setting of current standard treatment options for the group of patients with relapsed, refractory and relapsed and refractory MM comprising this pivotal study. It is likely that the comparison to DXM alone is relevant only for a subset of Australian patients today who would be eligible for plitidepsin. This has impact on the generalisability of the results from this

pivotal study to the Australian public. Advice on this choice of comparator and the impact on results interpretation have been requested.

The median time from first diagnosis for this cohort was 73.0 in Arm A and 70.1 in Arm B, with the median age of patients enrolled stated to be 64 and 65 years respectively. This is not representative of the general population of patients with MM in Australia, where the median age of first diagnosis is 70.9 years[36], thus limiting the generalisability of the results to the Australian population. This issue is especially pertinent when considering the results of the pre-planned subgroup analysis of PFS. Here, the results demonstrated that for patients aged ≥ 65 years, the difference in PFS between the two arms did not reach statistical significance.

The performance status and life expectancy of the study population must also be noted. Patients enrolled in the study met an ECOG performance status (PS) ≤ 2 and had a life expectancy of ≥ 3 months. Overall, 59.6% of patients enrolled had an ECOG PS score of 1 to 2, indicating that approximately 40% of patients enrolled in this study had an ECOG PS of 0. The absence of patients with ECOG PS ≥ 2 is considered to be a deficiency in the data. It can be anticipated that in clinical practice, a considerable proportion of patients with relapsed and refractory MM who are likely to be offered treatment with plitidepsin might be categorised with ECOG PS status ≥ 2.

When interpreting efficacy data, the difference in duration of therapy between the two arms was noted. In the plitidepsin + DXM arm, the median time on treatment 12.3 weeks and median number of cycles per patient was 3. In the DXM monotherapy arm, the median time on treatment was 8.3 weeks and median number of cycles at 2. This difference in exposure is likely impacted by the cross-over of patients to the plitidepsin + DXM arm, with the median time on treatment for the crossover population at 10.3 weeks. Other limitations of the data include the large amount of missing information on cytogenic risk.

Question for sponsor: Please clarify if the sensitivity analysis demonstrating a HR for PFS at 0.611 (reported in in your response to questions dated March 2018) was pre-planned. Please direct the TGA to where this data is presented in Study APL-C-001-09 (ADMYRE).

Question for sponsor: Is data available on ECOG PS of patients *during* the treatment duration or ECOG PS against treatment exposure within the pivotal study? Was any shift in ECOG score noted?

Question for the advisory committee: What is the committee's opinion of the efficacy of plitidepsin in combination with DXM? In particular, what is the committee's opinion in the clinical meaning of the PFS benefit with plitidepsin in combination with DXM?

Safety

There is an increase in toxicity with the addition of plitidepsin to DXM. Overall, the major toxicities of plitidepsin plus DXM combination consist of GI disorders (nausea, vomiting, diarrhoea), general disorders (fatigue), metabolic/nutritional disorders (decreased appetite), musculoskeletal disorders (myalgia, muscular weakness), haematological and biochemical (CPK, ALT or AST) laboratory abnormalities.

In the context of the median time on treatment in the pivotal study at 12.3 weeks (median number of cycles = 3), the most frequently reported AEs associated with the plitidepsin+DXM arm were GI disorders (nausea, 37.1% of patients; vomiting, 16.8%; diarrhoea, 14.4%), general disorders (fatigue, 36.5%; oedema peripheral, 12.0%), metabolic/nutritional disorders (decreased appetite, 12.6%), and musculoskeletal disorders (myalgia, 14.4%; muscular weakness, 9.6%). The most common Grade 3/4 AEs

[36] Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW

related to the study treatment (or with unknown causality) were fatigue (n = 18, 10.8%), myalgia (n = 9, 5.4%), muscular weakness (n = 6, 3.6%), and nausea (n = 6, 3.6%).

When compared to the DXM monotherapy group, rate of treatment related AE's was notably higher in the plitidepsin plus DXM group when compared to DXM alone, as was the rate of treatment related serious AEs (SAE's) and treatment related Grade ≥ 3 AE's.

The sponsor states that one may expect an increase in toxicity when a combination is compared to a single agent in the relapsed and refractory setting. The Delegate tends to agree with this general concept, especially when considering the difference in patient exposure between the two arms (see above). However, the rates of AEs in the plitidepsin group, both within the pivotal study and within the integrated safety analysis were significant. Further to this point, the sponsor considered that some of the toxicities are 'more apparent in numbers than severity ', noted the manageability of the toxicities and commented on the 'lack of clinical relevant of most of the observed side effects of this combination '. Once again, the Delegate does not disagree with the general concept of managing side effects through mechanisms such as dose adjustments and information in the PI. However, given: 1) the high rate of AEs leading to discontinuation in the plitidepsin + DXM arm of the pivotal study compared to DXM alone (25.1% versus 14.5% respectively); 2) the higher incidence of treatment related AEs leading to permanent discontinuation of study drug before crossover (9.6% versus 3.6% respectively); 3) the significant proportion of patients in the plitidepsin + DXM arm of the pivotal study who required cycle delays (50.8%), dose omissions (54.5%), dose reductions (33.5%) and; 3) the lack of quality of life data supporting the sponsor's position regarding patient treatment and AE tolerability; it is the Delegate's position that the toxicity experienced with plitidepsin is clinically relevant. The advice on the safety profile of plitidepsin in the context of the risk/benefit balance for Australian patients has also been requested. Other potential impacts on treatment tolerability as perceived by patients are largely unknown, such as the intravenous mode of administration of plitidepsin.

Across both the pivotal study and the Integrated Safety Analysis (ISA), a higher rate of AEs was noted in patients aged ≥ 65 compared to patients aged ≤ 64. More specifically, this trend was evident for the rates of Grade > 3 treatment related AE's, treatment related SAE's, treatment related grade > 3 SAE's, treatment related AE's leading to treatment discontinuation, death, death within 30 days of last dose and death within 60 days of first plitidepsin dose.

The sponsor states that hypersensitivity reactions have been uncommon with plitidepsin; however the rate of hypersensitivity reactions in the pivotal study appears to be approximately 3.9% (8/204). One case of anaphylactic shock and cardiac arrest was reported in the pivotal study. Rates of infusion related events in the pivotal study were approximately 3% (6/204). This is on a background of pre-treatment 20-30 min before infusion of plitidepsin of: Ondansetron 8 mg IV or equivalent (granisetron 3 mg IV preferred when available); Diphenhydramine hydrochloride 25 mg IV or equivalent, and; Ranitidine 50 mg IV or equivalent. All patients also received DXM. The draft PI document for plitidepsin reflects the pre-medication advice as per the pivotal study. The PI also states '*If dexamethasone treatment is discontinued due to toxicity, dexamethasone at a lower dose (8 mg) must be given as premedication for plitidepsin treatment.'* Information regarding infusion reactions is provided under Section 4.2 and information regarding '*injection site reactions and hypersensitivity reactions* ' is provided in 4.4 [of the PI]. Aspects of this information may require amendment following committee's advice regarding the risk/benefit balance of plitidepsin.

Events of myopathy including rhabdomyolysis were noted in the pivotal study, with one case of treatment related rhabdomyolysis which was fatal. In the pooled safety dataset, treatment related blood CPK increases in patients with haematological malignancies occurred in 17.6% of patients. The logistic regression analysis undertaken for CPK toxicity

(relying on the pooled dataset of patients exposed to plitidepsin), showed that plitidepsin increased the risk of having Grade ≥ 3 CPK elevation in relapsed and refractory MM patients up to 18.2% (95%CI: 13.2-24.5%). The risk of myopathy including rhabdomyolosis is identified in the PI, however the fatal case is not recorded under '*Special warning and precautions for use* '. Aspects of this information may require amendment following the committee's advice regarding the risk/benefit balance of plitidepsin.

In the sponsor's response to the negative decision in Europe; the sponsor considered that: '*A clear advantage of Aplidin is the favourable safety profile in terms of haematological toxicity, whereas most of the approved therapies induce moderate to high myelotoxicity. Note also that a proportion of patients in this stage of their disease may have limited marrow reserve or other comorbidities and may not tolerate currently approved therapies* '. Further information and data to support this statement has been requested from the sponsor. Haematological toxicity was still noted with plitidepsin use and the statement regarding comparison to other treatments requires clarification in the Australian context. Furthermore, the committee's advice on the risk/benefit balance in patients with reduced marrow reserve is appreciated.

Question for sponsor: Please provide further clarification, including data for plitidepsin and comparison to 'approved therapies 'in Australia, to support the phrase: *A clear advantage of Aplidin is the favourable safety profile in terms of haematological toxicity, whereas most of the approved therapies induce moderate to high myelotoxicity. Note also that a proportion of patients in this stage of their disease may have limited marrow reserve or other comorbidities and may not tolerate currently approved therapies*.'

Question for ACM: What is the committee's response to the sponsor's comment regarding the safety profile of plitidepsin in patients with reduced marrow reserve?

Indication and risk-benefit

The sponsor proposed an amended wording of indication for plitidepsin in their response; however the PI was not updated to capture this change. The response proposes the following wording:

> *'Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both a proteasome inhibitor and an immunomodulator.'*

Version 20180614_APD_PI_AU_Cat1_MS5-draft PI states:

> *'Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both a proteosome inhibitor and an immunomodulator.'*

This proposed indication is different to the patient population included in the pivotal study. Only 32.2% of patients in the plitidepsin + DXM group (Arm A) of the pivotal study were classed as relapsed and refractory. The pivotal study only included patients after at least three prior therapeutic regimes, with the median number of prior therapies of patients enrolled in the study at 4. This indication is also broader than that proposed in Europe.

The sponsor stated in their response that broadening the indication of plitidepsin to use after two prior therapies was to align with the approved indication for pomalidomide. The clinical data in plitidepsin to support broadening the indication to patients that have received *two* prior therapies is not clear and clarification from the sponsor has been requested. The sponsor's rationale for maintaining class specific wording is that it

provides the physician with flexibility to prescribe plitidepsin regardless of which specific therapeutic agent of each class was used in earlier lines of therapy.

The implications of using plitidepsin in preference to other currently available agents in this setting are not known. It is also not possible to determine if there would be any disadvantage to patients seeking subsequent therapies after plitidepsin or the potential to reduce performance status.

Balanced against the modest benefit in PFS (in a narrower population) and the toxicities associated with the combination of plitidepsin plus DXM; it is not possible to conclude a positive risk-benefit balance for the proposed indication.

Although narrower indications may be considered, this has not been accepted by the sponsor for Australian patients. A restriction of the indication to patients who have received at least three prior therapies was proposed by the clinical evaluator after the first round evaluation; however this was subsequently rejected by the sponsor. Furthermore, limiting to three prior therapies does not sufficiently capture other issues, such as the lack of efficacy benefit for patients who have not received a previous stem cell transplant. The sponsor noted that one European Rapporteur stated that the product could be approvable if the '*indication is restricted to patients with relapsed and refractory myeloma with no available alternative treatment options*.' This wording has potential clinical implications in Australia for the interpretation of appropriate sequencing of therapies for individual patients. Furthermore, this would not reflect the population studied in the pivotal trial. The committee's clinical advice on this is appreciated.

A clear complexity of this submission is the interpretation of the risk-benefit balance in the context of Australian patients with relapsed and refractory MM. Of particular concern is the generalisability of the results in light of the younger age of patients included in the pivotal study, lack of statistically significant PFS benefit for patients aged ≥ 65years and increased AEs in patients aged ≥ 65 years.

Question for sponsor: Please provide further justification and supportive data for broadening the proposed indication to patients who have received at least two prior treatment regimens.

Question for sponsor: Please provide further subgroup analysis of PFS and secondary endpoints for patients who: 1) were classed as 'relapsed and refractory '2) received two prior treatment regimes, 3) classed as 'relapsed and refractory 'and aged ≥ 65 years.

Question for the ACM: What is the committee's opinion of the risk-benefit balance of plitidepsin in the proposed indication? Is there a positive risk-benefit balance for a particular subgroup of Australian patients therefore warranting a narrower indication?

Question for the ACM: What is the committee's opinion of the wording of prior lines of therapy? Does the committee agree with maintaining class-specific wording to allow physician flexibility?

Conclusion

Pre ACM preliminary assessment

Due to the issues identified in this overview, the Delegate's pre-ACM preliminary assessment is that the Delegate is not in a position to say, at this time, that the application for plitidepsin (Aplidin) should be approved for registration.

Request for Advisory Committee on Medicines (ACM) advice

All questions have been placed in the document to allow for the context around each question to be understood. They are repeated here and numbers added for completeness.

1. What is the committee's opinion of the efficacy of plitidepsin in combination with DXM? In particular, what is the committee's opinion in the clinical meaning of the PFS benefit with plitidepsin in combination with DXM?
2. What is the committee's impression of the choice of comparator selected for the pivotal study? How might this impact on the generalisability of these results to the Australian public with relapsed and refractory MM?
3. What is the committee's response to the sponsor's comment regarding the safety profile of plitidepsin in patients with reduced marrow reserve?
4. What is the committee's opinion of the risk-benefit balance of plitidepsin in the proposed indication? Is there a positive risk-benefit balance for a particular subgroup of Australian patients therefore warranting a narrower indication?
5. What is the committee's opinion of the wording of prior lines of therapy? Does the committee agree with maintaining class-specific wording to allow physician flexibility?

Questions for sponsor

All questions have been placed in the document to allow for the context around each question to be understood. They are repeated here and numbers added for completeness.

1. Please provide the most recent clinical data regarding the rates of hypersensitivity reactions across all patients exposed to plitidepsin.
2. Is there any additional data, biopharmaceutical data or justification available to address the issues of the 'lipophilic phase' of plitidepsin and the persistence and fate of the micelles in vivo?
3. Are any formal drug-drug interaction studies planned for plitidepsin?
4. The multivariate analysis of PFS presented in the APL-C-001-09 Clinical Study Report investigated a parameter titled '≥ 65 years better than < 65 years '. The results of this multivariate analysis indicate that the HR was 0.642 with statistical significance. Could you please clarify the calculation of this result and how this compares to the data presented in Figure 3 above indicating that the PFS difference for patients ≥ 65 years did not reach statistical significance?
5. Please clarify why the patient who suffered anaphylactic shock and cardiac arrest was not reported as a Grade 5 SAE?
6. Please clarify why the patient with an infusion related reaction involving hypoxia requiring hospitalisation was classified as Grade 3? This appears to be a life-threatening AE related to an infusion reaction.
7. Please clarify why a total of 8 AEs related to hypersensitivity are recorded in Table 15 above, however the sponsor's Clinical Summary reports only 5 cases for the pivotal study.
8. Are further studies planned to investigate the potential cardiac effects of plitidepsin?
9. Please clarify if the sensitivity analysis demonstrating a HR for PFS at 0.611 (reported in your response to questions dated March 2018) was pre-planned. Please direct the TGA to where this data is presented in Study APL-C-001-09 (ADMYRE).
10. Is data available on ECOG PS of patients *during* the treatment duration or ECOG PS against treatment exposure within the pivotal study? Was any shift in ECOG score noted?

11. Please provide further clarification, including data for plitidepsin and comparison to 'approved therapies 'in Australia, to support the phrase: *A clear advantage of Aplidin is the favourable safety profile in terms of haematological toxicity, whereas most of the approved therapies induce moderate to high myelotoxicity. Note also that a proportion of patients in this stage of their disease may have limited marrow reserve or other comorbidities and may not tolerate currently approved therapies*.'
12. Please provide further justification and supportive data for broadening the proposed indication to patients who have received at least two prior treatment regimens.
13. Please provide further subgroup analysis of PFS and secondary endpoints for patients who: 1) were classed as 'relapsed and refractory '2) received two prior treatment regimes, 3) classed as 'relapsed and refractory 'and aged ≥ 65 years.
14. Please include the correct accompanying statement in the CMI next to the black triangle symbol. In addition, the black triangle symbol and statement should be placed at the very top of the first page of the CMI.
15. Please address the outstanding quality issues identified by the quality evaluator.

Response from sponsor

The sponsor agrees to restrict the indication to that proposed by the clinical evaluator to patients who have received at least *three* prior treatment regimens. However, the sponsor would like to maintain the class specific wording in order to provide the physician with flexibility to prescribe plitidepsin regardless of which specific therapeutic agent of each class was used in earlier lines of therapy. The proposed indication is:

> *Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator.*

The PI has been updated to include the proposed revised indication.

Questions for sponsor

1. *Please provide the most recent clinical data regarding the rates of hypersensitivity reactions across all patients exposed to plitidepsin.*

Sponsor response

The most recent clinical data regarding the rates of hypersensitivity AEs are provided.

2. *Is there any additional data, biopharmaceutical data or justification available to address the issues of the 'lipophilic phase' of plitidepsin and the persistence and fate of the micelles in vivo?*

Sponsor response

Further information and evidence addressing the issues of the 'lipophilic phase' of plitidepsin and the persistence and fate of the micelles in vivo are provided.

3. *Are any formal drug-drug interaction studies planned for plitidepsin*?

Sponsor response

As plitidepsin is mainly metabolised by CYP3A4, potent inhibitors of this enzyme may impact clearance rates of plitidepsin, then resulting in altered plasma exposure. Hence, the use of such agents in combination with plitidepsin should be used cautiously. In order to evaluate the pharmacokinetics and safety of plitidepsin when co-administered with potent CYP3A4 inhibitors, an open label, multicentre, randomised, two-way crossover, drug-drug

interaction study with plitidepsin plus DXM and a strong CYP3A4 inhibitor, such as itraconazole, is planned. The final results will be available no later than October 2020.

4. *The multivariate analysis of PFS presented in the APL-C-001-09 Clinical Study Report investigated a parameter titled '≥ 65 years better than < 65 years '. The results of this multivariate analysis indicate that the HR was 0.642 with statistical significance. Could you please clarify the calculation of this result and how this compares to the data presented in Figure 3 above indicating that the PFS difference for patients > 65 years did not reach statistical significance?*

Sponsor response

The Forest plot shown in in the CSR presented subgroup univariate analyses for the comparison of plitidepsin plus DXM versus DXM alone in each subset, whereas the multivariate analysis shown [table not included in this AusPAR] had more 'dimension 'comparisons. The main effects multivariate analysis included in a first step all the covariates and was followed by a stepwise process in which the most significant covariates were selected. The HR of 0.642 for age is the comparison between '< 65 years versus ≥ 65 years 'category. In addition, treatment arm was also selected as a significant covariate, which means that both variables may be considered independently relevant. In the Question 46 of the EMA's Day 120 List of questionsD120, this query was addressed in a section to examine a potential lack of internal consistency in some subgroups considered important. The sponsor studied each one by means of individual Cox regression adjustments with main effects, and with main effects including its interaction term. The conclusion for treatment arm and age variables was that both remained statistically significant; in the case of treatment arm, this favoured patients in Arm A (plitidepsin plus DXM). Interaction term between them was also relevant, with a clear impact in the DXM arm.

5. *Please clarify why the patient who suffered anaphylactic shock and cardiac arrest was not reported as a Grade 5 SAE?*

Sponsor response

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.0 used for grading the AEs in the ADMYRE study, an event is assessed as Grade 5 when the event's outcome is the death related to such an event. In patient [information redacted] both anaphylactic shock and cardiac arrest events were resolved and, therefore, did not cause the death.

Grade 4 is given for an event with life-threatening consequences and that requires urgent intervention, which was the case for this patient. Based on this information, anaphylactic shock and cardiac arrest were both assessed as Grade 4 by both the Investigator and the sponsor. The patient narrative was provided.

6. *Please clarify why the patient with an infusion related reaction involving hypoxia requiring hospitalisation was classified as Grade 3? This appears to be a life-threatening AE related to an infusion reaction.*

Sponsor response

Patient [information redacted] presented an oxygen desaturation to 88% during the first plitidepsin administration. The infusion was interrupted, and the patient required oxygen supply. Oxygen saturation increased to 93% two hours later, but the patient was admitted to the hospital for observation of the event. After one day of hospitalisation, the patient was discharged as the event was considered resolved.

According to the NCI-CTCAE v.4 used for grading the AEs in the ADMYRE study, Grade 3 hypoxia is defined as 'decreased oxygen saturation at rest (for example, pulse oximeter <88% or partial oxygen pressure (PaO_2) ≤ 55 mm Hg) and Grade 4 hypoxia is defined as

'life-threatening airway compromise; urgent intervention indicated (for example, tracheotomy or intubation) '. In the case of patient [information redacted],hypoxia was not life-threatening and did not require interventional measures such as tracheotomy or intubation. Only oxygen supply was required, the event was resolved in one day and, therefore, the event was considered Grade 3. Infusion related reaction was considered Grade 3 as hospitalisation was indicated to treat the clinical sequela (hypoxia) but was not life-threatening and resolved in one day.

7. *Please clarify why a total of 8 AEs related to hypersensitivity are recorded in Table 15 above, however the sponsor's Clinical Summary reports only 5 cases for the pivotal study.*

Sponsor response

The difference in reporting of hypersensitivity AEs is because Summary of Clinical Safety shows events which occurred in Group A used for the Integrated Safety Analysis. Group A comprised events reported in the 167 patients treated in Arm A but also events from the 37 patients from the crossover population, that is, events occurred after crossover. Six of these eight events occurred in Arm A and correspond to those described in the CSR (treatment- related AEs in Arm A or Arm B). They consisted of:

Grade 2 drug hypersensitivity (n = 1).

Grade 2 (n = 1) and Grade 3 (n = 1) hypersensitivity.

Grade 1 flushing (n = 1).

Grade 1 (n = 1) and Grade 3(n = 1) infusion related reaction.

The other two events (Grade 4 anaphylactic shock and Grade 1 infusion reaction) occurred in patients after crossover, and these events were described in the CSR (treatment related AEs in the crossover population).

8. *Are further studies planned to investigate the potential cardiac effects of plitidepsin?*

Sponsor response

To address potential cardiac effects of plitidepsin, including QT prolongation, a Phase I study is planned to formally investigate the effects of plitidepsin on cardiac repolarisation and QTc interval. The final results will be available no later than October 2020.

9. *Please clarify if the sensitivity analysis demonstrating a HR for PFS at 0.611 (reported in in your response to questions dated March 2018) was pre-planned. Please direct the TGA to where this data is presented in Study APL-C-001-09 (ADMYRE).*

Sponsor response

The sponsor confirmed that the evaluation of PFS with confirmation of disease progression (PD) was a pre-planned sensitivity analysis included in the SAP v4.0 lifecycle. Initial results were presented in the CSR. Nevertheless, in the Question 71 of the EMA's Day 120 List of questions, the EMA rapporteurs pointed out that a considerable high number of patients were censored in this supportive analysis. As all the information necessary for the determination of progression and confirmation provided by the investigators was collected in the Case Report Form, the sponsor reviewed all patient profiles to classify the information. PFS sensitivity analysis with confirmation of PD according to the investigator's assessment was updated with a lower rate of censoring and it was initially presented in the Responses to the EMA's Day 120 List of questions and included in the updated sponsor Clinical Overview.

10. *Is data available on ECOG PS of patients during the treatment duration or ECOG PS against treatment exposure within the pivotal study? Was any shift in ECOG score noted?*

Sponsor response

A section of the ADMYRE CSR is focused on Physical Health Condition results. In this section, a comparison of the median time to ECOG PS deterioration (that is, median time to reach an ECOG PS score ≥ 2) is provided. Results in Arm A (plitidepsin plus DXM) were longer (4.6 months) with respect to those in Arm B (DXM) (2.3 months) (HR = 0.688; p = 0.0759).

Study ADMYRE CSR includes a table with a detailed summary of ECOG PS values at baseline and during treatment study per patient.

11. *Please provide further clarification, including data for plitidepsin and comparison to 'approved therapies 'in Australia, to support the phrase: A clear advantage of Aplidin is the favourable safety profile in terms of haematological toxicity, whereas most of the approved therapies induce moderate to high myelotoxicity. Note also that a proportion of patients in this stage of their disease may have limited marrow reserve or other comorbidities and may not tolerate currently approved therapies.'*

Sponsor response

The safety profile of plitidepsin plus DXM is generally favourable considering the lack of major toxicities observed commonly with current treatments used in MM such as neuropathy, thrombosis, bleeding, or pneumonia and other infections. Plitidepsin presents a unique and characteristic safety profile, consisting of transient CPK and transaminase elevation, which in the vast majority of patients did not lead to treatment discontinuation and had no clinically relevant impact. The treatment related death rate of 0.6% is in the low boundary of the range for other therapies in the same disease setting.

Table 16 (below) shows Grade 3/4 adverse events and laboratory abnormalities (≥ 5%) reported for drugs approved in the EU (and Australia) in MM compared to the ADMYRE trial.

Table 16: Grade 3/4 adverse events and laboratory abnormalities (≥ 5%) reported for drugs approved in the EU (and Australia) in MM compared to ADMYRE

Grade 3-4 events in ≥ 5% of patients	Plitid-epsin-LoD ADM-YRE %	DXM ADM-YRE %	Bortez-omib [1] %	Carfil-zomib [2] %	Lena-Dex [3] %	Poma – LoD [4] %	Dara [5] %
Haematological AEs							
Anaemia	31*	35.4	10	22	9	33	24
Thrombo-cytopenia	22*	27.9	30	11	11	22	25
Neutropenia	16*	5.1	14	10	30	48	14
Non-haematological AEs							
Muscular weakness	-		-	-	7	5	-
Thrombo-embolism	-		-	-	11	-	-

Grade 3-4 events in ≥ 5% of patients	Plitid-epsin-LoD ADM-YRE %	DXM ADM-YRE %	Bortez-omib [1] %	Carfil-zomib [2] %	Lena-Dex [3] %	Poma – LoD [4] %	Dara [5] %
Febrile neutropenia	-		-	-	-	10	-
Infection	-			11	10	34	-
Neuropathy	-		8	-	-	-	-
Diarrhoea	-		7	-	-	-	-
Myalgia	5		-	-	-	-	-
CPK increased	20*		-	-	-	-	-
ALT increased	14*						-
Treatment related discontinuation	9		38.4	15	8.8	4.0	-
Treatment related deaths	0.6		1.3	2.7	2.8	4.6	-

Data shown are % of patients. * Laboratory abnormalities regardless of relationship. 1. Richardson PG, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* (2005) 352 (24): 2487-98.
2. Siegel DS, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* (2012) 120 (14): 2817-2825.
3. Dimopoulos M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* (2007) 357 (21): 2123-2132.
4. San Miguel J, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open label, phase 3 trial. *Lancet Oncol* (2013) 14 (11): 1055-1066.
5. Usmani SZ, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood* (2016) 128 (1): 37-44.

Haematological toxicities reported for plitidepsin are laboratory abnormalities regardless of relationship.

Aplidin demonstrates an improved safety profile over immunomodulatory drugs (IMiDs) due to the lower AE rates of some commonly observed toxicities during treatment in MM patients. In particular, the safety profile of Aplidin compares favourably with respect to that of pomalidomide to DXM, which is expected to be used in a similar patient population.

The safety profile of Aplidin should be considered in the context of the limited treatment options for the target population and the expected benefit in terms of survival. Median PFS observed with confirmation of PD by Investigator's assessment (3.8 months) is equivalent to that reported with pomalidomide in the same disease setting. Median OS of 11.6 months is comparable to the 12.7 months reported for pomalidomide plus DXM.

Aplidin introduces a new active therapeutic option, with a novel mechanism of action and an acceptable and distinct safety profile compared to other therapies currently available in relapsed and refractory MM.

12. Please provide further justification and supportive data for broadening the proposed indication to patients who have received at least two prior treatment regimens.

Please refer to the text at the beginning of this *Response from sponsor*.

13. Please provide further subgroup analysis of PFS and secondary endpoints for patients who: 1) were classed as 'relapsed and refractory '2) received two prior treatment regimens, 3) classed as 'relapsed and refractory 'and aged > 65 years.

Sponsor response

In response to the concern of the generalisability of the ADMYRE results to the Australian population, of the 37 Australian patients recruited into the study (which represents 15% of the total ADMYRE study population), the median age was 63.5 years in the plitidepsin + DMX arm and 65 years in the comparator (DXM) arm (age range of 45 to 82 years), which is consistent with the Intent-to-treat (ITT) population of 64 and 65 years, respectively (age range of 36 to 85 years). It also demonstrates the trial to be well balanced with respect to the under and over 65 age groups.

Furthermore, after reviewing the literature for the most recent pivotal registration studies (NIMBUS (pomalidomide) and ASPIRE (carfilzomib])) San Miguel et al.; (2013)[37] and Stewart et al.; (2015)[38] the median ages and range reported are consistent with the ADMYRE study population.

The indication requested is referred to in the CSR as 'Total refractory'. There is no clear reasoning for excluding 'refractory 'patients from 'relapsed and refractory 'patients, however, the SAS outputs for both were provided to the TGA.

Refer to response to Question 12.

Caution should be taken in interpretation of the results in 'refractory 'and 'relapsed and refractory 'subgroup analyses, which seem to be in line with the whole population recruited. When this subset is restricted to patients that are ≥ 65 years old, the sample size is much lower and precludes firm conclusions. In addition, multivariate PFS analysis by IRC presented in the CSR did not show the covariate 'status to prior therapy 'as significant. Therefore, the relevant effects of treatment arm and age cannot be discarded.

14. Please include the correct accompanying statement in the CMI next to the black triangle symbol. In addition, the black triangle symbol and statement should be placed at thevery top of the first page of the CMI.

Sponsor response

The correct accompanying statement has been included in the CMI next to the black triangle symbol. The black triangle symbol and statement has also been placed at the very top of the first page of the CMI.

15. Please address the outstanding quality issues identified by the quality evaluator.

Quality outstanding issues:

The 2016 GMP clearance for [information redacted] expired and the 2017 GMP clearance covers release for supply and secondary packaging only and not drug substance manufacture. As this is the only site performing drug substance manufacture evidence of GMP for drug substance manufacture must be provided.

[37] Miquel JS et al (2013). Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2013; 14: 1055-1066.

[38] Stewart KS et al (2015). Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. *N Engl J Med* 2015; 372: 142-152.

Sponsor response

The GMP clearance for [information redacted] as manufacturer of the drug substance, plitidepsin, has been renewed.

[Information redacted] is stated to perform manufacture and release of lyophilised plitidepsin vials. However, it is noted that the GMP clearance for this site covers 'full product manufacture – excluding Microbiological testing' and therefore the steps 'TMM' and 'TESST' will be removed from the PAR. The company should be asked to acknowledge this removal.

Sponsor response

The sponsor acknowledges removal of the step 'TMM' from the PAR for [information redacted]. However, 'TESST' should remain and 'ENDTEST' should also be included in the PAR. These steps will be covered by GMP clearance [information redacted], which is currently under review and should be approved by the end of July since evidence is provided via the MRA.

The specifications for control of mannitol and tert-butanol should be updated as outlined.

Sponsor response

The sponsor confirms that the Mannitol specification has been updated by the finished product manufacturer [information redacted] to state both impurities as the sum not exceeding 2.0 %, to be in line with the current version of the European Pharmacopoeia for Mannitol (Ph. Eur. 0559).

The *Tert*-butanol specification has been updated.

Advisory Committee Considerations[39]

The ACM, taking into account the submitted evidence of efficacy and safety agreed with the Delegate that Aplidin powder for injection containing 2 mg per vial of plitidepsin has an overall negative benefit-risk profile for the proposed indication:

> *Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator.*

The ACM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Aplidin powder for injection containing 2 mg per vial of plitidepsin.

In providing this advice the ACM noted the following:

- The pivotal trial, ADMYRE, was a Phase III study of plitidepsin in combination with DXM (Arm A) versus DXM alone (Arm B) in patients with relapsed, refractory or relapsed and refractory MM.
- The primary efficacy outcome was progression-free survival (PFS) according to Independent Review Committee (IRC) assessment. In ADMYRE, a statistically

[39] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

significant, yet modest increase in PFS, of plitidepsin in combination with DXM compared to DXM alone, was demonstrated.

- The median age of patients in ADMYRE (64 to 65 years) was younger compared to the median age of diagnosis in the Australian population (around 70 years). The median time from first diagnosis was 73.0 months in Arm A and 70.1 months in Arm B. Plitidepsin in combination with DXM did not show a benefit for patients aged 65 years and older in the trial. Therefore, the benefits likely don't apply to the majority of patients aged older than 65 years, limiting the ability to generalise these results to the Australian population.
- The choice of comparator arm (DXM) creates further complexity for extrapolating results to the Australian population, especially in light of current alternative treatment options for this target group.
- Further studies in a larger group of patients with different disease presentations and in an older age group would provide greater support for use in the Australian context.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *What is the committee's opinion of the efficacy of plitidepsin in combination with DXM? In particular, what is the committee's opinion in the clinical meaning of the PFS benefit with plitidepsin in combination with DXM?*

The ACM considered that the incremental effectiveness of plitidepsin with DXM compared to DXM alone demonstrated in ADMYRE was modest (statistically significantly longer median PFS with plitidepsin plus DXM of 2.6 months (95% CI: 1.9 to 3.0 months) compared to the median PFS in the DXM alone arm of 1.7 months (95% CI: 1.1 to 2.0 months)), and may not accrue for the majority of patients with MM. The ACM noted that other secondary endpoints, including OS and duration of response, were not statistically different between the treatment groups.

Further, the ACM noted subgroup analyses showing a lack of statistically significant benefit in a number of groups including patients aged 65 years and older and patients who were transplant ineligible.

The marginal PFS benefit shown in the trial had uncertain clinical value: especially since few patients in the Australian context are treated with DXM alone; and in the absence of improvement in other clinical outcomes.

2. *What is the committee's impression of the choice of comparator selected for the pivotal study? How might this impact on the generalizability of these results to the Australian public with relapsed and refractory MM?*

The ACM noted that in Australia, few patients currently receive DXM alone as treatment for MM. DXM alone is sometimes used in a palliative setting. Patients with MM, especially those younger, have a range of treatment options and therapy often includes use of multiple agents. Therefore the comparator arm of ADMYRE trial may only be representative of a small proportion of Australian patients.

Given that plitidepsin with DXM was not found to be beneficial for patients aged 65 years and older in the subgroup analysis, there is significant uncertainty regarding the generalisability of the trial data to the Australian setting, where the median age of diagnosis is around 70 years.

3. *What is the committee's response to the sponsor's comment regarding the safety profile of plitidepsin in patients with reduced marrow reserve?*

The ACM noted the sponsor's pre-ACM response which stated that the safety profile of plitidepsin plus DXM is generally favourable considering the lack of major toxicities observed commonly with current treatments used in MM such as neuropathy, thrombosis, bleeding, or pneumonia and other infections. However, the ACM considered that the data demonstrate that plitidepsin is associated with higher incidence of treatment related AEs and serious AEs when compared to DXM alone.

While these adverse effects are predictable and generally manageable, the higher rates of AEs and discontinuation may be significant in practice given the modest treatment benefit and considering that treatment at this stage of the condition is generally palliative.

4. *What is the committee's opinion of the risk-benefit balance of plitidepsin in the proposed indication? Is there a positive risk-benefit balance for a particular subgroup of Australian patients therefore warranting a narrower indication?*

The ACM could not conclude a clear favourable risk-benefit profile for plitidepsin, even in light of the sponsor's amended indication as stated in their pre-ACM response, for following reasons:

- The PFS benefit was quite modest, and comparison was only against DXM alone, rather than an alternative regimen such as thalidomide + DXM, pomalidomide + DXM, or carfilzomib.
- Benefit was limited in older patients (≥ 65 years), who would make up the majority of relapsed and refractory patients in the Australian setting.
- Rates of AEs, although manageable, were significant in the plitidepsin arm of the trial, and quality of life data was not assessed in the trial.
- The ability to clearly generalise these results to the Australian population is limited.

Based on the available evidence, the ACM could not clearly identify any subgroup of patients with MM for which plitidepsin had a positive risk-benefit profile.

5. *What is the committee's opinion of the wording of prior lines of therapy? Does the committee agree with maintaining class-specific wording to allow physician flexibility?*

The ACM noted that in its pre-ACM response, the sponsor had agreed to revise the indication wording for use in patients who have received at least *three* (instead of two) prior treatment regimens. This is more consistent with the ADMYRE trial population, where patients had at least three, and up to six prior regimens. Notwithstanding this amendment, the committee could not conclude a clear favourable risk-benefit profile for plitidepsin.

The ACM were generally in favour of class specific wording to allow physician discretion.

Addendum to Delegate's overview dated 3 July 2018 (Post ACM)

Background

This submission was presented to the ACM in August 2018, with the ratified minutes being delivered on 24 August 2018.

Arising from this ACM meeting, a face-to-face meeting was held with the sponsor on 12 September 2018 and subsequently a request for further information was sent to the sponsor on 25 September 2018.

This addendum to the Delegate's Overview assesses the information provided by the sponsor to the request. The sponsor presented their response to the request on 1 November 2018.

The request required the sponsor to address the following issues:

Please provide all relevant data, including the data from the Australian Myeloma Registry which indicates the age group of the target population (including how this was calculated and determined). This data must be presented in a format which Specialised Therapeutics believes is sufficient to allow for TGA evaluation and for the relevant TGA decision maker (the Delegate) to be in a position to rely on this data.

In Australia, patients with newly diagnosed MM are entered into the Australian Myeloma and Related Diseases registry (MRDR), with treatment and outcome data prospectively collected.

The sponsor states that the design and development of the registry, commencing in 2012, was published by Bergin et al.[40]

The proportion of patients in the MRDR having received numbers of line(s) of therapy, dichotomised by age 70 years, is shown in Table 17, below.

Table 17: Typical characteristics of patients in fourth lines or more of therapy (MRDR data)

Number of lines of prior therapy	Age <70 years	Age ≥ 70 years	Age (yrs), Median (IQR)
1	93%	88%	66.3 (58.2, 73.8)
2	59%	35%	65.5 (57.7, 73.0)
3	35%	17%	65.1 (57.8, 72.0)
4	18%	7%	62.1 (55.3, 68.7)

Additionally, the MRDR data presented states that the age range of patients receiving third line, or greater, therapy is 62.1 to 65.1 years, with 24% of patients with relapsed or refractory MM being aged > 70 years.

In their response, the sponsor re-iterated that the study protocol of the pivotal study (ADMYRE trial) was approved by the EMA, in particular the use of DXM as the sole treatment in the comparator arm for this patient population with multiply relapsed and refractory disease. In agreement with the opinion stated in the Delegate's Overview, the sponsor stated *'(dexamethasone, DXM) remains clinically relevant today for the proposed indication when there are so few treatments readily available. DXM is the current standard of care when all lines of treatment for relapsed and refractory have been exhausted'.*

There was no substantial difference in the age-range of Australian patients recruited to the ADMYRE trial as compared to the total study population:

[40] The MRDR was established in 2012 as an online database for a multi-centre collaboration across ANZ, collecting prospective data on patients with a diagnosis of MGUS, MM, solitary plasmacytoma or plasma cell leukaemia. Development of the MRDR required multi-disciplinary team participation, IT and biostatistical support as well as financial resources. Bergin K et al 2012. Bergin, K et al. 2016. Design and development of the Australian and New Zealand (ANZ) myeloma and related diseases registry. BMC Medical Research Methodology. 16 (151): pp. 1-8.

Table 18: Age distribution among ADMYRE trial participants

	ADMYRE (ITT population) (N = 171)	ADMYRE (Australian sub-population) (N = 37)
Median Age (years)	64	63.5
Age range (years)	36 - 85	45 - 82
Proportion aged 18 to 64 years	52%	54%
Proportion aged 65 to 74 years	33%	30%
Proportion aged > 75 years	15%	15%
Proportion with ECOG status 0 and 1	83%	86%
Proportion with ECOG status ≥ 2	17%	14%

Efficacy

The sponsor re-iterated the primary outcome of the ADMYRE trial was PFS. The primary analysis after 191 events, by independent review demonstrated the median PFS was 2.6 months (95% CI, 1.9 to 3.0 months) in the plitidepsin plus DXM arm and 1.7 months (95% CI, 1.1to 2.0 months) in the DXM arm (log-rank p = 0.0054).

PFS was statistically significantly different to the comparator arm at 3.8 months versus 1.9 months, HR = 0.611 (95% CI, 0.434-0.860), as assessed at the second pre-planned analysis by investigator review (after 203 events).

In regard to the ADMYRE trial secondary outcome, the sponsor stated:

> *'Secondary endpoints such as response rate, duration of response and time to first subsequent therapy also consistently demonstrated statistically significant positive outcomes.*
>
> *The study found that patients who respond well have a long duration of response to Aplidin.*
>
> *The time to response with Aplidin is rapid as is the time to failure; ensuring patients do not receive unnecessary treatment without a response to treatment. Aplidin's rapid onset of response enables the clinician to make the appropriate therapeutic changes if a response is not obtained.'*

The investigator-assessed median time to response among responders was reported by the sponsor at the face-to-face meeting with the TGA as is also shown in Table 19, below.

Table 19: Median time to response, ADMYRE trial population

	Plitidepsin + DMX	DMX
Investigator assessed; All responder patients Median, months (range)	1.0 (0.9 - 12.7)	2.9 (NR)
Investigator assessed; All responder patients (including MR)	1.1 (0 - 21.2)	2.9 (NR)

	Plitidepsin + DMX	DMX
Median, months (range)		

NR = not reported, MR = minor response

The proportion of responders (including those with MR) was 17/171 in the plitidepsin plus DXM arm.

The exploratory analysis of OS in this treatment arm according to response showed a median of 10.0 months (95% CI 6.9, 12.0) for non-responders as compared to 37.6 months (95% CI 13.1, NE). Similarly, the proportion of responders alive at 12 and 24 months was more than double that of non-responders in the plitidepsin plus DXM arm.

In regard to the assessment of OS in the ADMYRE trial, the sponsor stated:

> *'The overall survival (OS) in the intention to treat (ITT) population showed a strong treatment effect however it did not achieve statistical superiority. This outcome is confounded by the 44% of patients in the comparator dexamethasone (DXM) arm who crossed over to the plitidepsin + DXM arm upon disease progression. The CHMP(EU) acknowledged that 'any potential effect on OS would be likely to be underestimated in the ITT analysis due to the number of patients crossing over to the Aplidin + DXM arm from the DXM arm during the study'.*

The result of a pre-planned analysis of OS adjusting of the effect of cross-over demonstrated an improvement in OS with plitidepsin plus DXM (11.6 months) as compared to DMX alone (6.4 months).

Safety

In their response, the sponsor stated:

> '*Most of the toxicities reported with Aplidin plus DXM are transient, non-cumulative laboratory abnormalities that usually occur in the first two cycles of treatment and are controlled by dose adjustment (cycle delay, dose omission, and in ultimate instance, dose reduction). Despite that this was a heavily pre-treated population, only 15/167 patients (9.0%) discontinued treatment due to treatment related toxicity and 9/167 (5.4%) due to unrelated AEs (AEs).*
>
> *These figures fell within the low margin of the range of treatment discontinuation due to AEs reported in previous clinical trials evaluating standard therapies in RRMM of 4-38% (see* [Table 20] *below)*':

Table 20: AEs reported in previous clinical trials evaluating standard therapies in RRMM

Therapy	Grade 3/4 toxicity	
	Common >10%	Occasional 5-10%
Lenalidomide plus DXM Dimopoulos et al. (2007) [11]	Neutropenia 30% (Febrile neutropenia 3%) Infection 10% Thrombocytopenia 11% Venous thromboembolism 11%	Anaemia 9% Fatigue 7% Muscle weakness 7% Asthenia 6%
	Treatment discontinuation because of AEs: 31/351 (8.8%) (both groups including placebo) Treatment-related deaths: 5/176 (2.8%)	
Pomalidomide plus DXM San Miguel *et al.* (2013) [1]	Neutropenia 48% Infection 34% (grade 5, 4%) Anaemia 33% Thrombocytopenia 22% Pneumonia 14% (grade 5, 1%)	Febrile neutropenia 10% Leukopenia 9% Back pain 5% Fatigue 5% Muscle weakness 5%
	Treatment discontinuation because of AEs: 11/300 (4.0%) Treatment-related deaths: 7/153 (4.6%)	
Bortezomib Richardson *et al.* (2005) [12]	Thrombocytopenia 30% Neutropenia 14%	Anaemia 10% Peripheral neuropathy 8% Diarrhoea 7% Fatigue 5% Dyspnoea 5%
	Treatment discontinuation because of AEs: 121/315 (38.4%) Treatment-related deaths: 4/315 (1.3%)	
Therapy	**Grade 3/4 toxicity**	
	Common >10%	**Occasional 5-10%**
Daratumumab **Lonial *et al.* (2016) [13][b]**	Infusion-related reactions 48% Anaemia 17% Thrombocytopenia 14% Neutropenia 12%	Pneumonia 6% Lymphopenia 6%
	Treatment discontinuation because of AEs: 5/106 (4.7%) Treatment-related deaths: 0/106 (0.0%)	
Carfilzomib **Siegel *et al.* (2012) [14]**	Thrombocytopenia 29% Anaemia 24% Lymphopenia 20% Neutropenia 11%	Pneumonia 9% Hyponatremia 8% Fatigue 8% Leukopenia 7% Hypophosphatemia 6%
	Treatment discontinuation because of AEs: 31/257 (12%) Treatment-related deaths: 4/266 (1.5%)	
Panobinostat plus bortezomib plus DXM **Richardson *et al.* 2013 [15, 16]**	Thrombocytopenia 64% Diarrhoea 20% Fatigue 20% Neutropenia 14% Anaemia 15% Pneumonia 15%	Asthenia 9% Hypotension 9% Syncope 9% Sepsis 9% Abdominal distension 7% Hypokalaemia 7% Abdominal pain 6% Flatulence 6% Hypophosphatemia 6% Nausea 6% Septic shock 6% Dehydration 5%
	Treatment discontinuation because of AEs: 10/55 (18.2%) Treatment-related deaths: 30/387 (7.8%) (PANORAMA 1)	
Plitidepsin plus DXM (APL-C-001-09, ADMYRE)[a]	**Anaemia 31%** **Lymphopenia 23%** **Thrombocytopenia 22%** **CPK increased 20%** **Neutropenia 16%** **ALT increased 14%** **Fatigue 11%**	**Leukopenia 10%** **AST increased 9%** **Myalgia 5%**
	Treatment discontinuation because of AEs: 15/167 (9.0%) (treatment-related) and 9/167 (5.4%) (unrelated to treatment) **Treatment-related deaths: 1/167 (0.6%)**	

[a] For APL-C-001-09 (ADMYRE), haematological and biochemical laboratory abnormalities shown in this table are regardless of their relationship with the study treatment; thus can differ in other studies where data could came from reported adverse events and not from laboratory data.
[b] Includes data from daratumumab Summary of Product Characteristics (SmPC).
ALT, alanine aminotransferase; CPK, creatine phosphokinase; DXM, dexamethasone.

Discussion

The sponsor has satisfactorily demonstrated the comparability of the baseline age and ECOG status of the sub-group of Australian patients as compared to the total study population. Furthermore, the median age of patients in the MRDR who have received 3 or 4 prior lines of myeloma therapy to be similar to the median age of the total ADMYRE trialstudy population. The ADMYRE trial can therefore be considered sufficiently generalisable to the wider Australian population with multiply relapsed and refractory myeloma to currently registered therapies. In particular, the proportion of patients in the MRDR aged less than 65 years who have received 3 or more therapies is consistent with the sub-group analysis of ADMYRE.

The choice of DXM as a comparator in ADMYRE is considered appropriate, given the therapies available at the time of study design and the study population having received at least three and up to six prior lines of therapy, to which they were refractory or had relapsed.

Of note, as a result of the date of study commencement, only three ADMYRE patients had received prior elotuzumab and none had received prior daratumumab, therefore there can be no meaningful assessment of the relative efficacy of plitidepsin against regimens containing there two agents. The sponsor's proposed indication, see below, is appropriately silent on specifically naming either of these therapies.

It is well-recognised that with increasing number of lines of myeloma therapy, the expectation of similar minimal residual disease, response rate, or prolongation in PFS, reduces compared to the earlier line of therapy. In a myeloma population who have been exposed to at least three lines of registered therapies, the aim treatment is increasingly unlikely to be curative, and the pragmatic outcome can be plausibly expected to move from prolongation of PFS to increasing the duration of treatment response. In Study ADMYRE, the intent of treatment was not curative since PFS was the primary outcome.

There is a general recommendation that reconsideration of prior therapy may be considered in the patient previously responded and relapsed at least 6 months after prior use was tolerated.[41] Patients eligible for the re-administration of a therapy previously received would plausibly not receive plitidepsin ahead of this. Furthermore, as stated in the sponsor's response, the potential benefit of using early triplet or quadruplet therapy in myeloma is hampered by the lack of Pharmaceutical Benefits Scheme (PBS) funding in Australia, but where used will potentially exhaust registered therapies more rapidly than when used in dual, or monotherapy.

The EMA *Guideline on the evaluation of anticancer medicinal products in man* (revision 4, 2014) states that PFS is an appropriate end-point and that OS should be reported as a secondary end-point; both end-points were appropriately reported in the pivotal study. In regard to the appropriate end-point in relapsed and refractory myeloma, the 2008 American Society of Hematology and US FDA workshop on clinical end-points in MM recommendations included: '*overall response and duration of disease control are appropriate end-points for regulatory approval in this population*'.[42]

The secondary end-point of ORR (including, or excluding, patients with minor response) in ADMYRE was statistically significantly different, favouring the plitidepsin arm:

- ORR including patients with MR: 22.8% in the plitidepsin plus DXM arm as compared to 3.6% in the DXM arm ($p < 0.0001$)

[41] Nooka, A, et al. Treatment options for relapsed and refractory multiple myeloma. *Blood* 2015; 125: 3085-3099

[42] Anderson, KC et al on behalf of the ASH/FDA panel on Clinical Endpoint in Multiple Myeloma. Clinically relevant end points and new drug approvals for myeloma*. Leukaemia* 2008; 22: 231-239

- ORR excluding patients with MR: 9.9% in the plitidepsin plus DXM arm compared to 1.2% in the DXM arm (p = 0.0085)

Given the overall response rate (including MR) for each treatment arm, the calculated estimate of number needed to treat (NNT) to achieve an additional response is 5.2, whereas the NNT for patients estimated to achieve one additional response excluding MR is 11.5.

Duration of response was also statistically significantly different with a median duration of response of 3.7 months (95% CI, 2.7 to 10.5 months) in the plitidepsin plus DXM arm as compared to 1.8 months (95% CI, 1.8 to 5.5 months) in the DXM arm.

For the sub-group of patients (approximately one third of the study population) with high-risk cytogenetics, the HR of PFS was similar to that of those with standard risk (see Figure 3).

While there is a growing body of evidence of the use of CAR-T cell therapy;[43] in improving MRDR negativity, ORR and CR rate in patients with relapsed and refractory myeloma, however, there are currently no such registered products available in Australia.

In the assessment of OS, the effect of cross-over of 44% of the placebo arm patients is to effectively introduce a further line of therapy prior to plitidepsin administration in these patients; that is a comparison of 'early' versus 'late' plitidepsin. The analysis of OS prior to cross-over is relevant in this situation; the median duration of OS in the plitidepsin + DXM arm was 11.3 months (95% 8.7 to 16.1) and that for the DXM arm was 5 months (95% CI 2.8, 6.4) (HR = 0.614 (95%CI , p = 0.0104).

Assessment of patient responses following crossover demonstrated that:

- The only patient with PR prior to crossover had PD following
- Of the 18 patients with SD prior to crossover, eleven had the same, or better, disease response following crossover
- Of the 17 patients with PD prior to crossover, the status of eleven changed to either PR (n = 3) or SD (n = 8)
- One patient who had non-evaluable disease prior to crossover had PD following crossover

Among the three supportive studies for this submission, one hypothesis generating Phase I study utilised a combination of plitidepsin, bortezomib and DXM, which demonstrated a higher ORR than in the pivotal study. However, as per a search of the clinicaltrials.gov website on 19 November 2018 there appear to be no current ongoing Phase III studies of the use of plitidepsin in this, or other uses.

The resolution of the ACM meeting stated that '*PFS benefit was quite modest'* which is consistent with the opinions in the pre-ACM Delegate's overview, and the clinical evaluation reports. This Delegate does not have a different opinion as to the magnitude of PFS improvement, as demonstrated from ADMYRE, being 'modest'.

The ACM also stated *'benefit was limited in older patients (> 65 years)…'*. This statement could equally be made for the whole ADMYRE study population given the ORR rate of 9.9% (excluding MR) among patients who received plitidepsin plus DXM. Despite this evidence of efficacy in a small proportion of study participants, there are patients who

[43] A type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is being studied in the treatment of some types of cancer. Also called chimeric antigen receptor T-cell therapy. From NCI Dictionary of Cancer Terms 30 January 2019.

have obtained benefit from this combination with the median duration of response to plitidepsin plus DXM being independently assessed as 12.0 months (95% CI 2.8, 23.2) among responders.

The ACM resolution stated that '*other secondary endpoints, including overall survival and duration of response, were not statistically different between the treatment groups*'. This is not the case; independently assessed ORR, with or without MR, was statistically significantly different between the two treatment arms.

There is no stated regulatory minimum level of ORR or PFS below which registration would categorically be precluded. As discussed above, the aim of treatment for patients with very advanced myeloma is to improve or control symptoms, with or without a significant prolongation of life. Notwithstanding cross-study comparisons, as per the approved product information of pomalidomide, lenalidomide, daratumumab and elotuzumab, the magnitude of PFS among the studies leading to registration for patients with relapsed and refractory myeloma ranged approximately 10 to 19 months. Whether the modest magnitude of PFS observed within the pivotal trial translates to the wider myeloma population cannot be pre-judged.

The median time to response of one month, if achieved, was approximately within the first assessment time-point in ADMYRE.

In relation to the age distribution of ADMYRE patients, the ACM stated that the '*ability to clearly generalise these results to the Australian population is limited*'. The data presented from the MRDR (see Table 16, above) sufficiently refutes this argument, given the age-distribution of patients having received three or more lines of prior therapy.

The ACM did not state that the safety profile of plitidepsin, alone, precludes registration, rather it was the benefit-risk profile as considered at that time, on the basis of the understanding of the contemporary age-distribution of the Australian population with myeloma.

Sponsor's proposed indication

> *Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator. Aplidin may be used after two prior lines of therapy if refractory and/or intolerant to both a proteasome inhibitor and an immunomodulator.*

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application for plitidepsin should not be approved for registration.

It is the opinion of this Delegate that if the efficacy and safety of plitidepsin in combination with DXM are sufficiently well documented in the PI, there may be a place for its use in patients who fulfil the proposed indication provided by the sponsor, above, if informed consent has been obtained from their treating specialist haematologist.

Providing the proposed changes to the PI are agreed to, the PI would satisfactorily enable clinicians to obtain informed consent from their patients and registration of plitidepsin may proceed.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Aplidin plitidepsin 2 mg powder for infusion vial and diluent ampoule composite pack, indicated for:

Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator. Aplidin may be used after two prior lines of therapy if refractory and/or intolerant to both a proteasome inhibitor and an immunomodulator.

Specific conditions of registration applying to these goods

Aplidin (plitidepsin) is to be included in the Black Triangle Scheme. The PI and CMI for Aplidin must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

The Aplidin EU-Risk Management Plan (RMP) (version 2.0, dated 6 July 2017, data lock point 31 March 2016), with Australian Specific Annex (version 1.2, dated 26 February 2018), included with submission PM-2017-02669-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Aplidin approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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