



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Daclizumab

Proprietary Product Name: Zinbryta

Sponsor: Biogen Australia Pty Ltd

May 2017

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ALT	Alanine transaminase
ARR	Annualised relapse reduction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate transaminase
AUC	Area under the drug concentration curve
AUC _{0-last}	Area under the curve from dosing to last measurable concentration
AUC _{0-τ}	Area under the drug concentration curve to end of dosing period
BBB	Blood-brain barrier
CDC	Complement-dependent cytotoxic(ity)
CDR	Complementary determining regions
CHMP	Committee for Medicinal Products for Human Use (EMA)
CL	Clearance
C _{max}	Maximum (peak) serum concentration
CNS	Central nervous system
CYP	Cytochrome p450
DAC HYP	Daclizumab High Yield Process
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency

Abbreviation	Meaning
ER	Exposure ratio
EU	European Union
FDA	Food and Drug Administration (US)
FLAIR	Fluid-attenuated inversion recovery
FS	Functional system
GCP	Good Clinical Practice
GD	Gestation day
Gd	Gadolinium
GGT	Gamma glutamyl transaminase
HI	Haemagglutinin
ICH	International Conference on Harmonisation
IFN	Interferon
IFN α -2a	Interferon alpha-2a
IFN β -1a	Interferon beta-1a
IFN β -1b	Interferon beta-1b
IgG1	Immunoglobulin G1 isotype
IL-2	Interleukin-2
IL-2R	Interleukin-2 receptor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
kDa	Kilodaltons
LOEL	Lowest observable effect level
LTi	Lymphoid tissue inducer
MAb	Monoclonal antibody

Abbreviation	Meaning
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Physical Impact Scale
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events (US)
NK	Natural killer (cells)
NOEL	No observable effect level
PBMC	Peripheral blood mononuclear cells
PBS	Pharmaceutical Benefits System
PD	Pharmacodynamic
PFP	Pre-filled pen
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PHA	Phytohaemagglutinin
PI	Product Information
PK	Pharmacokinetic
popPK	Population pharmacokinetic
PPMS	Primary progressive multiple sclerosis
PWG	Pathology Working Group
QS	Quantity sufficient
rDNA	Recombinant deoxynucleic acid
RMP	Risk Management Plan
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SC	Subcutaneous(ly)
SCE	Summary of Clinical Efficacy

Abbreviation	Meaning
SCS	Summary of Clinical Safety
SJS	Stevens-Johnsons syndrome
SOC	System organ class
SPMS	Secondary progressive multiple sclerosis
$t_{1/2}$	Half life
TGA	Therapeutic Goods Administration
T_{max}	Time from dosing to maximum (peak) serum concentration
TNF α	Tumour necrosis factor gamma
T_{reg}	Regulatory T cells
ULN	Upper limit of normal
US	United States (of America)
V_d	Volume of distribution
w/v	Weight to volume
WBC	White blood cell
WCB	Working cell bank
K	Kappa

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	20 September 2016
<i>Date of entry onto ARTG</i>	22 September 2016
<i>Active ingredient(s):</i>	Daclizumab
<i>Product name(s):</i>	Zinbryta
<i>Sponsor's name and address:</i>	Biogen Australia Pty Ltd PO Box 380, North Ryde BC, NSW 1670
<i>Dose form(s):</i>	Solution for injection
<i>Strength(s):</i>	150 mg/mL
<i>Container(s):</i>	Glass type I closed syringe
<i>Pack size(s):</i>	1 pre-filled syringe 3 pre-filled syringes 1 pre-filled pen 3 pre-filled pens
<i>Approved therapeutic use:</i>	<i>'Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse.'</i>
<i>Route(s) of administration:</i>	Subcutaneous (SC)
<i>Dosage:</i>	The recommended dose of Zinbryta is 150 milligrams injected subcutaneously once a month.
<i>ARTG number (s):</i>	243872 (pre-filled syringe) 243873 (pre-filled pen)

Product background

This AusPAR describes the application by the sponsor (Biogen Australia Pty Ltd) to register Zinbryta daclizumab 150 mg/mL solution for subcutaneous (SC) injection in the form of a pre-filled pen (PFP) and pre-filled syringe (PFS) for the following indication:

'Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (MS).'

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the CNS.

There are a number of clinical sub-types of MS according to the guideline *Clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CHMP/771815/2011 Rev. 2, Effective: 1 October 2015 TGA adopted guideline at time of the sponsor's submission):

Relapsing MS:

1. patients with Relapsing-remitting MS (RRMS), 2) patients with SPMS and superimposed relapses and 3) patients with a clinically isolated demyelination event and evidence of dissemination of lesions in time and space on the MRI.

Relapsing MS is characterised by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability. The disease does not progress during periods of relapse.

Secondary progressive MS (SPMS):

Initial RRMS disease followed by ongoing deterioration, there may be occasional relapses or minor remissions.

Primary progressive MS (PPMS):

Progressive disability from the onset of the disease.

Patients most commonly have RRMS at onset and progress to develop secondary progressive MS. The level of activity of MS is determined by the frequency of relapses or MRI evidence of lesions.

The Guideline includes the following specific considerations when developing products for the treatment of multiple sclerosis:

2. Specific considerations when developing products for the treatment of multiple sclerosis:

Treatments of MS may have different goals with different clinical development plans and clinical trial designs:

- a. *Treatment of acute relapses to shorten their duration and/or severity of symptoms and/or preventing their sequelae.*
- b. *Modification of the natural course of the disease. This includes:*
 - i. *Preventing or delaying the accumulation of disability.*
 - ii. *Preventing or modifying relapses.*
- c. *Treatment intended to improve an apparently stable residual disability.*

Most approved therapies for MS are thought to reduce the incidence of relapses by modifying the immune system, and in some cases this has been shown to reduce the accumulation of disability. Immunomodulatory agents intended to alter the course of MS include interferons (IFN) such as IFN beta-1a (IFN β -1a), IFN beta-1b (IFN β -1b) and INF alfa-2a (IFN α -2a); glatiramer, natalizumab, fingolimod, teriflunomide, dimethyl fumarate and the most recently approved agent, peg-IFN β -1a (Plegridy).

Daclizumab is a humanised monoclonal antibody (MAb) of the immunoglobulin G1 isotype (IgG1) that binds specifically to the alpha subunit of the interleukin 2 receptor (IL-2R). The sponsor claims it selectively blocks signalling through high affinity IL-2R, a receptor that is upregulated on the surface of activated lymphocytes, while leaving IL-2 signalling by intermediate affinity IL-2Rs intact. Daclizumab is also thought to produce its benefits in

MS by modifying the immune response and reducing CNS inflammation. Specifically, by blocking high-affinity IL-2 receptors, it produces the following immunomodulatory effects:

- Selective antagonism of activated T-cell responses.
- Expansion of immunoregulatory CD56^{bright} natural killer (NK) cells which have been shown to selectively decrease activated T cells.

Daclizumab in the drug product Zinbryta is a new form of daclizumab produced using a high yield process (DAC HYP).

While it has the same primary amino acid sequence as an earlier form of daclizumab (Zenapax), it is produced by a different manufacturing process and using a different production cell line. DAC HYP and Zenapax have physical and functional differences. Zenapax was previously registered for the prophylaxis of acute organ rejection in patients receiving renal transplants but was discontinued by the sponsor for commercial reasons in 2005.

DAC HYP (Zinbryta) has a unique product profile that is distinct from Zenapax through its different indication, formulation, the route of administration, dosing schedule, and treatment duration. DAC HYP differs from Zenapax in molecular structure, nature of the source material used in the cell culture production steps, and manufacturing process to produce the recombinant protein. For these reasons the data package submitted did not rely on previously submitted data and DAC HYP is considered a new chemical entity and is proposed for a new indication.

Regulatory status

This is an application to register a new chemical entity and this product received its initial registration on the Australian Register of Therapeutic Goods on 22 September 2016.

At the time the TGA considered this application, similar applications for marketing authorisation of daclizumab for the same indications proposed for Australia were submitted to the European Medicines Agency (EMA) in March 2015, to the US Food and Drug Administration (FDA) in February 2015 and to Health Canada.

Zinbryta was granted a marketing authority in the US in March 2016 for the indication of the:

'...treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.'

In April 2016 the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for Zinbryta with the proposed indication of:

'Zinbryta is indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).'

It is proposed in the European Union (EU) that Zinbryta be prescribed by physicians experienced in the management of MS.

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. Quality findings

Introduction

Daclizumab is a recombinant humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates interleukin-2 (IL-2) signalling. This marketing application is being submitted to support the approval of Daclizumab High Yield Process (DAC HYP), a new form of daclizumab, as a disease-modifying therapy (DMT) for the treatment of patients with relapsing forms of multiple sclerosis (RMS).

Some of the standards and guidelines relied on in completing this evaluation includes:

- CPMP/ICH/294/95, International Conference on Harmonisation (ICH) Topic Q 5 D; Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.
- CPMP/ICH/139/95, ICH Topic Q 5 B: Quality of Biotechnological Products; Analysis of the Expression Construct in Cell Lines Used for Production of recombinant deoxyribonucleic acid (rDNA) Derived Protein Products.
- ICH guideline Q2 (R1): Validation of Analytical Procedures: Text and Methodology.
- European Pharmacopoeia (Ph. Eur.) monograph: Antibodies for Human Use.

Drug substance (active ingredient)

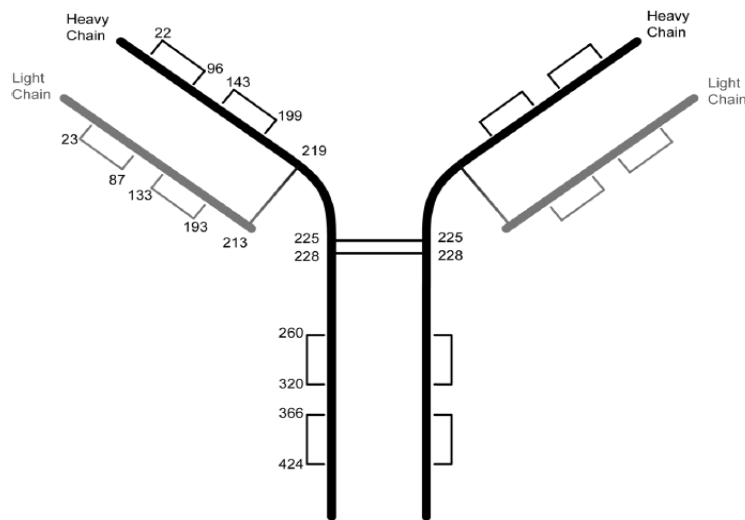
Structure

As shown in Figure 1 (below), the DAC HYP antibody is expressed as a disulphide-linked tetramer of two heavy and two light chains. It consists of human constant regions and engineered variable regions composed of human frameworks and murine complementarity determining regions (CDR). The isotype of DAC HYP is IgG1-kappa (κ); the heavy chain is human gamma-1 and the light chain is human kappa. The mass of the intact DAC HYP molecule is approximately 144 kilo daltons (kDa) without the N-glycan.

DAC HYP is glycosylated at amino acid 296 of both heavy chain subunits, with the major oligosaccharide form existing as a core fucosylated biantennary structure. The N-terminus of the DAC HYP heavy chain exists as three major forms.

Comment: The characterisation section of the report demonstrates the consistency of the charged variant contents resulting from the major forms of the N-terminus of the DAC HYP heavy chain among the 2013 (5 batches) and 2014 batches (3 batches). The batches also met the potency test specifications for release and up to date available stability including 36 months drug substance stability.

The C-terminus of the DAC HYP heavy chain exists with and without the C-terminal lysine residue. The major form lacks the C-terminal lysine residue, resulting in a C-terminal glycine.

Figure 1. DAC HYP predicted disulphide linkages

Manufacturing process and process controls

DAC HYP is produced by expression in NS0 cells, a mouse myeloma cell line, following vector transfer of DAC HYP expressing genes.

The manufacturing process is comprised of cell culture expansion, production of culture in a bioreactor, harvest of the cell culture fluid, purification, and dispensing, resulting in highly purified DAC HYP drug substance.

The sponsor supplied flow charts matching and detailing each step in the drug substance manufacture with the relevant control parameters and in-process controls and testing. One Working Cell Bank (WCB) thaw vial is used to produce one discrete batch of drug substance. Each discrete batch of drug substance is identified by a unique batch number, which is maintained throughout drug substance production.

Cells are recovered from WCB thaw operations and the culture expanded to inoculate the seed train bioreactors. The seed train bioreactors are then used to expand the culture volume in order to inoculate the production bioreactor. This operation is to produce product suitable for clarification and downstream purification operations. It comprises the operation of the bioreactor and associated equipment. The resulting product then undergoes harvest by centrifugation and depth filtration. The function of this unit operation is to clarify the cell culture medium in advance of chromatographic purification. The cell culture is harvested and clarified using centrifugation. The centrifugation process separates particle depending on size and density differences between the solid particles (intact cells and large debris particles) and the liquid phase (product containing the liquid stream centrate).

After harvest, DAC HYP is initially captured and purified by Protein A affinity chromatography before undergoing a low pH incubation step designed to inactivate low pH-sensitive endogenous and adventitious viruses.

Following low pH virus inactivation and neutralisation, the product stream is further purified using an anion exchange chromatography step. The product stream is then passed through a virus reduction filter. Following viral filtration, the product stream is concentrated initially to an intermediate concentration and the buffer is exchanged using tangential flow filtration. The product stream is then further concentrated in a second ultrafiltration step and formulated with drug product excipients to the final concentration (150 g/L). The bulk drug substance is then filtered into ultra-low density polyethylene bags and stored at suitable temperature.

The raw materials used in the drug substance manufacturing process are controlled to ensure the quality and safety of the drug substance and to maintain the consistency of the manufacturing process. Lists of the raw materials (compendial, non-compendial, and chromatography resins and viral filters) used during the production of DAC HYP drug substance were supplied for this submission.

Drug product

DAC HYP (drug product) is a colourless to slightly yellow, clear to slightly opalescent liquid, which is essentially free of visible particles for subcutaneous administration.

The drug product is supplied in 2 presentations, which contain a single 150 mg dose of DAC HYP solution for injection:

- 1 mL sterile, Type 1 glass PFS sealed with a bromobutyl stopper. The PFS is assembled with a finger flange and plunger rod.
- 1 mL sterile, Type 1 glass pre-filled pen which encloses the PFS container closure inside a front and rear sub-assembly to produce the final assembled pre-filled pen.

The DAC HYP (drug substance) formulation has identical composition to the drug product. It is formulated at a concentration of 150 mg/mL at pH 6.0 and stored at 2 to 8°C. The drug substance demonstrated acceptable stability at the recommended storage condition of 2 to 8°C for 24 months. The only processing that occurs between drug substance and drug product is sterile filtration and aseptic filling into syringes.

The choice of formulation components and solution pH was based upon early phase development work in which the drug product stability and degradation pathways were evaluated as a function of pH, buffer species, and excipients. Later development work supported the final choices made for the excipients and pH.

Excipients

The drug product excipients are listed as follows:

- sodium succinate (anhydrous)
- succinic acid
- sodium chloride
- polysorbate 80
- water for injection

There were no novel excipients in this product.

Quality summary and conclusions

The sponsor provided responses to the quality evaluation report that satisfactorily addressed all issues raised by the evaluator.

III. Nonclinical findings

Introduction

An adequate nonclinical dossier of good quality studies was submitted. Relevant studies were GLP compliant. Most in vivo studies were supported by toxicokinetic and antibody data.

Pharmacology

Primary pharmacology

MS is a demyelinating inflammatory disorder of the central nervous system (CNS) involving autoimmune responses to myelin antigens. Studies demonstrating the presence of inflammatory cells and their products in the brain lesions of MS patients, in addition to reports from animal models, have led to the generally accepted hypothesis that MS is mediated by pathogenic T cell responses against myelin antigens, followed by a broader neurodegenerative process.¹

The IL-2R has two forms, a trimeric high-affinity receptor composed of CD122, CD132 and CD25, and a dimeric intermediate-affinity receptor composed of only CD122 and CD132. Daclizumab would therefore be expected to modulate high-affinity IL-2 receptor signalling, but not to affect intermediate-affinity IL-2 receptor signalling. Data from studies on the expansion of CD56^{bright} natural killer (NK) cells in daclizumab-treated patients with MS are consistent with this expectation.^{2, 3} Activated T cells express CD25 and IL-2 signalling drives the proliferation and differentiation of these cells.⁴ Modulation of IL-2 signalling via inhibition at the high-affinity IL-2 receptor is believed to selectively inhibit activated T cell responses that are involved in the pathogenesis of MS.

Although CD25 was shown to be expressed by activated mouse, rat and human T cells, DAC HYP bound only to the human cells and not the rodent cells, and inhibited IL-2-induced proliferation only in the human cells. Subsequent studies were therefore conducted with human cells in vitro.

In addition to inhibiting IL-2-induced T cell proliferation, DAC HYP was shown to inhibit inflammatory cytokine production (tumour necrosis factor alpha (TNF α), interferon gamma (INF γ), IL-5, IL-9 and IL-13) in activated peripheral blood mononuclear cells (PBMC). A number of other activities of daclizumab in MS patients have been reported in the literature but are the purview of the clinical evaluator.

To investigate the impact of the changes in the manufacturing process for the production of DAC HYP on the function of the antibody, several studies were conducted comparing DAC HYP with other forms of daclizumab (DAC Nutley and DAC Penzberg, both manufactured on smaller and larger scales, respectively), and DAC IgG2M3-QL which has mature heavy and light chain regions nearly identical to those of DAC HYP but built onto an IgG2M3 backbone, a mutated form of IgG2 that minimises activation of antibody-dependent cell-mediated cytotoxicity (ADCC). These studies revealed comparable binding affinity of DAC HYP and DAC Nutley to recombinant human and cynomolgus monkey CD25. They also revealed broadly comparable effects of the various forms of daclizumab in inhibiting IL-2-induced proliferation of lymphoblasts, phytohaemagglutinin (PHA) induced proliferation of PBMCs, PHA-induced and anti-CD3/anti-CD28-induced release of cytokines by PBMCs and down-modulation of cell surface CD25 expression in PHA-activated T cells (an exception was a lack of down-modulation of cell surface CD25 expression in activated T cells by IgG2M3-QL; DAC Penzberg was not tested for down-modulation of cell surface CD25 expression).

Several studies examined ADCC activity of the various forms of daclizumab, revealing weaker ADCC activity of DAC HYP compared to DAC Nutley and DAC Penzberg

¹ Compston, A et al. (2008) Multiple sclerosis. *Lancet* 372: 1502–17.

² Martin, J et al. (2010) An IL-2 paradox: Blocking CD25 on T cells induces IL-2-driven activation of CD56^{bright} NK cells. *J. Immunol.* 185: 1311-1320

³ Sheridan, J et al. (2011) Intermediate-affinity interleukin-2 receptor expression predicts CD56^{bright} natural killer cell expansion after daclizumab treatment in the CHOICE study of patients with multiple sclerosis. *Multiple Sclerosis J.* 17: 1441-1448

⁴ Malek, et al. (2008) The biology of interleukin-2. *Annu. Rev. Immunol.* 26: 453-479

(DAC IgG2M3-QL did not show ADCC activity). In the case of DAC Nutley, this was shown to be associated with this form of daclizumab having greater CD16 (FcγRIII) binding compared to DAC HYP, and correlating with this, a greater ability to down-modulate CD16 than DAC HYP.

None of the tested forms of daclizumab (DAC HYP, DAC Nutley and DAC Penzberg) elicited significant complement-dependent cytotoxic (CDC) activity.

Secondary pharmacodynamics and safety pharmacology

No secondary or safety pharmacology studies were submitted, with safety pharmacology end-points (electrocardiogram (ECG), blood pressure) being incorporated in the repeat-dose studies and a neurobehavioural assessment being incorporated in a mechanistic study (see below). This is acceptable.

Pharmacokinetics

The single pharmacokinetic (PK) study conducted (intravenous (IV) in cynomolgus monkeys) investigated pharmacokinetic differences between 3 lots of daclizumab (DAC HYP, DAC Nutley and DAC Penzberg). According to the strict equivalence criteria, DAC HYP was equivalent to the Nutley reference material for the critical parameters of the area under the curve from dosing to last measurable concentration (AUC_{0-last}) and maximum (peak) serum concentration (C_{max}), but not for the half-life ($t_{1/2}$). However, DAC HYP showed greater equivalence to the Nutley material than did the Penzberg material which failed to meet the criteria for both AUC_{0-last} and $t_{1/2}$. The development of anti-daclizumab antibodies in some of the animals may have interfered with the accuracy of the comparisons. All materials showed slow clearance (CL) of approximately 0.163 L/h/kg, a small volume of distribution (V_d) (approximately 58 mL/kg) and a long half-life ($t_{1/2}$ approximately 275 h). Similar values for half-life were observed in the single-dose IV toxicity study. These pharmacokinetic characteristics of DAC HYP are similar for cynomolgus monkeys and humans.

Distribution (including protein binding), metabolism, and excretion studies were not conducted and are not considered to be necessary for DAC HYP. For therapeutic proteins which modulate cytokines, an investigation of the effect of cytokine modulation on cytochrome p450 (CYP) enzymes is appropriate. While an in vitro study was not submitted, a clinical study evaluated the effect of DAC HYP on the activities of CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A in MS patients, with negative results reported.

Toxicokinetic data from the single-dose, repeat-dose and reproductive toxicity studies, all by the SC route in cynomolgus monkeys, revealed broad dose-proportionality of exposure over the range 5-200 mg/kg. Absorption following SC administration was slow, with time from dosing to maximum (peak) serum concentration (T_{max}) values being about 62 h (data from all studies). No sex differences in pharmacokinetics were evident from the pharmacokinetic or toxicokinetic studies. Accumulation of about 1.7-fold was observed in the repeat-dose toxicity studies (steady state AUC: AUC after the first dose).

In the majority of studies, anti-daclizumab antibodies, and neutralising antibodies (when assessed), were detected in some animals following both single and repeated SC administration of DAC HYP, particularly at the lower dose levels (5 and 10 mg/kg/administration) and resulted in a decrease or loss of serum DAC HYP concentrations. In general, the exclusion of antibody-positive animals from the group toxicokinetic evaluations did not compromise the toxicokinetic assessment, and overall, toxicokinetic data were broadly consistent across studies. While it should be borne in mind that animals which developed antibodies were exposed to daclizumab for less than the full duration of the study, given that most antibody-positive animals were in the lower

dose groups, this is not considered to have compromised interpretation of the toxicity data. Although relevant to the interpretation of the toxicokinetic and toxicology data, the development of anti-daclizumab antibodies in animals is not predictive of responses in humans, and anti-daclizumab antibodies were observed in clinical studies at relatively low levels, with the majority of subjects that became antibody-positive, doing so during the first year of treatment, and typically having a transient response.

Toxicology

Acute toxicity

One single-dose toxicity study was conducted at IV doses of 0, 15 and 30 mg/kg DAC HYP in cynomolgus monkeys, with observation for 16 days. As is usual for single dose studies with monoclonal antibodies, this study did not reveal any treatment -related effects. Although animal numbers were low (n = 1 of each sex), this is adequate for a study of a monoclonal antibody.

Repeat-dose toxicity

Four repeat-dose studies of DAC HYP in cynomolgus monkeys were submitted. This is considered an appropriate species based on primary pharmacology (expression of the epitope), pharmacokinetic data and broadly comparable tissue cross-reactivity (although some tissue elements showed DAC HYP-specific staining in humans but not cynomolgus monkeys (see below)). All studies used the SC route (the clinical route), with frequency of dosing being fortnightly. This was a higher dosing frequency than that proposed clinically (once monthly), which is consistent with the shorter half-life of DAC HYP in cynomolgus monkeys compared to humans (approximately 11 days versus approximately 21 days, respectively).

Study duration and dose levels were adequate. Study durations were 4, 13 and 39 weeks (3, 7 and 20 doses, respectively) and doses were up to 200 mg/kg/fortnight in all studies. Centre A conducted the 13 week study and 39 week study, while Centre B conducted the 4 week study and a second 39 week study. Animal numbers were adequate, although the small numbers of animals generally used in monkey studies can make interpretation difficult. End-points examined were appropriate and included ECG, ophthalmology, blood pressure and immunophenotyping (each examined in the 13 week study and both 39 week studies, except for blood pressure in the 39 week study; all findings of these examinations were negative), as well as the standard end-points (note that there was no necropsy in the 4 week study).

All repeat-dose studies included a recovery period of 8 to 12 weeks, and all included toxicokinetic monitoring and screening for anti-daclizumab antibodies, with the 13 week and 39 week studies including monitoring for neutralising antibodies.

Relative exposure

Exposure ratios have been calculated based on cynomolgus monkey: human serum area under the drug concentration curve (AUC). Human reference values for the area under the drug concentration curve to end of dosing period (AUC_{0-τ}) are from clinical Study 205MS302 (26 patients enrolled, 25 completed, age 18 to 65 years inclusive, 6 doses administered at 4 week intervals) as described in Table 1, below.

Table 1. Relative exposure in repeat-dose toxicity studies in cynomolgus monkeys (combined data for males and females at steady state)

Species	Study duration dose number	Dose ¹ mg/kg	AUC ^{2,3} µg h/mL	Exposure ratio ⁴
Monkey Cynomolgus	4 weeks (dose 3) (Centre B)	5	20,004	2.6
		50	227,484	30
		125	428,934	56
		200	673,784	88
	13 weeks (dose 6) (Centre A)	5	15,209	2.0
		50	147,441	19
		125	384,127	50
		200	575,310	75
	39 weeks (Centre A) (doses 10 and 19)	10	36,527&	5
		50	197,250	26
		200	708,000	92
	39 weeks (Centre B) (doses 10 and 20)	10	30,400	See footnote
		35	107,250	See footnote
200		564,000	See footnote	
Human MS patients	steady state	(150 mg)	15,314	–

1. fortnightly doses in cynomolgus monkeys and monthly doses in humans; 2. AUC_{0-τ} for the 4- and 13 week studies and AUC_{all} for the 39 week Centre A study; 3. at steady state; 4. calculated as 2 x monkey AUC: human AUC; note that values from some animals that developed anti-daclizumab antibodies were excluded from the analysis; and based on mean of 11 individual AUC values, since group sizes differed.

Toxicokinetic data from the 39 week Centre B study were inadequate for estimating AUC values because blood samples were taken at time points only up to 168 h after dosing. Whilst the determined AUC_{0-last} values (30,400, 107,250 and 564,000 µg/h/mL at the respective dose levels of 10, 35 and 200 mg/kg/fortnight) would be expected to underestimate real AUC values for the fortnightly dosing period, multiplying the determined AUC_{0-last} values by 2 would be expected to result in an overestimate. A

comparison of AUC values (and corresponding exposure ratio (ER) values) estimated by these methods at the 10 and 200 mg/kg dose levels with AUC (and ER) values obtained in the Centre A study at the same dose levels confirmed this expectation, with the former method giving the closer estimate at both dose levels. Thus, at the 10 mg/kg dose level, ER was estimated as 4.0 and 8 by the respective methods (Centre A study value, 4.8; approximately 17% underestimate and approximately 67% overestimate, respectively, relative to the Centre A value), and at the 200 mg/kg dose level, ER was estimated as 74 and 148 (Centre A study value, 92; approximately 20% underestimate and approximately 61% overestimate, respectively, relative to the Centre A value). For the remainder of this evaluation, the ER values that will be used for the 39 week studies at the 10 and 200 mg/kg dose levels are 5 and 92, respectively (from the Centre A study), while an ER value of 18 will be used at 35 mg/kg (the only dose level in the Centre B study that differed from the Centre A study). This value has been calculated by extrapolation from the Centre A study ($4.8 \times 35/10$ and $26 \times 35/50$ give values of approximately 18).

High exposure ratios were achieved (75 to 92 at the high dose).

Major toxicities

Skin

Changes in the skin were observed in both 39 week studies (20 doses), but not in the studies of shorter duration (4 weeks and 13 weeks (3 and 7 doses), nor in the fertility studies in either males or females (5 doses in both sexes). The skin changes were observed as clinical signs (increased incidence, duration of occurrence and earlier onset of dry skin, and also red and darkened skin in the Centre A study), upon macroscopic examination at necropsy (increased incidence of yellow scale, Centre B study only) and upon histological examination (increased incidence of acanthosis, hyperkeratosis, and inflammation /mononuclear cell inflammatory infiltration). Generally, the severity of skin changes was minimal to mild, but one low dose monkey in the Centre A study had severe, non-resolving skin lesions that necessitated euthanasia. Given the background incidences, it was difficult to establish no observable effect levels (NOEL), but effects were seen at the low dose (10 mg/kg/fortnight) in the Centre A study and at the middle dose (35 mg/kg/ fortnight) in the Centre B study (giving NOELs of 'not established' and 10 mg/kg/fortnight (ER of approximately 5), respectively), indicative of expected skin reactions in patients given the recommended dose. In the Centre A study, there was no clear evidence of recovery of skin histopathological observations, whereas in the Centre B study, there was evidence of partial resolution. In clinical trials, DAC HYP increased the incidence of skin reactions, most commonly, rash, dermatitis and eczema. The majority of patients had skin reactions that were of mild or moderate severity, and generally resolved with appropriate treatment (such as steroids), although about 4% of patients discontinued treatment due to skin reactions.

Brain and spinal cord

Microglial aggregates in the brain were observed in most studies in which these organs were examined histologically (the 13 week and both 39 week repeat-dose studies, as well as the male fertility study and the mechanistic study), but not in the female fertility study. The incidence was dose dependent.

Table 2. Incidences of microglial aggregates in the brain in studies in which this organ was examined histologically

Study reference	Dose (mg/kg/fortnight)							
	Sex	0	5	10	35	50	125	200
13 weeks n = 3/sex	M	0	0	-	-	0	2	2
	F	0	0	-	-	1	2	1
39 weeks (Centre A) n = 4/sex	M	0	-	0	-	2	-	3b
	F	0	-	0	-	0	-	4b
39 weeks (Centre B) n = 4/sex	M	0	-	1a	0	-	-	3
	F	0	-	0	2	-	-	3
Male fertility, n = 5	M	0	-	0	-	2	-	5
Female fertility, n = 5	F	0	-	0	-	0	-	0
Mechanistic (single dose), n = 4	M	0	-	0	0	-	-	3c
Mechanistic (double dose), n = 4	M	0	-	0	0	-	-	3b

M = male; F = female; absent values = dose level not tested; a) = equivocal relationship to treatment (see text); b) = brain haemorrhage noted in 1 animal/group; c) brain haemorrhage noted in 2 animals/group.

Microglial aggregates in the brain were not observed at 5 mg/kg/fortnight (13 week study; ER 2.0), while at 10 mg/kg/fortnight in the combined studies at this dose level (ER approximately 5), they were found in only a single animal (40 animals investigated; 2.5% incidence). This was a single microglial aggregate and the incidence is within the background historical control incidence for the facility of 6.6% (see below). Therefore, 10 mg/kg/fortnight is considered the NOEL, as a substantial incidence (2/8 (25%), well above the background incidence of 6.6%) was observed at 35 mg/kg/fortnight (ER approximately 18) in the 39 week Centre B study. A substantial incidence was also observed at 50 mg/kg/fortnight in the 39 week Centre A study (ER 26) and the male fertility study (ER 28), with incidence rising to 13/16 at 200 mg/kg/fortnight (combined data for both 39 week studies; ER approximately 92). The severity of the microglial aggregates in the brain was graded as minimal in all 3 repeat-dose studies.

The finding had resolved at the end of the recovery periods in the 13 week and male fertility studies and had partially resolved in the remaining studies.

Microglial aggregates were less commonly observed in the spinal cord than in the brain, but were observed in both 39 week studies and in the male fertility study (the spinal cord was not examined in the female fertility study). The lowest dose at which they were observed (and then in only a single animal, in the male fertility study) was 50 mg/kg/fortnight (ER 28); the NOEL was 35 mg/kg (ER approximately 18).

Microglial aggregates in either the brain or spinal cord were not observed in any control animals in any of the studies submitted, but a detailed review of control cynomolgus monkeys from the testing facility revealed that they do exist as a background finding in the brain (seen in about 6.6% of control animals).⁵ Data were from 9 studies conducted between 2009 and 2011 involving a total of 76 animals (38/sex). Microglial aggregates were observed in the brain of animals from 4 of the 9 studies at incidences of 1/2, 2/12, 1/12 and 1/12, giving a total incidence of 5/76 (6.6%). The finding was described as 'focal gliosis' in the published paper, with 6 animals affected (4 males and 2 females), but in only 5 of the animals was the finding characterised by the presence of microglial cells (in the remaining animal, the focus was composed of oligodendrocytes).

Table 3. Incidences of microglial aggregates in the spinal cord in studies in which this organ was examined histologically

Study		Dose (mg/kg/fortnight)							
		Sex	0	5	10	35	50	125	200
13 weeks n = 3		M	0	0	-	-	0	0	0
		F	0	0	-	-	0	0	0
39 weeks Centre A n = 4	cervical	M	0	-	0	-	0	-	2
		F	0	-	0	-	0	-	0
	thoracic	M	0	-	0	-	0	-	0
		F	0	-	0	-	0	-	1
39 weeks, Centre B; n = 4		M	0	-	0	0	-	-	3
		F	0	-	0	0	-	-	1
Male fertility (thoracic), n = 5		M	0	-	0	-	1	-	0

A mechanistic study (Study P019-08-01) using a variety of stains for the brain and spinal cord sections was conducted in male cynomolgus monkeys to gain further insight into the characteristics of the microglial aggregates. This study used doses of up to 200 mg/kg/administration including a single dose phase (euthanised on Days 4 and 28/29) and a repeat dose phase (2 doses (Days 1 and 15), euthanised on Days 18 and 74). Microglial aggregates in the brain and/or spinal cord were observed at similar incidences after the single dose and two doses of DAC HYP. Staining for indications of myelin alterations and neuronal necrosis was negative (the latter finding is consistent with the results of a similar investigation made in the male fertility study), as were results of neurobehavioural assessment and ophthalmological examination, so the presence of microglial aggregates did not appear to result in neuronal damage or neurological dysfunction.

⁵ Butt et al. (2015) Microscopic background changes in brains of cynomolgus monkeys. *Toxicol Pathol.* 43: 513-518.

Two *in vitro* studies (Study RD-13-953 using human fetal microglia and Study R&D/13/970 using cultured primary microglia isolated from brains of adult cynomolgus monkeys) were conducted to investigate a possible mechanism by which DAC HYP caused the increase in microglial aggregates in cynomolgus monkeys. Two hypotheses were examined: firstly, microglial cells express CD25 so DAC HYP has direct effects on microglia, or alternatively, the second hypothesis was that DAC HYP had indirect effects on microglial cells. Neither human fetal microglia nor cultured primary microglia isolated from the brains of cynomolgus monkeys expressed CD25, the target of DAC HYP. Both the human fetal and the cynomolgus monkey microglia proliferated in response to IL-2, although, consistent with lack of CD25 expression, CD25-blocking antibody fragments did not affect IL-2 induced proliferation in either microglial population. The lack of expression of CD25 by cynomolgus monkey microglia makes the first hypothesis untenable and suggests that the increased incidence of microglial aggregates observed in the brain and spinal cord of DAC HYP-treated monkeys may have been an indirect effect, a consequence of increased IL-2 bioavailability within the CNS resulting from DAC HYP saturation of CD25 on cells other than microglial cells. The nonclinical evaluator considered this finding 'a pharmacological response to DAC HYP whose clinical relevance remains unknown'.

In a review of these CNS findings in monkeys by an Expert Pathology Working Group (6 veterinary pathologists), it was concluded that the microglial aggregates represented random focal accumulations of mononuclear cells, most of which appeared to be microglial cells, with no histological evidence of neuronal degeneration, axonal fragmentation, or demyelination in association with the aggregates.

In light of the indication and for the following reasons, the finding of microglial aggregates in the brain may appear not to be a major concern: the ER at the NOEL was approximately 5, the ER at the lowest observable event level (LOEL) (35 mg/kg/fortnight) was approximately 18 and correspondingly larger at higher doses (19 to 26 at 50 mg/kg/fortnight, ≥ 50 at ≥ 125 mg/kg/fortnight), the finding was of low severity, there was a lack of any detectable functional disturbances or neuronal damage, and there was evidence of recovery (either full or partial) after cessation of dosing. For microglial aggregates in the spinal cord, the low incidence and acceptable safety margin (ER of approximately 18 at the NOEL, 26 at the lowest observed effect level (LOEL)) is sufficient to alleviate major concern.

Haemorrhage in brain was observed in 2 studies, the 39 week Centre A study and the *in vivo* mechanistic study (P019-08-01), but only at 200 mg/kg/fortnight with high exposure (ER 92) (ER 26 at the NOEL (50 mg/kg/fortnight)). There was also a trend for an increase in the incidence of mononuclear cell infiltrates in various regions of the brain, but mainly at 200 mg/kg/fortnight, and these increases were against a variable and sometimes substantial incidence in the control group.

However, notwithstanding the conclusions of the above risk assessment regarding the microglial aggregates in the CNS, the finding was still reported across a majority of studies and its clinical relevance is not known. If the underlying mechanism is indeed increased IL-2 bioavailability, there is the possibility that the estimated safety margins for these changes could be lower than those calculated because the increased IL-2 levels may be exerted on a higher background level of IL-2 in MS patients compared with the cynomolgus monkey model.⁶ In order to provide more information on this issue, the TGA requested that the sponsor was asked to provide any available data on the relative CNS levels of IL-2 in cynomolgus monkeys and in MS patients. The sponsor replied that CNS and serum IL-2 concentrations were not measured in any of the nonclinical studies, so it is

⁶ Sharief M et al. (1993) Correlation of interleukin-2 and soluble interleukin-2 receptor with clinical activity of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 56: 169-174.

therefore not possible to make the comparison. The sponsor noted that in the pivotal clinical studies, no adverse events that were considered adverse drug reactions were reported under the nervous system disorders system organ class (SOC) for DAC HYP. Adverse events (AEs) in nervous system disorders SOC occurred at a lower incidence in patients in the DAC HYP group than in patients in the comparator group (placebo for Study 205MS201 or IFN β -1a for Study 205MS301). Many of the adverse events that were observed were representative of the symptoms or comorbidities of MS.

The proposed inclusion of these findings in the PI under the heading 'Toxicology' is considered warranted, and is supported by the nonclinical evaluator.

Lymph nodes

In the 39 week Centre B study, an increased incidence of increased size/number of germinal centres in various lymph nodes was observed histologically, with accompanying enlargement of the lymph nodes observed macroscopically. Histological changes were observed at all test doses (ER at the LOEL of approximately 5) in some lymph nodes. In the 39 week Centre A study, similar findings were only occasionally observed, with histological changes seen only in males at the high dose. Given that the findings were largely restricted to the 39 week Centre B study, there was a background incidence of the same finding in concurrent control animals, severity was minimal to moderate, there was evidence for partial recovery, there was no evidence for immunotoxic potential of DAC HYP, and that the finding was possibly related to the primary pharmacological activity of the drug, lymph node hyperplasia is not considered a major concern.

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies were not submitted. MAbs are not expected to enter the cell and interact with DNA and there is no specific genotoxicity concern for DAC HYP, so genotoxicity studies are not required. Standard carcinogenicity studies are generally inappropriate for MAbs. Unless the mechanism of action of the drug or findings from other studies, such as proliferative findings in the repeat-dose toxicity studies, suggest concern regarding potential carcinogenicity, which does not apply to DAC HYP, no assessment of carcinogenic potential is required.

Reproductive toxicity

An acceptable package of reproductive toxicity studies covering investigations of fertility, embryofetal development and pre-/postnatal development, was submitted. Dosing was in cynomolgus monkeys by the SC route in all studies, fortnightly in the studies investigating fertility and weekly in the remaining studies, which is appropriate.

Potential effects of DAC HYP on fertility in males and females were investigated by examining fertility markers (sperm quality, menstrual cycling, reproductive hormones, and organ weights and gross and histological changes for reproductive organs) rather than assessing the outcome of matings. This is acceptable.

Study designs were appropriate, including investigation of appropriate end-points and the timing and duration of dosing. Five doses were given in the male and female fertility studies (approximately 60 days, sufficient time to cover all stages of spermatogenesis in males, and about 2 menstrual cycles in females), dosing in the embryofetal development studies was from gestation day (GD) 20 to 50 (covering the period of organogenesis), while dosing in the pre-/postnatal development study was from GD 50 to parturition (which covers the remainder of the gestation period; animals were not dosed during lactation). All studies included toxicokinetic monitoring and screening for anti-daclizumab antibodies.

Relative exposure

High exposure ratios were achieved (up to 102 and 85 in the male and female fertility studies, respectively, up to 139 in the main embryofetal development study and 55 in the pre-/postnatal development study) (Table 4).

Serum daclizumab concentrations were similar in pregnant animals (embryofetal development and pre-/postnatal studies) and non-pregnant animals (fertility studies and repeat-dose toxicity studies).

Table 4. Reproductive toxicity studies

Species	Study dose no.	Dose mg/kg ¹	AUC0- τ ² $\mu\text{g}\cdot\text{h/mL}$	Exposure ratio ³
Cynomolgus monkey	Fertility (males; dose 4)	10	41,623	5
		50	211,945	28
		200	784,071	102
	Fertility (females; dose 5)	10	39,626	5
		50	193,403	25
		200	647,282	85
	Embryofetal development (pilot study; dose 5)	200	630,000	165
	Embryofetal development (main study; dose 5)	10	24,000	6
		50	128,000	33
		200	533,000	139
Pre-/postnatal development (dose 13)	50	209,000	55	
Human (MS patients)	steady state	(150 mg)	15,314	-

1) fortnightly doses in the fertility studies, weekly doses in the embryofetal development and pre-and postnatal development studies in cynomolgus monkeys and monthly doses in humans; 2) at steady state; 3) animal:human serum AUC

Placental transfer and excretion in milk were both demonstrated in cynomolgus monkeys. These characteristics are expected for a monoclonal antibody.

Fertility studies

Animals were given 5 fortnightly SC doses of up to 200 mg/kg DAC HYP, with 5 main study animals sacrificed one week (males) or one month (females) after the last dose and 3 recovery animals sacrificed after a 12 week (males) or 60 day (females) recovery period.

Adequate pre-dose measurements (sperm quality, menstrual cycling and reproductive hormones) were conducted.

There were no findings indicative of an effect of DAC HYP on fertility in males. In a study of females menses ceased in one female (female no. 8) after the commencement of high dosing with DAC HYP. No hormone samples were taken from this animal during the dosing cycles, but in the post dosing cycle they showed no ovulatory oestradiol surge and no post ovulatory increase in progesterone (results from this animal were normal in the pre-study cycle). Ovary weight was markedly (11-fold for relative weight) increased in this female, and macroscopic examination revealed bilaterally and markedly enlarged ovaries and oviducts, with multiple cysts in each ovary, and microscopic examination of these cysts revealed that they were lined by simple, columnar, ciliated epithelium and most were filled with eosinophilic proteinaceous material resembling thyroid colloid. Marked papillary hyperplasia of the oviduct epithelium was also observed histologically and was considered to probably be a non-specific response to the ovarian cysts, which seems likely. There were no similar findings in other animals, although one low dose (50 mg/kg/fortnight) animal also had increased ovary weight (6-fold for relative weight), but menstrual cycling was normal.

The report of the study was amended to include the results of the Pathology Working Group (PWG) which conducted an independent review of the histopathology of the existing ovarian tissue slides from the affected high dose female. In the original study report, it was stated that the ovarian cysts in this animal most closely resembled 'serous cystadenoma', a benign ovarian epithelial tumour; given the presence of the finding in a high dose female, it was considered that a relationship to treatment with DAC HYP could not be ruled out, but that given the normal hormonal patterns in other high dose animals, it was not possible to establish a definitive relationship to DAC HYP. The PWG revised the histopathology interpretation for this animal, considering that the ovarian cysts were consistent with cystic rete ovarii, and that any relationship of DAC HYP to this finding was improbable.

Cysts in and around the ovary are common incidental findings in macaques of all ages, and can arise from the rete ovarii, embryonic remnants, or the cycling ovarian structures (follicles, corpora lutea).⁷ Ovarian cysts were occasionally observed in females in the repeat-dose studies at similar doses, but there was no evidence of a treatment-related effect. Given this, and the interpretation of the PWG (a consensus of 5 pathologists), the ovarian cysts in female no. 8 in the fertility study seem unlikely to be treatment-related, although the fact that this female had normal menstrual cycles prior to treatment (2 cycles investigated) and that these ceased in the first cycle following the start of treatment is a surprising co-incidence.

Brain, and in males, spinal cord, were also examined (gross and histological) in these studies to contribute to the repeat-dose data on changes in these organs. The results are discussed under 'Repeat-dose toxicity' above.

Embryofetal development studies

The only adverse finding in the embryofetal development studies was an increase in the incidence of fetal loss during the period of organogenesis in the high dose group (200 mg/kg/week) in the main study (3/15 (20%), more than double the loss in the concurrent control group (1/13 (7.7%)) and the mean historical control value for the testing facility (8.3% fetal loss between GD 20 and GD 100 (n = 217)), and outside the historical control range for the testing facility (0 to 18.2%) at the time the study was conducted. The animal/human serum exposure ratio at this dose was approximately 140.

⁷ Cline, J et al. (2008) Selected background findings and interpretation of common lesions in the female reproductive system in macaques. *Toxicol. Pathol.* 36: 142s-163s.

The no-effect dose for fetal loss in this study was 50 mg/kg/week (ER 33). There were no fetal losses in the pilot embryofetal development study at 200 mg/kg/week (n = 5). The combined fetal loss for the main and pilot embryofetal development studies (3/20 (15%)) was still above the control value (1/13 (7.7%), main study; no control in the pilot study) and mean historical control value, but lay within the historical control range for the testing facility (0 to 18.2%). There was no evidence of a teratogenic effect of DAC HYP.

Fetal losses in the pre/postnatal development study were lower in the treated group than the control group (1/20 compared with 3/20), although this study was conducted over a different period of gestation and at a lower dose (50 mg/kg/week) (see below).

Pre/postnatal development study

In the pre/postnatal development study, infants were evaluated for 180 days after birth and extensive observations were made, including viability, growth and development, neurobehavioural evaluation, immunological assessment, external assessment and necropsy findings, both macroscopic and histological.

The only adverse finding was an increase in the incidence of infant losses in the first 29 postnatal days in the treated group (7/19 (36.8%)), more than double the loss in the concurrent control group (3/17 (17.6%)). Death of infants due to lack of maternal care was higher in the test group (3/19 (15.8%)) than the control group (1/17 (5.9%)) but was within the test facility historical control range (mean 5.6%, range 0 to 16.7%), although towards the upper end. Disregarding the infant that was euthanised with a fractured femur (not considered treatment-related), the incidence of infant losses not related to lack of maternal care was 3/19 (15.8%) but was within the test facility historical control range (mean 4.9%, range 0 to 20.0%). The historical control data for infant losses related to lack of maternal care were provided by the sponsor following a TGA request. The study authors did not consider the infant losses treatment-related, and given that incidences lay within the historical control range and that the nature of the infant losses was varied, this evaluator concurs with that conclusion.

Pregnancy classification

In the original submission and following requests from the TGA for more information, the sponsor has proposed Pregnancy Category B1.⁸ The sponsor's response to requests for more information regarding justification of Pregnancy Category B1 referred a question (and the sponsor's response to it) related to infant losses (that is, post birth) rather than fetal losses (during pregnancy). Although there was no evidence of teratogenicity with daclizumab treatment in the submitted studies with cynomolgus monkeys, there were increased fetal losses in the embryofetal development study. An increased risk of early prenatal loss in cynomolgus monkeys has also been reported for another daclizumab product registered in the USA, Zenapax, which has a Pregnancy Category of C⁹ (Zenapax PI document, USA), which aligns with the Australian Pregnancy Category of B3.¹⁰ A Pregnancy Category of B3 for Zinbryta is recommended.

⁸ Pregnancy Category B1 (TGA; Australia): Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

⁹ Pregnancy Category C (FDA; United States): Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. (Note: This is the pregnancy risk category according to the FDA: Labeling for Prescription Drugs Used In Man (1979) and has been replaced by FDA: Pregnancy and Lactation Labeling Final Rule (PLLR) (2015)).

¹⁰ Category B3 (TGA; Australia): Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Local tolerance

Local tolerance studies (one in vitro and one in vivo) were submitted but were relevant to the IV route, whereas the proposed clinical route is SC. For a potential future IV route, it is noted that DAC HYP was not found to be haemolytic in vitro. Following injection into the rabbit ear vein, DAC HYP was not found to cause irritation, although the incidence of erythema was increased in the treated ear. Incidences and severity of perivascular haemorrhage were also above control levels, but this finding was not associated with an inflammatory cell infiltrate and was considered to be due to injection trauma.

The SC injection sites were examined histologically in the male fertility study and the 39 week repeat-dose study conducted by Centre B. Multifocal perivascular mononuclear cell infiltrates in the subcutis (of minimal-moderate severity) at the injection sites were observed at ≥ 50 mg/kg/fortnight in the male fertility study and at ≥ 10 mg/kg/fortnight in the 39 week study. No NOEL was established in the latter study, with 3/8 animals affected at the LOEL of 10 mg/kg/fortnight (ER approximately 5), suggesting the possibility of injection site irritation in the clinic.

Immunotoxicity

A stand-alone immunotoxicity study was not conducted, but the immunotoxic potential of DAC HYP was investigated as part of the repeat-dose toxicity studies, which is acceptable. As noted above, immunophenotyping of lymphocyte populations by flow cytometry was included in the 13 week and both 39 week studies. Additionally, the 39 week Centre B study included an evaluation of T lymphocyte proliferation, NK cell activity and serum immunoglobulins. The pre-/postnatal study also included serum immunoglobulin evaluation of maternal animals, as well as more detailed immunological evaluation of infants. The only positive finding in all these tests was an increase in IgG levels at the high dose (200 mg/kg/week) in the 39 week Centre B study which may have been due to the detection of test article by the assay.

Tissue cross-reactivity

Study DAC.08.01 revealed binding of DAC HYP to a broad range of tissue elements in tissue sections from both humans and cynomolgus monkeys. The study authors noted that some of the tissue elements that showed DAC HYP-specific staining have been reported to express CD25, including various epithelia (breast and kidney), mononuclear leukocytes (lymphocytes), neurons, glial cells, dendritic and spindloid cells, skeletal myofibres, retina, and testicular germinal epithelium, whereas some of the other tissue elements that showed DAC HYP-specific staining (various epithelia, cardiac and smooth myofibres, glomerular cells, hepatocytes, ovarian granulosa and stromal cells, islet cells, decidual cells, meninges, testicular interstitial cells, myofibrocytes, and epithelial-reticular cells) have not been reported to express CD25. Most of the tissue elements that showed DAC HYP-specific staining in human tissues but not cynomolgus monkey tissues have not been reported to express CD25, but the significance of this to the use of cynomolgus monkeys as a model is unclear.

Paediatric use

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

Nonclinical summary and conclusions

Nonclinical summary

- An adequate nonclinical dossier of good quality studies was submitted. Relevant studies were GLP compliant. Most in vivo studies were supported by toxicokinetic and antibody data.
- Although CD25 was shown to be expressed by activated mouse, rat and human T cells, DAC HYP only bound to, and showed activity in, the human cells and not the rodent cells. DAC HYP and Roche's daclizumab showed comparable binding affinity to recombinant human and cynomolgus monkey CD25, comparable activity in various functional assays, and both lacked CDC activity, but DAC HYP showed lower ADCC activity, consistent with its lower ability to compete for CD16 binding.
- No secondary or safety pharmacology studies were submitted. Safety pharmacology end-points (ECG, blood pressure) were incorporated in the repeat-dose studies, with no effects of treatment observed. Neurobehavioural assessment in a mechanistic study also revealed no effects of treatment.
- In cynomolgus monkeys, DAC HYP and other forms of daclizumab showed slow clearance, a small volume of distribution and a long half-life. Absorption following SC administration was slow. Exposure was broadly dose-proportional over the range 5-200 mg/kg. No sex differences in pharmacokinetics were observed. Accumulation of about 1.7-fold was observed in the repeat-dose toxicity studies (steady state AUC: AUC after the first dose). The pharmacokinetic characteristics of DAC HYP were similar in cynomolgus monkeys and humans.
- In a single-dose IV toxicity study in cynomolgus monkeys at doses up to 30 mg/kg, DAC HYP did not show any adverse effects.
- Four repeat-dose SC studies of DAC HYP were conducted in cynomolgus monkeys. Study durations were 4, 13 and 39 weeks (one 39 week study was conducted by Centre A and one by Centre B) and doses were up to 200 mg/kg/fortnight in all studies (achieving ERs of approximately 90). All studies included a recovery period of 8 to 12 weeks.
- Target organs were skin (dry and/or red skin observed clinically, and increased incidences of acanthosis, hyperkeratosis and inflammation/mononuclear cell inflammatory infiltration observed histologically), brain and spinal cord (microglial aggregates in the brain and spinal cord, an increased incidence of mononuclear cell infiltrates in various brain regions, and occasional incidences of haemorrhage/microhaemorrhage in the brain at a high dose), and lymph nodes (enlargement observed macroscopically and lymphocytic hyperplasia observed histologically).
- No NOAEL was established for changes in the skin, and the skin is affected by treatment in a small proportion of patients. Lymph node findings were largely restricted to the 39 week Centre B and were assessed not being of major concern. There was a substantial safety margin for brain haemorrhage/microhaemorrhage and mononuclear cell infiltrates in the brain (ER 92¹¹). For the finding of microglial aggregates in the brain, a NOEL was established at 10 mg/kg (ER approximately 5)), ERs (\geq approximately 18) at the higher doses were moderate-high, the finding was of low severity, there were no functional disturbances or neuronal damage, and there was evidence of recovery (full or partial) after cessation of dosing. A mechanistic study

¹¹ ER = animal/human systemic (serum AUC) exposure ratio.

showed that microglia did not express CD25, suggesting that the aggregates in the brain were unlikely to be a direct effect of DAC HYP, but possibly a pharmacological response to increased IL-2 bioavailability.

- Genotoxicity and carcinogenicity studies were not conducted and are not required.
- Reproductive toxicity studies included fertility studies (males and females separately; 5 doses), embryofetal development studies (GD 20 to 50) and a pre-/postnatal development study (GD 50 to parturition, with monitoring of infants for 6 months), all in cynomolgus monkeys by the SC route. Dosing was fortnightly in the fertility studies and weekly in the other studies. A single dose level (50 mg/kg/week) was used in the pre-/postnatal development study (ER 55), while other studies used doses up to 200 mg/kg/administration (ER 85 to 165). Animals were not mated in the fertility studies, but fertility markers (sperm quality in males, menstrual cycling in females, reproductive hormones, and organ weights and gross and histological changes for reproductive organs) were assessed. There were few effects of treatment in any of the studies. Menses ceased in one high dose female in the fertility study; the animal was diagnosed with cystic rete ovarii (unlikely to be treatment-related). Fetal loss was increased at the high doses in the main (but not the pilot) embryofetal development study.
- Local tolerance studies were relevant to IV rather than SC administration, but there was no evidence of haemolysis or an irritant effect in rabbit ear veins. Multifocal perivascular mononuclear cell infiltrates in the subcutis (of minimal-moderate severity) were observed at the SC injection sites in some studies. In the 39 week Centre B study, no NOEL was established (ER approximately 5 at the LOEL of 10 mg/kg/fortnight), suggesting the possibility of injection site irritation in the clinic.
- Potential immunotoxicity was investigated in several repeat-dose toxicity studies and the pre-/postnatal study. Investigations included immunophenotyping of lymphocyte populations by flow cytometry, and evaluation of T lymphocyte proliferation, NK cell activity and serum immunoglobulins. Results were not indicative of an immunotoxic potential of DAC HYP.
- Tissue cross-reactivity was broadly similar in humans and cynomolgus monkeys, although some tissue elements not previously reported to express CD25, showed DAC HYP-specific staining in human tissues but not cynomolgus monkey tissues.

Nonclinical conclusion

- An adequate dossier of nonclinical data was submitted.
- Primary pharmacology (in vitro) studies focused on demonstrating similar functional activity of DAC HYP and other forms of daclizumab (except for lower ADCC activity than Roche's daclizumab).
- The pharmacokinetics of DAC HYP in cynomolgus monkeys were characteristic of a monoclonal antibody. The development of anti-daclizumab antibodies in a number of animals reduced serum daclizumab concentrations but overall did not jeopardise the interpretation of the toxicity studies or toxicokinetic data.
- The cynomolgus monkey was used in all the main toxicity studies and is an appropriate model. The main target organs were skin, brain and spinal cord. The nonclinical studies predicted the potential for skin changes that were observed clinically at low incidence. The clinical relevance of the main finding in the monkeys (microglial aggregates in the brain) is unknown.
- Genotoxicity and carcinogenicity studies were not conducted and are not required.

- Reproductive toxicity studies covered fertility (markers of fertility), embryofetal development and pre/postnatal development end-points. There was some evidence for increased fetal loss in the embryofetal development study.
- In general, the nonclinical studies and risk assessment of DAC HYP do not raise undue concerns; however, the clinical significance of the CNS finding of microglial aggregates (and microhaemorrhage at high doses) remains unknown, and its inclusion in the Product Information (PI) document is supported.
- Amendments to the draft PI were recommended by the nonclinical evaluator but these are beyond the scope of this AusPAR.

IV. Clinical findings

The full clinical evaluation of Zinbryta (daclizumab) was comprised of two parts; the initial clinical evaluation was supplemented by a secondary supplementary clinical evaluation which concentrated on efficacy, particularly the post hoc analyses and safety. A secondary evaluation was requested by the Delegate (for details see below and Attachment 3).

A summary of the clinical findings is presented in this section. Further details of the clinical findings can be found in Attachment 2 for the initial clinical evaluation; and Attachment 3 for the supplementary clinical evaluation.

Introduction

Clinical rationale

The main magnetic resonance imaging (MRI) markers of MS disease activity are lesion load and atrophy. Lesion load is assessed on conventional T2-weighted, fluid-attenuated inversion recovery (FLAIR) and post-contrast T1-weighted MRIS sequences.

The prevention of clinical relapses and disability progression as well as the subclinical brain injuries that occur during the relapsing phase of MS are recognised as important therapeutic benefits for MS patients.

MS pathology in the cerebral white matter is characterised by focal areas of demyelination and axonal injury and, in acute lesions, by activated T-lymphocytes in the adjacent perivascular spaces and migration of inflammatory cells through a compromised blood-brain barrier (BBB). Autoreactive T-cells directed against myelin antigens in the CNS play a role in the initiation and propagation of MS lesions, contributing to the destruction of myelin, axons, and oligodendrocytes through both direct and indirect effects of inflammation.

DAC HYP works through a novel, reversible modulation of IL-2 signalling, inhibiting CD25 dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact. This signalling modulation results in several well-characterised immunologic changes that were hypothesized to result in selective targeting of both white and grey matter MS pathology while also preserving key protective functions of the immune system, as follows:

- Since activated but not resting T-cells express CD25 and depend on the high-affinity receptor to respond efficiently to IL-2, DAC HYP selectively inhibits activated T-cells without causing a nonspecific immune-depletion of lymphocytes.
- DAC HYP treatment results in an expansion of immune-regulatory NK cells, the CD56^{bright} NK cell. CD56^{bright} NK cells have been shown to selectively target activated

but not resting T-cells in MS, and the magnitude of their expansion post-treatment has correlated with the therapeutic response to DAC HYP.

- Regulatory T-cells (T_{reg}) express CD25 and play an important role in immune system homeostasis and regulation. While there is a reversible decrease in the number of circulating T_{reg} cells during DAC HYP treatment, T_{reg} cells express high levels of the intermediate affinity IL-2 receptor, thereby enabling continued response to IL-2 signals. The cellular proliferation status, cytokine production profile, and epigenetic markers of the FOXP3 promoter indicate that a stable and functionally competent population of T-reg cells is maintained in the presence of long-term DAC HYP treatment despite CD25 antagonism. Compared to other forms of daclizumab, DAC HYP has a decreased amount of antibody-dependent cellular cytotoxicity, and this was believed to be advantageous for maintaining T-reg cell populations during long-term use.

In summary, the novel IL-2 signalling modulation of DAC HYP represents a targeted and reversible therapeutic approach to MS treatment that can selectively impact both grey and white matter MS pathology without causing nonspecific immune-depletion. DAC HYP's mechanism of action is distinct and differentiated from other therapies available to treat RMS. The impact of DAC HYP on T-reg cells was an area of potential concern but the demonstration of functional adaptation by T-reg cells during DAC HYP use as well as the expansion of other immune-regulatory cell populations provided a basis for managing any potential impact on T-regs; therefore, DAC HYP was systematically evaluated in clinical studies to define its risks and benefits in relapsing MS.

Contents of the clinical dossier

The submission contained the following clinical data:

- 5 clinical pharmacology studies, including 5 that provided PK data and 3 that provided PD data.
- 1 population pharmacokinetic (popPK) analysis.
- 2 pivotal efficacy/safety studies.
- 1 dose-finding study.
- 3 other efficacy/safety studies, 2 of which are ongoing.
- An Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS).

In addition, the sponsor's submission contained a clinical overview, Summary of Clinical Efficacy (SCE), Summary of Clinical Safety (SCS) and literature references.

Paediatric data

The submission did not include paediatric data. MS is a condition that most commonly has an onset in adults (usually aged over 20) resulting in very limited clinical value in the paediatric population. The sponsor has submitted paediatric investigation plans in the EU and the US (United States). The applicant proposes to investigate the DAC HYP in children and adolescents aged between 10 and 18 years.

Good clinical practice

The studies used as a basis for clinical data presented in this dossier were conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6 'Guideline for

Good Clinical Practice.¹² The studies also meet with the requirements of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each PK topic.

Table 5. Submitted pharmacokinetic studies

PK topic	Subtopic/dose	Study ID	Study aims ¹
PK in healthy adults	General PK (Multiple dosing) DAC HYP 200 mg every 2 weeks x 9 doses DAC HYP; 200 mg loading dose plus 100 mg every 2 weeks x 8 doses; placebo Subcutaneous administration	DAC-1014	To determine the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of multiple doses of DAC HYP administered by SC injection
	General PK (Single dosing) DAC HYP: 50 mg; 150 mg; 300 mg; placebo Subcutaneous administration	DAC-1015	To determine the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of SC DAC HYP
	General PK (Single dosing) DAC HYP 200 mg; 400 mg; placebo Subcutaneous administration	DAC-1018	To determine the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of IV DAC HYP
Genetic/gender-related PK	PK Profile in Japanese and Caucasian healthy volunteers Single dose PK	205HV102	To evaluate the PK, safety, and tolerability of DAC HYP administered as a single SC dose in Japanese and Caucasian adult healthy volunteers
PK in target population	Auto-injector sub-study. DAC HYP 150 mg SC from a PFS by either manual injection or by auto-injector every 4 weeks for 4 doses-16 weeks	205MS203	To compare the systemic exposure of daclizumab following SC administration of 150 mg DAC HYP using the single use auto-injector (PFP) to the systemic exposure

¹² ICH E6 (R1): The tripartite harmonised ICH Guideline was finalised under Step 4 in May 1996. This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and institution review boards (or ethics committees). GCPs cover aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process.

PK topic	Subtopic/dose	Study ID	Study aims ¹
			following manual PFS injection
	Intensive PK sub-study DAC HYP 150 mg SC by PFS every 4 weeks for 6 doses-24 weeks	205MS302	To characterize the PK of DAC HYP following single and multiple doses of SC DAC HYP administered by the PFS in a subset of subjects with RRMS
	DAC HYP 150 mg SC by PFS every 4 weeks for 3 Doses 12 weeks	205MS302	To evaluate the effect of DAC HYP on the PK of probe substrates for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in MS subjects
Population PK analyses	Derived from DAC-1014, DAC1015 DAC-1018 and 205MS301		

(1) Indicates the primary aim of the study. Note PK = pharmacokinetics; PD = pharmacodynamics; SC = subcutaneous

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

First clinical evaluator's conclusions on pharmacokinetics

- Since the expected consequence of metabolism of DAC HYP is degradation to small peptides and single amino acid, no studies were performed to assess the route of excretion of DAC HYP; this is in line with ICH S6(R1) guideline and accepted by the evaluator.¹³ As a high molecular weight protein, the contribution of renal clearance is considered to be negligible.
- At the proposed dosing interval accumulation is anticipated and has been estimated to be about 2.5 fold.
- No data were submitted regarding hepatic impairment. The clearance of DAC-HYP is dependent on proteolysis which in turn dependent on the production of proteolytic enzymes the effect of basal albumin levels should be investigated (which is altered in hepatic impairment) as this is known to have an influence on other humanised MAb therapies.
- The development of anti-drug antibodies (ADAs)/neutralising antibodies (Nabs) has no clinically significant effect on clearance of DAC HYP.
- The PK of DAC HYP is similar in subjects with RRMS and healthy volunteers.
- The findings for the population PK analysis show that body weight has an influence on clearance; higher body weight increases the clearance.
- Multiple dosing of DAC HYP 150 mg SC every 4 weeks in MS patients had no effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A.

¹³ ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals: a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. It applies to products derived from characterised cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells. Published 30 September 1997; Effective 01 March 1998.

Supplementary evaluator's conclusions on pharmacokinetics

Pharmacokinetic data was not assessed by the supplementary clinical advisor.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 (below) shows the studies relating to each PD topic.

Table 6. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on relative peripheral levels of CD25+ T-cells and absolute CD4+ T-cell counts by flow cytometry analysis.	DAC 1014
		DAC 1015
		DAC 1018
Secondary Pharmacology	Levels of circulating anti-Daclizumab antibodies (ADA) were assessed. (Immunogenicity)	DAC1014
		DAC 1015
		DAC 1018

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

First round clinical evaluator's conclusions on pharmacodynamics

A pharmacodynamic effect was observed that supported the proposed mechanism of action with a serum level of at least 5 µg/mL is required to maintain the PD effect.

Supplementary clinical evaluator's conclusions on pharmacokinetics

Pharmacodynamic data was not assessed by the supplementary clinical evaluator.

Dosage selection for the pivotal studies

The dose selection for the pivotal efficacy studies was made based on an investigational form of daclizumab manufactured using a different process and cell line (DAC Penzberg) and was undertaken in subjects with RRMS based on the results of this study 150 mg SC and 300 mg SC were selected as the doses to carry forward. No difference in efficacy was seen in Study 205MS201 between the 150 mg SC and 300 mg SC dose, this may mean that 150 mg is in the maximum efficacious dose range. That the use of a lower dose, which may still achieve efficacy but minimise adverse events has not been explored is a deficiency.

First round clinical evaluator's overall conclusions on dosage selection for the pivotal studies

It has not been made clear how the dose selection was made. There was no statistically significant difference seen between the 150 mg dose and 300 mg dose. This may mean that

the 150 mg dose is in the maximum effective dose range and the lowest effective dose has not been established.

Supplementary clinical evaluator's overall conclusions on dose selection for the pivotal studies

A full evaluation of these claims is beyond the scope of this SCER, but the sponsor's selection of 150 mg and 300 mg as doses worthy of further study appears broadly reasonable.

Based on the results of DAC-1012, 150 mg SC 4 weekly and 300 mg SC 4 weekly were selected for the Phase II placebo-controlled study, 205MS201 (later designated as a pivotal study). In Study 205MS201, no difference in efficacy was observed between the 150 mg and 300 mg doses, so the lower dose was selected for the Phase III active-controlled study, 205MS301.

As noted by the first clinical evaluator, this development path suggests that efficacy plateaus above 150 mg, but it does not establish with certainty whether lower doses could still achieve comparable efficacy with an improved safety profile. The evidence suggests that, for DAC Penzberg, the optimal dose is greater than 75mg 4 weekly, and may be as high as 300 mg 4 weekly. To the extent that DAC HYP is equivalent to DAC Penzberg, Study 205MS201 further narrows down the optimal dose to somewhere above 75mg and up to 150 mg. It is not clear, though, that a 2 weekly dose with a different preparation of daclizumab is sufficient to guide dosing with a 4 weekly regimen of DAC HYP. Also, there is a two-fold range of doses between 75 mg and 150 mg, leaving a wide range of doses untested. This represents a significant deficiency in the study program.

Efficacy

Studies providing efficacy data

Pivotal studies

The sponsor submitted two studies that were considered as pivotal for evaluation of efficacy; these were:

- Study 205MS201
- Study 205MS301

Study 205MS201 investigated the efficacy and safety of DAC HYP 150 mg every 4 weeks and DACHYP 300 mg every 4 weeks versus placebo. It was a multicentre, double-blind, placebo controlled, dose ranging study that included a 52 week treatment phase in subjects with RRMS. Subjects who completed the 52 week treatment phase without a major change in their medical status were eligible to enrol in the double blinded extension Study 205MS202 to continue dosing with DAC HYP.

Study 205MS301 investigated the efficacy and safety of DAC HYP 150 mg every 4 weeks versus IFN β -1a once weekly for up to 144 weeks in patients with RRMS by measuring the effects on relapse rate.

Other studies

The sponsor submitted three studies that were considered as non-pivotal for evaluation of efficacy as follows:

- Study 205MS202 was an open label extension study with subjects who completed treatment in Study 205MS201. The primary objective was to assess the safety and immunogenicity of extended treatment with DAC HYP.

- Study 205MS203 is a multicentre, single-arm, open label, extension study to evaluate the long-term safety and efficacy of DAC HYP in subjects with RRMS who have completed study treatment in 205MS202. At the time of evaluation, this study is ongoing and an interim report had been provided. It is an ongoing uncontrolled single arm study.
- Study 205MS303 is an extension to Study 205MS301. It is a single-arm open-label study and is ongoing. It is designed to assess the safety and efficacy of long-term treatment with DACHYP and will provide data for up to six years of treatment. An interim report had been provided. An influenza vaccine sub-study was part of the protocol for this study.

There were limitations to all three non-pivotal studies affecting use in the clinical evaluation of efficacy. For further details, please see Attachment 2 and Attachment 3.

Additional efficacy data evaluated by the supplementary evaluator only

The following efficacy data were supplied following the first clinical evaluation and evaluated by the supplementary clinical evaluator only:

- Additional efficacy analyses for the pivotal studies (Study 205MS201 and Study 205MS301).
- EMA questions (Q. 70, Q. 94 and Q. 95) and sponsor's responses to these questions.

First round clinical evaluator's conclusions on efficacy

The sponsor has complied with the relevant TGA adopted guidelines in the development of DAC HYP for the submitted indication.

The evidence of efficacy is dependent on two double-blind controlled studies one of which was placebo-controlled, the other active controlled. The studies were of adequate design and evaluated appropriate endpoints for the proposed indication.

The placebo controlled study (205MS201) was of 52 weeks duration the accepted duration of studies that utilise the annualised relapse reduction (ARR) as a primary endpoint is 2-years however it is recognised that there are ethical considerations regarding the use of placebo for such a period of time when effective treatments are available. Patients in the placebo controlled study were therefore given the opportunity to continue in a further dose blinded extension phase where patients who previously had not received treatment could cross-over onto active treatment and patients already on active treatment continued on such, this is considered acceptable.

Study 205MS301 was of a satisfactory duration to measure treatment effect in patients with MS that is a chronic, relapsing and remitting disease in its earlier phase. The studies were both randomised and adequate measures were in place to preserve the blind.

The studies utilised accepted and standard endpoints for clinical studies in MS that are recognised in the adopted guidelines. The primary endpoint for both clinical studies was the ARR. This is a clinical relevant endpoint for patients with RRMS in that the goal of treatment with disease modifying drugs for RRMS is to reduce the number of relapses (and to reduce disability).

Although there was no placebo arm in the active controlled pivotal study, which would have been desirable for assay sensitivity, the magnitude of the treatment effect observed for DAC HYP was similar to that seen in the placebo controlled study that had a similar study population. This study also demonstrates reproducibility of results seen in the placebo study.

Further evidence to support reproducibility is derived from Study 205MS202 that is a blinded, extension to Study 201. In this study, subjects that were previously on placebo were commenced on DAC HYP the result for the ARR for this patient group is similar to that seen in both the original study and those who received DAC HYP in the active controlled study. Sustained response rates in terms of reduction in ARR were demonstrated in this study.

The magnitude of the reduction of ARR versus placebo was about 54% and about 45% versus the active comparator IFN β -1a.

A clinically meaningful reduction in risk of disability progression as measured by Expanded Disability Status Scale (EDSS) of 57% versus placebo was seen in Study 205MS201. This result was also reported as statistically significant however as a tertiary endpoint no adjustment was made for multiple comparisons or endpoints.

In the active controlled study DAC HYP reduced the risk of disability progression by 16% ($p = 0.1575$) compared with IFN β -1a. Kaplan-Meier analysis estimated that 20.3% of subjects in the IFN β -1a group and 16.2% in the DAC HYP group had 12 week confirmed disability progression over 144 weeks.

In the placebo controlled study the results from the patient reported Multiple Sclerosis Impact Scale (MSIS-29) was not considered statistically significant per the sequential closed testing procedure because the procedure required that the 300 mg dose group be tested first and achieve statistical significance before the 150 mg dose group could be tested.

In the active controlled study the results from the patient reported MSIS-29 were reported in terms of a clinically meaningful deterioration of physical impact and achieved statistical significance in favour of DAC HYP. The magnitude of the difference is about 5%, which appears small but may be of clinical relevance in a population of patients where one of the goals of impact is to limit the physical effects of MS on the patient and may represent a very modest incremental benefit over an established active treatment.

Given that there was no difference in efficacy between the 150 mg SC dose and the 300 mg SC dose it may be the case that the 150 mg dose is the maximum effective dose range and the sponsor has not adequately explored the efficacy of lower doses.

The efficacy of DAC HYP in special populations has not been investigated and this should be reflected in the PI.

Supplementary evaluator's conclusions on efficacy

The sponsor provided a summary table of the key results of the two pivotal studies, and this table is reproduced below. It should be noted that the p-values flagged in the table as 'nominal' should not be considered statistically significant, indeed by a strict application of the closed testing procedure, these values should not even have been calculated or reported. Also, the cited p-values do not include any correction for multiplicity. In particular, despite the nominal p-value of 0.0211 cited for sustained disability progression in Study 205MS201, a significant benefit on progression cannot be inferred.

The table also uses relative risk estimates that have been inflated by the practice of using instantaneous hazard ratios to estimate relative risk (for discussion of these findings, please see Attachment 3, Sections: Results for the Efficacy Outcomes (for the 2 pivotal studies)).

Finally, the benefits of DAC HYP have only been demonstrated in subjects with RRMS who satisfied the entry criteria for the two pivotal studies. Extrapolation to a broader population is not warranted.

With these limitations in mind, the evaluator concludes that the following efficacy benefits are supported by the evidence:

- DAC HYP at a dose of 150 mg or 300 mg SC 4 weekly reduced ARR by 50 to 54%, relative to placebo ($p \leq 0.0002$).
- DAC HYP at the proposed dose of 150 mg SC 4 weekly reduced relapse rate by 45%, relative to once weekly IFN β -1a ($p < 0.0001$).
- DAC HYP at the proposed dose reduced the proportion of subjects relapsing by 44 to 47%, relative to placebo, and by 34 to 35%, relative to IFN β -1a, depending on the duration of follow-up. Note: this is less benefit than claimed by the sponsor (for discussion of these findings, please see Attachment 3, Sections: Results of Efficacy Outcomes (for both pivotal studies)).
- DAC HYP at the proposed dose reduced the number of new gadolinium (Gd)-enhancing lesions by 69 to 78%, relative to placebo ($p < 0.0001$).
- DAC HYP at the proposed dose reduced the number of new or newly enlarging T2 lesions by 70 to 79% relative to placebo ($p < 0.0001$), and by 54% relative to IFN β -1a ($p < 0.0001$).
- Compared to placebo, DAC HYP showed a trend to benefits in quality of life at the proposed dose, as estimated by the MSIS-29 physical impact score, but by the closed testing procedure failed to achieve significance, and trends were inconsistent across dose groups.
- Compared to IFN β -1a, DAC HYP showed significant superiority in quality of life, as estimated by the MSIS-29 physical impact score.
- DAC HYP is associated with a strong trend to reduced disability progression.
- DAC HYP produced a broadly similar benefit across all major subgroups in the study population.
- DAC HYP at the proposed dose has better efficacy, relative to IFN β -1a, in a population enriched for subjects with proven resistance to IFN β -1a, and in this population a nominally significant post hoc p-value can be obtained for the endpoint of progression.
- DAC HYP at the proposed dose has a broadly similar efficacy to other new disease-modifying agents.
- DAC HYP has not been studied in subjects with overt SPMS, and its efficacy in this population is unknown.

Despite the fact that the supplementary evaluator and the sponsor have drawn different conclusions about the statistical robustness of the progression data, these efficacy results are considered satisfactory. The supplementary clinical evaluator does not believe that a clear benefit on progression endpoints should be an absolute requirement for a new disease-modifying agent in MS. In subjects with RRMS, a large proportion of disability progression is due to damage sustained during relapses, and preventing relapses is a worthwhile achievement in its own right, provided that there is at least no adverse effect on progression. Although the data do not provide robust confirmation of a benefit for progression endpoints, there is a consistency across multiple different analyses that, in aggregate, strongly suggest that DAC HYP has a favourable effect on progression, and at least DAC HYP appears highly unlikely to have an adverse effect on progression. Coupled with strong evidence of a reduced relapse rate, this is sufficient to support the claim of efficacy in RRMS.

The efficacy of DAC HYP in subjects with SPMS has not been characterised, and there is currently no basis for recommending this treatment in subjects with SPMS.

The lowest dose of DAC HYP capable of producing a substantial reduction in relapse rate has not been established.

Table 7 (below) summarises the primary, secondary, and selected tertiary efficacy endpoints in the DAC HYP pivotal studies 205MS201 and 205MS301, DAC HYP 150 mg.

Table 7. Primary, secondary, and selected tertiary efficacy endpoints in the DAC HYP pivotal studies 205MS201 and 205MS301, DAC HYP 150 mg

Primary, Secondary, and Selected Tertiary Efficacy Endpoints in the DAC HYP Pivotal Studies 205MS201 and 205MS301 - DAC 150mg

Efficacy Endpoints	Study 205MS201 reduction vs. Placebo	Study 205MS301 reduction vs. IFN β -1a
Clinical		
Annualized relapse rate*	53.9% p<0.0001	45.0% p<0.0001
Proportion of subjects relapsed	54.9% p<0.0001**	40.9% p<0.0001*#
Disability progression sustained for 12 weeks as measured by EDSS Score	56.6% p=0.0211***	16.1% p=0.1575**
Disability progression sustained for 24 weeks as measured by EDSS Score	76.4% p=0.0037	27.0% p=0.0332***
The change from baseline in MSIS-29 physical score	-4.27 p=0.0008*#	-2.09 p=0.0008***
Proportion of subjects with a \geq 7.5 point worsening from baseline in the MSIS-29 physical impact score	44.2% p=0.0125	24.2% p=0.0176*#
MRI endpoints		
The number of new Gd-enhancing lesions between weeks 8 and 24	69.5% p<0.0001**	n/a
The number of new or newly enlarging T2 hyperintense lesions	70.2% p<0.0001**	54.4% p<0.0001**
The number of Gd-enhancing lesions at week 96	n/a	75.0% p<0.0001***
The number of new T1 hypointense lesions at week 96	n/a	51.8% p<0.0001***

* Primary endpoint; Secondary endpoints for each study were ranked and a sequential closed testing procedure was employed to control for type I error at 5%; Tertiary endpoints were pre-specified in each statistical analysis plan but the analyses were not adjusted for multiplicity.

** Secondary endpoint

*# Secondary endpoints that was not tested based on the closed testing procedure. Nominal p-values are presented.

*** Tertiary endpoint

Note: the above table is a summary of sponsor findings for aforementioned studies. As per the supplementary clinical evaluation 'the [supplementary] clinical evaluator does not agree with all of the figures of this table'. Please see Attachment 3 for details.

Safety

Studies providing safety data

Pivotal studies

Two studies were considered as pivotal for evaluation of safety. These are:

- Study 205MS201
- Study 205MS301

Both studies were also considered pivotal for evaluation of efficacy as described above. The following safety data were collected: general adverse events (AEs); AEs of particular interest including included cutaneous events, autoimmune disorders, hepatic events, injection site reactions, and allergic conditions; laboratory tests including haematology and clinical chemistry; and immunogenicity.

Studies evaluable for safety only

- Study 205MS203

Study 205MS203 is an open-label single arm extension study in patients with RRMS that is currently ongoing. Subjects were recruited from Study 205MS202. It includes an influenza vaccine sub-study that evaluates the safety and efficacy of influenza vaccine when administered concurrently with DAC HYP. An interim report for this study dated 20 January 2014 was provided.

- Study 205MS302

Study 205MS302 is an ongoing 3-year study. It was a multicentre, single-arm, open-label study to assess the immunogenicity, PK, PD, and tolerability of DAC HYP when administered SC using a PFS in subjects with RRMS. In addition to the main study, 2 sub-studies (an intensive PK sub-study and a therapeutic protein-drug interaction sub-study) were performed. An interim study report with a data cut-off date of 3 February 2014 was included in the submission.

- Study 205MS303

Study 205MS303 is a multicentre, open-label, extension study to evaluate the long-term safety and efficacy of DAC HYP 150 mg in subjects with RRMS who had completed the parent study, 205MS301. The parent study was a multicentre, double-blind, randomised, parallel-group, active-controlled study designed to evaluate the efficacy and safety of DAC HYP versus IFN β -1a in subjects with RRMS. In this extension study up to 1841 subjects were allowed to participate for up to 144 weeks. All subjects in the extension study received DAC HYP 150 mg by an SC injection every 4 weeks.

Additional efficacy data evaluated by the supplementary clinical evaluator only

Safety data with extra post hoc safety analyses supplied by the sponsor in response to EMA questions was evaluated by the supplementary clinical evaluator.

Patient exposure

In Study 205MS201, a total of 417 subjects were exposed to at least 1 dose of DAC HYP; 208 subjects received DAC HYP 150 mg and 209 received DAC HYP 300 mg with 204 subjects receiving at least 1 dose of placebo. The percentage of subjects receiving all planned doses was similar across treatment groups (placebo, 87%; DAC HYP 150 mg, 84%; and DAC HYP 300 mg, 81%). The mean time on study treatment was similar across the treatment groups: 323.0, 320.5, and 321.9 days in the placebo group, DAC HYP 150 mg group and DAC HYP 300 mg group respectively. The overall mean follow-up time in the study was 53.3 ± 10.12 weeks with 635 subject-years accrued. Follow-up time was similar across the 3 treatment groups; placebo, 209 subject years; DAC HYP 150 mg, 212 subject years; and DAC HYP 300 mg, 214 subject years.

In Study 205MS301, the mean (median) time on treatment was 100.54 (111.43) weeks for the IFN β -1a group and 102.04 (108.71) weeks for the DAC HYP group. The total number

of subject-years on treatment was 1776.56 years in the IFN β -1a and 1797.17 years in the DAC HYP group.

The overall exposure to DAC HYP reflects a sufficient number of patients, for a satisfactory duration of treatment, for a medicine that is used for long-term treatment of a chronic condition as outlined in ICH E1. Further safety data have been provided for 358 patients treated with DAC HYP (any dose) for at least 24 months; this is considered an adequate number for this period of time and is compliant with the relevant adopted guideline. The extent of exposure is sufficient to pick up adverse events that occur at a frequency of about 1/1000 this is not sufficient to pick up cases of PML that have been associated with the use of immunomodulatory MAb.

Safety issues with the potential for major regulatory impact

A summary of the issues addressed by each clinical evaluator is provided. For a detailed overview of safety issues with the potential for major regulatory impact, please see Attachment 2 and Attachment 3.

First round clinical evaluation

Specific safety issues with the potential for major regulatory impact, addressed by the first clinical evaluator, included liver toxicity, serious skin reactions, unwanted immunological events, gastrointestinal (inflammatory) disorders, lymphadenopathy, depression/suicidal ideation and injection site reactions.

Supplementary clinical evaluation

Specific safety issues addressed by the supplementary clinical evaluator included liver injury, hypersensitivity reactions, infection, reductions in white blood cells (including CD4+ and CD8+ cells) and progressive multifocal leukoencephalopathy (PML).

Post-marketing data

As this submission involves a new drug substance (DAC HYP) with submissions ongoing at the time of evaluation in the EU, US and elsewhere, no specific post-marketing data was available for evaluation. The supplementary clinical evaluator addresses the similarities and difficulties in comparing other drugs targeting CD25 with DAC HYP including Zenapax (DAC Nutley) and Simulect (basiliximab) used in the prophylaxis of acute organ rejection in patients receiving renal transplant. For details of this evaluation, please see Attachment 3.

Evaluator's conclusions on safety

First round clinical evaluator's conclusions on safety

AEs were common in subjects treated with DAC HYP. Treatment related AEs occurred in about 22% of subjects treated with DAC HYP the most common being were injection site pain, influenza-like illness, headache, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, liver function test (LFT) abnormal, gamma glutamyl transaminase (GGT) increased, nasopharyngitis, pyrexia, injection site erythema, injection site bruising, upper respiratory tract infection, pharyngitis, MS relapse, fatigue, rash, eczema, nausea, lymphadenopathy, and lymphopenia. The majority were mild to moderate and were manageable with standard treatment or interruption or discontinuation of DAC HYP.

There were two deaths attributed DAC HYP, one was a case of autoimmune hepatitis following planned washout and re-initiation of DAC HYP, the second a case of bacteraemia, following an exfoliative rash leading to the development of a psoas abscess, emboli and bowel ischemia. The case of hepatitis lead to more intensive monitoring in the clinical

study programs, though derangements in LFTs remained common in the DAC HYP studies these were managed by interruption or discontinuation of treatment. No further Hy's Law cases were seen and there were no further episodes of hepatitis. It is considered that the risk can be adequately managed in the post-market environment with a program that frequently monitors LFTs and the provision of adequate advice with regard to managing derangements. The second death was related to DAC HYP but appears to have been as a secondary consequence of the adverse event of skin rash. It is unclear whether this case was true Stevens-Johnson syndrome (SJS) and, at the very least, was a case of a severe skin hypersensitivity reaction.

Skin reactions were common treatment emergent AEs and occurred in about 37% of subjects in the active control study, 2% of cutaneous adverse events met the criteria for serious. Typically the cutaneous adverse events were mild to moderate in nature and resolved with treatment. The serious cases were treated with systemic corticosteroids, this should be reflected in the PI.

A low incidence of colitis was seen in patients treated with DAC HYP this largely resolved after DAC HYP was discontinued, the mechanism, optimal treatment and long-term management remains unknown.

An excess of mild to moderate depression in subjects treated with DAC HYP was seen in the placebo-controlled study. The incidence of depression appears to be no worse than that for IFN β -1a a standard treatment for MS. DAC HYP should be contra-indicated in patients with a recent history of severe depression.

With regard to laboratory evaluation the most common finding was an increase in liver transaminases. DAC HYP treatment was discontinued in subjects with ALT or AST $> 5 \times$ upper limit of normal (ULN), or for elevations of ALT or AST $> 3 \times$ ULN that lasted longer than 1 week. LFTs returned to normal values with temporary cessation of treatment or discontinuation of treatment.

Overall the safety profile would indicate that with appropriate monitoring and physician and patient education patients may be expected to be managed on DAC HYP and that the safety profile is by and large in line with that seen for other disease modifying treatments of MS.

Supplementary clinical evaluator's conclusions on safety

Overall, the safety profile of DAC HYP has been reasonably well characterised in terms of tolerability and common side effects, but the extent to which it may cause serious idiosyncratic reactions is still unclear. Although it might be expected to pose a risk of PML, it has not yet been used in a large John Cunningham (JC) virus-positive population for long enough to characterise this risk accurately.

In terms of tolerability and common AEs, DAC HYP has an acceptable profile. In the placebo controlled study, 205MS201, the incidence of AEs was 74% in DAC HYP recipients (73% for 150 mg, 76% for 300 mg), compared to 79% in placebo recipients, as summarised in Table 8 below.

Although these percentages appear to favour DAC HYP over placebo, a direct comparison of AE incidence is unreliable because of the inclusion of MS relapses. 'MS relapse' was the most commonly reported AE, but clearly reflected efficacy rather than safety. It would have been appropriate to report total AEs excluding MS-relapse.

'Treatment-related AEs were thought to have occurred in about 22% of subjects treated with DAC HYP. The most common AEs with an apparent causal relation to DAC HYP consisted of: injection-site pain, influenza-like illness, headache, abnormal LFTs (ALT increased, AST increased, LFT abnormal, or GGT increased), injection-site erythema or bruising, rash, eczema, nausea, lymphadenopathy, and lymphopenia. Many other common AEs seem less likely to have been causally related to treatment: nasopharyngitis, pyrexia,

upper respiratory tract infection, pharyngitis, MS relapse, and fatigue. The majority of AEs were mild to moderate and responded to standard treatment or interruption or discontinuation of DAC HYP.

Skin reactions were common treatment emergent AEs (TEAEs) and occurred in about 37% of subjects in the active-control study, 205MS301. Most of the cutaneous adverse events were mild to moderate and resolved with topical treatment or interruption of DAC HYP. About 2% of cutaneous adverse events were rated as serious. The serious cases were usually treated with systemic corticosteroids, and this should be mentioned in the PI. One severe skin hypersensitivity reaction to DAC HYP led to a patient death, albeit indirectly: the patient developed bacteraemia in the setting of an exfoliative rash, leading to the development of a psoas abscess, emboli and bowel ischaemia. It remains unclear whether this was a case of SJS.

Another death attributed to DAC HYP was a case of autoimmune hepatitis, which occurred during re-initiation of DAC HYP in a patient involved in two DAC HYP studies. This case led to more intensive monitoring in the clinical study programs. Abnormal LFTs were common in the DAC HYP studies, and were managed by interruption or discontinuation of treatment. There were no further episodes of autoimmune hepatitis, but the increased vigilance could have led to a lower incidence of severe hepatic abnormalities in this closely monitored environment than might be expected in routine clinical use. At least one DAC HYP recipient in Study 205MS301 satisfied Hy's Law. Other subjects had abnormal LFTs sufficient to be characterised as Hy's Law cases, but were not classified as satisfying Hy's law because alternative explanations of abnormal LFTs were considered possible. The risk of severe hepatic abnormalities has led US authorities to place a boxed warning in the US PI. It appears likely that the risk could be adequately managed in the post-marketing environment with a program of monitoring LFTs and ceasing treatment when these become sufficiently abnormal. The precise level of LFT derangement that should trigger a cessation of treatment is unclear.

Colitis was observed in some patients treated with DAC HYP. This largely resolved after DAC HYP was discontinued. The mechanism and optimal management of colitis in this setting remain unknown.

Table 8. Adverse events, DAC HYP versus placebo, Study 205MS201

	Placebo	150 mg DAC HYP	300 mg DAC HYP	DAC Total
Number of subjects in safety population	204 (100)	208 (100)	209 (100)	417 (100)
Number of subjects with an event	161 (79)	151 (73)	159 (76)	310 (74)
MULTIPLE SCLEROSIS RELAPSE	77 (38)	47 (23)	42 (20)	89 (21)
NASOPHARYNGITIS	31 (15)	30 (14)	30 (14)	60 (14)
HEADACHE	21 (10)	20 (10)	20 (10)	40 (10)
UPPER RESPIRATORY TRACT INFECTION	14 (7)	18 (9)	22 (11)	40 (10)
PHARYNGITIS	9 (4)	13 (6)	13 (6)	26 (6)
ORAL HERPES	10 (5)	10 (5)	13 (6)	23 (6)
RASH	6 (3)	12 (6)	11 (5)	23 (6)
ALANINE AMINOTRANSFERASE INCREASED	4 (2)	10 (5)	12 (6)	22 (5)
DEPRESSION	3 (1)	10 (5)	12 (6)	22 (5)
PYREXIA	2 (<1)	7 (3)	15 (7)	22 (5)
RESPIRATORY TRACT INFECTION	11 (5)	7 (3)	13 (6)	20 (5)
URINARY TRACT INFECTION	9 (4)	9 (4)	10 (5)	19 (5)
BACK PAIN	10 (5)	8 (4)	10 (5)	18 (4)
RESPIRATORY TRACT INFECTION VIRAL	5 (2)	8 (4)	10 (5)	18 (4)
INFLUENZA	11 (5)	5 (2)	12 (6)	17 (4)
DIARRHOEA	4 (2)	7 (3)	0 (0)	15 (4)
RHINITIS	3 (1)	9 (4)	6 (3)	15 (4)
FATIGUE	10 (5)	6 (3)	8 (4)	14 (3)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (<1)	7 (3)	6 (3)	13 (3)
VIRAL INFECTION	4 (2)	4 (2)	9 (4)	13 (3)
BRONCHITIS	5 (2)	4 (2)	8 (4)	12 (3)
NAUSEA	2 (<1)	4 (2)	8 (4)	12 (3)
INFLUENZA LIKE ILLNESS	6 (3)	6 (3)	5 (2)	11 (3)
OROPHARYNGEAL PAIN	4 (2)	6 (3)	5 (2)	11 (3)
ANAEMIA	1 (<1)	6 (3)	4 (2)	10 (2)
PARAESTHESIA	10 (5)	3 (1)	6 (3)	9 (2)
DIZZINESS	5 (2)	2 (<1)	6 (3)	8 (2)
ACNE	1 (<1)	1 (<1)	6 (3)	7 (2)

NOTE 1: Numbers in parentheses are percentages.

2: A subject was counted only once within each preferred term.

3: Preferred terms are presented by decreasing incidence in the total column.

An excess of mild to moderate depression was observed in subjects treated with DAC HYP, compared to placebo, in Study MS201. The incidence of depression appeared to be similar to that observed with IFN β -1a in Study MS301. DAC HYP should be contraindicated in patients with a recent history of severe depression.

The use of DAC HYP was associated with a significant reduction in CD4+ and CD8+ T-cells, which might be expected to increase the risk of PML. Experience with other disease-modifying agents in MS suggests that this risk will not be fully characterised until the drug has been used in a large population of at-risk, JC-positive subjects.

The pivotal studies showed a mild excess of infections in DAC HYP recipients, but a substantially increased risk of opportunistic infections, was not observed. The risk of infections should remain a focus of post marketing surveillance.

In conclusion, the tolerability of DAC HYP is broadly acceptable. In terms of serious but rare safety issues, DAC HYP appears to be associated with a risk of severe reactions in a small proportion of subjects. These include:

- hepatic reactions, including autoimmune hepatitis
- hypersensitivity reactions, including skin reactions and anaphylaxis
- lymphopaenia, especially affecting CD4+ and CD8+ lymphocytes
- a theoretical risk of progressive multifocal leukoencephalopathy

First round benefit-risk assessment

The following is the first round clinical evaluator's benefit-risk assessment:

First round assessment of benefits

The benefits of DAC HYP in the proposed usage are:

- A reduction in the ARR for subjects with RRMS with superiority demonstrated against placebo and standard IFN β -1a therapy.
- DAC HYP does delay disability progression as measured by the EDSS and appears to be equivalent to IFN β -1a in its ability to do this.
- A reduction in CNS lesion load as measured by standard MRI techniques for CNS imaging in MS patients.
- Maintenance of efficacy for at least 2-years (and up to 144 weeks) has been demonstrated.
- DAC HYP provides another treatment option for patients who have RRMS this expands the range of treatment such that it increases the chance that a patient can find a tolerable treatment for them.
- DAC HYP is more conveniently administered than other injectable treatments for MS such as IFN β -1a or natalizumab. It is a subcutaneous injection administered every four weeks versus daily injection or intravenous infusion.
- Based on the total number of relapses seen for the DAC HYP 150 mg group versus the placebo group the number needed to treat is approximately 4 over 52 weeks.

First round assessment of risks

The risks of DAC HYP in the proposed usage are:

- There are few safety data and no efficacy data for adults older than 65 years.
- The use of DAC HYP is associated with skin hypersensitivity reactions that in rare cases have resulted in exfoliation.
- Rarely subjects treated with DAC HYP developed colitis the number needed to harm is estimated at 105 based on the frequency observed in the active controlled study.
- The risk for the development of PML, which has been observed with other therapeutic agents that have an immunomodulatory action, is unknown.
- DAC HYP treatment appears to have an association with the development of mild to moderate depression the number needed to harm based on the placebo controlled study is 25. The incidence of depression compared to IFN β -1a is the same.
- Based on the frequency of any observed treatment related adverse event for DAC HYP 150 mg or placebo in study 205MS201 the number need to harm is approximately 14 over 52 weeks.

First round assessment of benefit-risk balance

The benefit-risk balance of daclizumab high yield production (Zinbryta), given the proposed usage, is favourable.

In clinical practice one of the goals of treatment of RRMS as patients with a high rate of relapse and active lesions are likely to progress and experience sustained disability. The data presented in this submission support the efficacy of daclizumab in reducing the risk of relapse and the lesion load as measured by MRI techniques. This should be balanced with the risk of side effects that include changes in LFTs, skin hypersensitivity reactions, colitis and mood disorder. Overall the safety profile (with regard to risks) is in line with that of other disease modifying treatments for MS.

It is considered that the risk can be managed in the post-market environment which may include measures such as appropriate monitoring or alertness to the possibility of these events and early institution of treatment. It is therefore essential that the prescribing information and information is clear and concise. Consideration should also be given to a physician education program and a monitoring program for liver function tests. A satisfactory risk minimisation plan is considered critical for a positive benefit-risk balance for this product.

Finally it is noted that there are ongoing studies of daclizumab and the applicant should commit to providing these data for evaluation upon completion of the final study reports as the results of these studies may have an impact on the benefit risk balance.

First round recommendation regarding authorisation

Approval of daclizumab high yield production (Zinbryta) is recommended subject to:

1. Amendment of the indication so that is narrower and more consistent with the population studied in the clinical trials. The indication, treatment of relapsing forms of MS, is considered too broad and should be amended to reflect the target patient population and the primary endpoint investigated in the clinical studies. For example:
'DAC HYP is indicated in patients aged 18-years or over who have RRMS who have had two or more clinical relapses within the previous 3 years with at least 1 clinical relapse in the 12 months prior to treatment'; or
'One or more clinical relapses and 1 or more new MRI lesions (Gd-enhancing and/or T2 hyper-intense lesion) within the previous 2 years, with at least one of these events in the 12 months prior to treatment.'
2. Satisfactory changes to the PI and CMI.
3. That the risk minimisation plan is evaluated as satisfactory.
4. That the sponsor commits to supplying the final study reports for ongoing clinical studies upon completion of the reports.

Clinical questions

The first round clinical evaluator had no clinical questions for the sponsor.

Second round evaluation of clinical data submitted

For details of the evaluation of additional clinical data submitted by the sponsor, please see Attachment 3.

Second round benefit-risk assessment

The following is the supplementary evaluator's benefit-risk assessment:

Second round assessment of benefits

The benefits of DAC HYP in the proposed usage are:

- DAC HYP appears to reduce annualised relapse rate by about 50 to 54%, relative to placebo ($p \leq 0.0002$).

- DAC HYP reduces relapse rate by about 45%, relative to once-weekly IFN β -1a ($p < 0.0001$).
- DAC HYP reduces the proportion of subjects relapsing by 44 to 47%, relative to placebo, and by 34 to 35%, relative to IFN β -1a, depending on the duration of follow-up. (Note that this is less benefit than claimed by the sponsor).
- DAC HYP reduces radiological evidence of disease activity, including the reduction of new Gd-enhancing lesions by 69-78%, and new or newly enlarging T2 lesions by 70-79%, relative to placebo ($p < 0.0001$).
- DAC HYP is associated with a strong trend to reduced disability progression
- DAC HYP produced a broadly similar benefit across all major subgroups in the study population.
- DAC HYP has not been studied in subjects with overt Secondary Progressive MS, and its efficacy in this population is unknown.

Second round assessment of risks

The risks of DAC HYP in the proposed usage are:

- a high incidence of skin reactions (about 37%, with about 2% rated as serious).
- hepatic reactions, including potentially severe or fatal autoimmune hepatitis.
- hypersensitivity reactions, including anaphylaxis.
- lymphopaenia, especially affecting CD4+ and CD8+ lymphocytes.
- a theoretical risk of progressive multifocal leukoencephalopathy.

Second round assessment of benefit-risk balance

DAC HYP reduces relapse rate in subjects with RRMS, but its use is associated with significant safety concerns. The efficacy of DAC HYP appears to be broadly comparable to other new disease-modifying agents, in terms of reducing relapse rate in subjects with RRMS, so it needs to be considered alongside those other agents. Like most other disease-modifying agents at the time of their registration, DAC HYP has not produced clear benefits in terms of reducing disease progression, but it is expected to reduce the accumulation of disability by preventing overt clinical relapses as well as new plaques evident on MRI. The submitted evidence suggests that a benefit on progression is very likely, but robust statistical proof is still lacking. Despite this, a benefit in terms of reducing relapse rate is a worthwhile clinical achievement in its own right, even without a proven benefit on progression, and one that would be attractive to patients and clinicians, if that reduction in relapse rate could be delivered with acceptable risk, relative to other available agents. Whether the observed reduction in relapse rate outweighs the safety concerns will depend on the extent to which the individual patient considering treatment is at risk of further relapses (and at risk of disability related to those relapses).

Compared to the first generation disease-modifying agents, such as beta interferon and glatiramer acetate, DAC HYP does not offer the same relatively benign safety profile. Although beta interferons have been associated with a number of tolerability concerns, and can cause abnormalities of liver function tests, the risk of severe reactions (including severe derangements of liver function) appears higher with DAC HYP. The risk of skin reactions also appears high, with 2% of subjects experiencing serious skin reactions that led to use of systemic steroids. Like other monoclonal antibody preparations, DAC HYP may also cause acute hypersensitivity reactions and poses a risk of anaphylaxis. It is likely to increase the risk of PML, but this remains unclear.

The efficacy of DAC HYP is clearly superior to once-weekly IFN β -1a, which might justify increased safety risks, but DAC HYP has not been directly compared to more frequently administered beta interferon, which is widely believed to be more effective than once-weekly IFN β -1a and has proven to be superior to IFN β -1a in head-to-head comparisons. The benefit of DAC HYP against more effective interferon regimens is likely to be minor, meaning that a substantial safety risk may not be justified.

For subjects with highly active disease, and particularly for subjects with a proven failure of beta interferon therapy, a low risk of serious complications is likely to be considered acceptable when choosing a new disease-modifying agent. Balanced against the high likelihood of frequent relapses, progressive motor disability, sensory disturbances and cognitive decline in the absence of an effective MS treatment, the rare occurrence of hepatic reactions and other serious complications carries less weight. If DAC HYP were known to reduce disability progression, patients would be expected to accept significant safety risks, but unfortunately there is no robust confirmation of this at present. The fact that DAC HYP reduces relapse rate by at least 50%, coupled with the fact that a large proportion of disability progression is known to come from incomplete recovery from relapses, suggests that DAC HYP could have a useful role in subjects with a high risk of relapses. Provided that the risks and benefits are made clear to patients and clinicians, they are in the best position to decide what risk they are prepared to accept to achieve a 50% reduction in relapse rate, and whether DAC HYP is an appropriate choice compared to other available agents. None of the new agents is without some significant safety concerns, and some patients show poor tolerability of other new agents, such as dimethylfumarate, so it is expected that DAC HYP will find a use in some patients.

Like most other disease-modifying agents, DAC HYP has *not* been tested in subjects with overt secondary progressive MS (SPMS), so the benefit-risk profile in this group is unknown. Immune-modifying agents have generally been less effective in subjects with progressive disease, and the same is expected to be true of DAC HYP. The Supplementary Evaluator was not convinced by the Sponsor's argument that, despite clear entry criteria that excluded SPMS, the pivotal studies inadvertently included some SPMS subjects, and this inadvertent inclusion therefore justifies use of DAC HYP in the broader population of subjects with SPMS. Only a study that explicitly focussed on SPMS subjects could demonstrate efficacy in this group with sufficient clarity that a rational decision could be made about the benefit-risk profile in SPMS.

In conclusion, the benefit-risk balance of DAC HYP for the *proposed* indication, which includes all forms of relapsing MS, is not known to be favourable. There is not sufficient evidence to recommend the use of DAC HYP in subjects with Secondary Progressive MS, and the proposed indication does not match the entry criteria of the pivotal studies.

The benefit-risk balance for DAC HYP for a *modified* indication is expected to be favourable, if DAC HYP is used exclusively in subjects with Relapsing and Remitting MS, who are still experiencing relapses (or who are avoiding relapses by use of an alternative disease-modifying agent), who accept the risks, and who can receive DAC HYP in a closely monitored prescribing environment.

Second round recommendation regarding authorisation

The sponsor's application to register DAC HYP for all subjects with relapsing forms of MS should be rejected.

Authorisation should be reconsidered after the sponsor has:

- provided adequate answers to the clinical issues raised;
- addressed concerns raised about the proposed PI;

- provided a satisfactory mechanism to ensure DAC HYP is only prescribed by clinicians aware of its safety issues, with appropriate monitoring of LFTs;
- modify the wording of the indication so that it matches the study population in the two pivotal studies.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan: EU-RMP version 1.0 dated 11 February 2015 (data lock point 28 July 2014) and ASA 1.0 dated June 2015 which was reviewed by the RMP evaluator.

The sponsor also provided an updated EU-RMP version 3.0 dated 22 January 2016 (data lock point 28 July 2014) and the ASA version 2.0 dated February 2016.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 9 below.

Table 9. Summary of ongoing safety concerns provided by sponsor

Safety concerns	
Important identified risks	Transaminase elevations and serious hepatic injury Serious skin reactions Infections and serious infections Colitis Depression Serious lymphadenopathy
Important potential risks	Acute serious hypersensitivity reactions Opportunistic infections (including PML) Malignancies (particularly lymphoma) Sustained severe lymphopenia
Missing information	Use in patients under the age of 18 years Use in patients over the age of 55 years Use during pregnancy Exposure during lactation Use in patients with hepatic impairment Use in patients taking concomitant hepatotoxic medications

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance for all the safety concerns. Additional pharmacovigilance comprises three planned studies:

- Study 205MS401 – a five-year post-authorisation observational study to determine the incidence, type, and pattern of serious adverse events (SAEs) and the incidence and types of adverse events (AEs) leading to treatment discontinuation in patients with MS being treated with DAC HYP in routine clinical practice.
- Study 205MS402, a pregnancy registry prospectively evaluate pregnancy outcomes in pregnant women with MS who were exposed to DAC HYP since the first day of their last menstrual period prior to conception or at any time during pregnancy. The registry is to follow up 300 pregnancy outcomes.
- Paediatric investigation plan EMEA-001349-PIP01-12-M01 – an open-label, randomized, active controlled study to evaluate activity, safety/tolerability, and pharmacokinetics of daclizumab in children from 10 to less than 18 years of age with relapsing- remitting multiple sclerosis followed by a 24-month extension study.
- Physician survey – a survey assesses the effectiveness of the additional risk minimisation activities targeting the identified risk ‘transaminase elevations and serious hepatic injury’.

Risk minimisation activities

In addition to routine risk minimisation to mitigate all the safety concerns, the sponsor has also proposed the following additional risk minimisation activities for the risk of ‘transaminase elevation and serious hepatic injury’:

- A Hepatic Risk Management Guide for prescribers; and
- A patient alert card.

Reconciliation of issues outlined in the RMP report

Table 10 (below) summarises the first round evaluation of the RMP, the sponsor’s responses to issues raised and the TGA’s evaluation of the sponsor’s responses.

Table 10. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor’s response	RMP evaluator’s comment
Safety considerations may be raised by the non-clinical and clinical evaluators through consolidated request for information and/or the Non-clinical and Clinical evaluation reports respectively. It is important to ensure that the information provided in response to these	The sponsor acknowledges this statement and confirms that consideration has been given to comments raised through the consolidated request for more information. No safety considerations have been raised to date by the nonclinical or clinical evaluators that impact the RMP.	The sponsor’s response is acceptable given the time of the response was provided. Since February 2016, the clinical evaluation report has raised safety

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>		<p>issues which have an impact on the RMP.</p>
<p>2. As advised in the draft PI, depression is a common adverse event that was reported at a $\geq 2\%$ higher incidence for the daclizumab group compared to the placebo group. The sponsor should add this to the ASA as an important potential risk.</p>	<p>Depression has been added as an important identified risk to the EU-RMP version 3.0.</p>	<p>The sponsor's response is satisfactory.</p>
<p>3. The evaluator has noted the sponsor's explanation of the differences between daclizumab HYP, daclizumab Nutley, daclizumab Penzberg and basilixumab (another IL-2Rα inhibitor) in the EU-RMP. However, due to their similar pharmacological effects, adverse events related to other daclizumab products and other IL-2Rα inhibitor cannot be ruled out for daclizumab HYP unless compelling</p>	<p>The sponsor believes that comparing the safety profile of Zenapax to DAC HYP to establish potential risks attributable to DAC HYP is not medically appropriate for several reasons. There are marked differences in the co-morbid medical conditions of the treated populations and the renal allograft transplant population is not believed to be comparable to the MS population. Secondly, the dosing is markedly different, where Zenapax is dosed 5 weekly, most of the time in combination with immunosuppressive medications cyclosporine and corticosteroids compared to chronic monthly dosing with DAC HYP alone. Additionally, at the molecular level, there are significant structural differences in the glycosylation profile, levels of alpha-gal (galactosealpha-1,3-galactose) and heavy chain N-terminal variants that distinguish it from Zenapax. Glycosylation profiles are known to significantly modulate bioactivity,</p>	<p>The sponsor's response is noted.</p> <p>The TGA Delegate has raised safety concerns with autoimmune hepatitis, colitis, severe skin reactions, and infections following the evaluation of the additional clinical data submitted by the sponsor after the request for information</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>evidence proves otherwise. The sponsor should provide justification to why the following risks are not relevant to the use of daclizumab HYP, or add them to the ASA as potential risks:</p> <ul style="list-style-type: none"> a. Hypertension (related to other daclizumab products and basilixumab); b. Peripheral oedema (related to other daclizumab products and basilixumab); c. Increase in serum creatinine (related to basilixumab); d. Impaired healing and wound infection (related to other daclizumab products); e. Secondary autoimmune diseases including but not limited to inflammatory bowel disease, autoimmune hepatitis, thyroiditis, and psoriasis (related to other daclizumab products). 	<p>immunogenicity, and clearance rate from circulation.^{14,15} The glycosylation differences between DAC HYP and Zenapax manifest as significantly and reproducibly less antibody dependent cellular-cytotoxicity (ADCC) activity. These structural and biological differences are relevant to the safety profile of DAC HYP.</p> <p>The adverse events noted by TGA for possible inclusion as potential risks for DAC HYP, because they were considered as risks for Zenapax, include hypertension, peripheral oedema, increased serum creatinine, and impaired wound healing. These adverse events are commonly reported in renal transplant patients. For example, the KDIGO clinical practice guidelines, which discuss the management of these commonly observed medical conditions in the transplant setting, note 'hypertension seen in the transplant settings is attributable to corticosteroids, cyclosporin A (CsA), and to a lesser degree tacrolimus', decreased renal function (increased creatinine) 'may be caused or exacerbated by CsA and tacrolimus', delayed healing 'may be caused or exacerbated by MTOR inhibitors', including everolimus. Peripheral oedema is recognised as a commonly seen consequence of the transplantation which may be exacerbated by proteinuria. The sponsor does not believe that any of the mentioned adverse events should be considered as potential risks for DAC HYP on the basis that they are common co-morbid conditions in the renal transplant population or known complications of concomitant medications with Zenapax given for renal transplant.</p> <p>The sponsor believes that there is insufficient evidence to include inflammatory bowel disease, autoimmune hepatitis, thyroiditis, and psoriasis under a separate category of autoimmune diseases. The effect of IL-2R inhibition is to cause the downstream effect of an intense lymphocytic infiltration of many organs, and subsequent immune mediated</p>	<p>response. It is noted that all of these concerns have been included in the EU-RMP version 3 except autoimmune hepatitis. The sponsor should add this to the ASA.</p>

¹⁴ Arnold JN, Wormald MR, Sim RB, Rudd PM. and Dwek RA. The Impact of Glycosylation on the Biological Function and Structure of Human Immunoglobulins. *Annu. Rev. Immunol.* 2007. 25:21–50

¹⁵ Shi HH and Goudar CT. Recent Advances in the Understanding of Biological Implications and Modulation Methodologies of Monoclonal Antibody N-linked High Mannose Glycans. *Cellular and Metabolic Engineering Biotechnology and Bioengineering* DOI 10.1002/bit.25318

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p>adverse events. However, most of these events are transient with event resolution when the DAC HYP is discontinued, in contrast to a true autoimmune process which persists. The sponsor believes that it is most appropriate, given the information available, to categorise the events of autoimmune hepatitis, inflammatory bowel disease and psoriasis under the existing categories of important identified risks in the RMP: serious hepatic injury, colitis, and cutaneous events, respectively.</p> <p>The sponsor does not believe autoimmune thyroiditis qualifies as a potential risk, given the single case of autoimmune thyroiditis in Study 205MS201 and equal numbers of adverse events of autoimmune thyroiditis and Basedow's syndrome in the IFN and DAC HYP arms in Study 205MS301.</p>	
<p>3. The evaluator has noted that patients with a history of HIV or other immunodeficient conditions, and patients with a history of or positive screening test result for hepatitis C virus or hepatitis B virus have been excluded from clinical trials. As the immune modulatory effects of daclizumab can have a significant impact on the patients' existing conditions and/or treatment, the sponsor should add 'use in patients with a history of human immunodeficiency virus or other immunodeficient conditions', and 'use in patients with a history of or positive screening test result for hepatitis C virus or hepatitis B virus'</p>	<p>The sponsor is not proposing to include the requested changes as missing information to the ASA.</p> <p>In Study 205MS201, patients with a positive screening test for active infection with HBV or HCV were excluded. In Study 205MS301, patients with a known history of, or positive screening test result for HCV or HBV were excluded. In both studies, patients with a history of HIV or other immunodeficient conditions were excluded. As noted in the EU RMP version 3.0, SIV.2, inclusion of these criteria in the protocols was not due to a specific safety concern; this type of exclusion criteria is standard for clinical trials, so as not to confound the safety assessment.</p> <p>The ASA has been revised to include the latest version 3.0 of the EU RMP. 'Use in patients with a history of HIV or other immunodeficient conditions', and 'use in patients with a history of or positive screening test result for hepatitis C virus or hepatitis B virus' have not been considered as missing information in the EU RMP version 3.0 and are also not included in the ASA.</p>	<p>The sponsor's response is noted. It is recognised that patients with hepatitis, HIV and other immunodeficient conditions are commonly excluded from clinical trials. However, the use of immune modulators can often have safety impact on the patients' existing conditions and/or treatment. For example, patients with HIV are already at a higher risk of PML. The combined impact of daclizumab with HIV</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
as missing information to the ASA.		infection is a relevant safety question. The sponsor should undertake to investigate and report severe adverse events, in particular, opportunistic infections including PML, and reactivation of hepatitis viruses in the Periodic Safety Update Reports.
4. The heading on page 56 of the EU-RMP is 'Transaminase elevations and serious hepatic injury', whilst the content is about cutaneous adverse events. This should be corrected.	This has been corrected in the EU RMP version 3.0.	The sponsor's response is satisfactory.
5. The sponsor's plan to use routine and additional risk minimisation is acceptable. The sponsor should provide the draft educational materials and the physician survey to the TGA for review before they are distributed.	The sponsor commits to provide the draft educational materials and physician survey to the TGA for review before launch of Zinbryta locally.	The sponsor's response is noted. Please refer to 'additional recommendations to address safety concerns raised by the Delegate'.
6. The sponsor should also address the potential of off-label use in other forms of MS.	It is possible that DAC HYP could be considered as treatment in non-relapsing forms of MS, but the potential for its use in these populations is considered to be low. Any off-label use, including as treatment for other forms of MS,	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	will be monitored through routine pharmacovigilance.	
7. The sponsor should provide additional patient educational material for self-administration or CMI adaptation with pictures.	The sponsor provided a Package insert	The evaluator has noted the package insert which provides instructions and picture on self-administration . The sponsor's response is satisfactory.
<p>8. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:</p> <p>a. It is recommended that the Delegate considers the following advice is added under 'Dosage and administration': <i>'[Tradename] treatment should be initiated and supervised by a neurologist. Specialists and equipment required for the timely diagnosis and management of serious adverse reactions should be available.'</i></p> <p>b. It is recommended that the Delegate considers adding advice to reflect the fact that patients with a history of HIV or other</p>	<p>a) The sponsor accepts the recommendation to include additional advice under 'Dosage and administration' for initiation of treatment, however, proposes alternate wording to reflect the method of administration and the safety profile of Zinbryta. Zinbryta is administered as a subcutaneous injection, whereas the suggested statement is typically seen with products that are administered intravenously. Additionally, in the total Zinbryta experience, 1 out of 1785 subjects (0.06%) had a SAE of potential anaphylaxis that was characterised by dizziness, hypotension, and syncope after the first dose of Zinbryta; the event was non-life-threatening. As the evaluator notes in the Clinical Evaluation Report: <i>'the event described does not have features typical for anaphylaxis and may equally be a vasovagal episode, particularly as the subject continued in the study with no further events'</i>. No other events of anaphylaxis were reported. Based on these data, there does not appear to be an increased risk of anaphylaxis or immediate-type hypersensitivity events in subjects treated with Zinbryta. The sponsor believes that the alternate proposed wording is appropriate for Zinbryta.</p> <p>The following addition to the PI, Dosage and Administration section is proposed: <i>'Zinbryta should be initiated by a physician experienced in the management of multiple sclerosis.'</i></p> <p>b) Regarding the recommendation to consider adding advice to reflect the fact that patients with a history of HIV or other immunodeficient conditions were excluded from clinical trials, the sponsor proposes to include the statement</p>	The sponsor's response is noted. The recommendations made on the draft PI remain, awaiting consideration by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>immunodeficient conditions, and patients with a history of or positive screening test result for hepatitis C virus or hepatitis B virus have been excluded from clinical trials.</p>	<p><i>'Zinbryta has not been studied in patients with immunodeficiency syndromes'</i> to the PI under the heading Precautions – Infections. The term 'immunodeficiency' is defined by the World Health Organization (WHO) as the presence of 'defects in one or more components of the immune system, resulting in inability to eliminate or neutralise non-autoantigens. Congenital or primary immunodeficiencies are genetic or due to developmental disorders (such as congenital thymic aplasia). Acquired or secondary immunodeficiencies develop as a consequence of malnutrition, malignancies, immunosuppressive compounds, radiation, or infection of immunocompetent T cells with human immunodeficiency virus (HIV).'</p> <p>Therefore, a wide ranging term encompassing various clinical situations. Based on data from clinical trials with DAC HYP, patients with immunodeficiency syndromes, such as HIV, were not studied.</p> <p>Regarding the recommendation to consider adding advice to reflect the fact that patients with a history of or positive screening test result for hepatitis C virus or hepatitis B virus were excluded from clinical trials, the sponsor wishes to clarify this point. In Study 205MS201, patients with a positive screening test for active infection with HBV or HCV were excluded (Study 205MS201), Patients with a known history of, or positive screening test result for HCV or HBV were excluded. As noted in the EU RMP version 3.0, SIV.2, inclusion of these criteria in the protocols were not due to a specific safety concern; this type of exclusion criteria is standard for clinical trials, so as not to confound the safety assessment. Among all subjects treated with DAC HYP, 87 subjects with evidence of prior HBV infection and 6 subjects with evidence of prior HCV infection were enrolled. There was no evidence of viral reactivation in these subjects during the studies. Considering that the Precautions - Infections section of the PI already warns of the risk of infection and provides advice regarding patients with serious infections, the sponsor does not believe it is necessary or helpful to physicians to add a statement to the PI indicating that patients with active HBV or HCV infection were not studied. Additionally, since DAC HYP is associated with an increased risk of hepatic transaminase elevations and serious hepatic injury, the PI includes advice</p>	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	for monitoring and managing patients in this regard in the Precautions – Hepatic injury section.	

Summary of recommendations

Issues in relation to the RMP

- It is noted that all important risks raised by the supplementary clinical evaluator have been included in the EU-RMP v3.0 except autoimmune hepatitis. The sponsor should add this as an important potential risk to the ASA.
- It is recognised that patients with hepatitis, HIV and other immunodeficient conditions are commonly excluded from clinical trials. However, the use of immune modulators can often have safety impact on the patients' existing conditions and/or treatment. For example, patients with HIV are already at a higher risk of PML. The combined impact of daclizumab with HIV infection is a relevant safety question. The sponsor should undertake to investigate and report severe adverse events, in particular, opportunistic infections including PML, and reactivation of hepatitis viruses in the Periodic Safety Update Reports.
- The RMP evaluator supports the comments made by the first round clinical evaluator. It is recommended that the Delegate considers enhanced advice on the risk of opportunistic infections, including PML, to be provided in the Australian PI.
- The proposed additional risk minimisation activities in Australia contain a patient alert card and a risk management guide for prescribers to mitigate the risk of hepatic injury. It is recommended that advice on the risk of opportunistic infections, in particular PML, should be included in the educational materials. The sponsor should provide updated draft educational materials to the TGA for review prior to the due date on which the TGA Delegate makes the decision on the submission. If certain educational materials are to be distributed online only, an active website address should be provided for the TGA's review of the materials.
- The sponsor should also provide a distribution plan to the TGA about how the additional educational materials including the patient alert card are to be distributed, the number of the materials to be distributed, who are the targeted healthcare professionals, and in what time frame.
- The sponsor has provided justification to the different plans to evaluate the effectiveness of the additional risk minimisation activities between the EU and Australia. This is reasonable except that the sponsor has not provided sufficient justification to why it considers Australia should not take part in Study 205MS401 which measures the outcome indicators for the effectiveness of the additional risk minimisation activities. Considering the lack of outcome indicator measurements in the proposed plan of a physician survey, the sponsor should include Australia in Study 205MS401 or provide compelling justification to the applicability of overseas study results in the Australia.
- The sponsor's plan to conduct a physician survey in Australia is acceptable in measuring the relevant process indicators. However, the survey should be conducted within two years of the supply of Zinbryta in Australia, regardless of Pharmaceutical benefits Scheme (PBS) listing.

- The sponsor should provide a draft physician survey and a study plan to the TGA for review. The study plan should include the objectives of the survey and quantitative targets for relevant indicators to be measured, the number of the survey participants to be included, practice specialties of the participants, the target participation rate, relevant time frames, the methods of survey distribution, evaluation of the survey results, and plans for alternative measures if the targets are not achieved.
- The sponsor should provide an evaluation report to the TGA once the evaluation process is completed. The evaluation report should include an assessment of clinical knowledge/awareness, and the representativeness of the survey sample. Other process indicators to be reported should include, but not limited to: the number of the materials distributed, the time frame of the distribution, and the characteristics of the healthcare professionals who have received the educational materials.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There are no objections on quality grounds to the approval of Zinbryta (daclizumab).

Nonclinical

There were no objections on nonclinical grounds to approval of Zinbryta (daclizumab).

- Primary pharmacology (in vitro) studies focused on demonstrating similar functional activity of DAC HYP and other forms of daclizumab (except for lower ADCC activity than Roche's daclizumab).
- The pharmacokinetics of DAC HYP in cynomolgus monkeys was characteristic of a MAb. The development of anti-daclizumab antibodies in a number of animals reduced serum daclizumab concentrations but overall did not jeopardise the interpretation of the toxicity studies or toxicokinetic data.
- The cynomolgus monkey was used in all the main toxicity studies and is an appropriate model. The main target organs were skin, brain and spinal cord. The nonclinical studies predicted the potential for skin changes that were observed clinically at low incidence. The clinical relevance of the main finding in the monkeys (microglial aggregates in the brain) is unknown.
- Genotoxicity and carcinogenicity studies were not conducted and are not required.
- Reproductive toxicity studies covered fertility (markers of fertility), embryofetal development and pre/postnatal development end-points. There was some evidence for increased fetal loss in the embryofetal development study.
- No NOEL was established for changes in the skin, and the skin is affected by treatment in a small proportion of patients. Lymph node findings were largely restricted to the 39 week Centre B study and were assessed as not being of major concern. There was a substantial safety margin for brain haemorrhage/microhaemorrhage and mononuclear cell infiltrates in the brain (ER: 92). For the finding of microglial aggregates in the brain, a NOEL was established at 10 mg/kg (ER: approximately 5)), ERs (\geq approximately 18) at the higher doses were moderate-high, the finding was of low severity, there were no functional disturbances or neuronal damage and there was

evidence of recovery (full or partial) after cessation of dosing. A mechanistic study showed that microglia did not express CD25, suggesting that the aggregates in the brain were unlikely to be a direct effect of DAC HYP, but possibly a pharmacological response to increased IL-2 bioavailability.

In general, the nonclinical studies and risk assessment of DAC HYP do not raise undue concerns; however, the clinical significance of the CNS finding of microglial aggregates (and microhaemorrhage at high doses) remains unknown, and its PI document is supported.

Clinical

The initial clinical evaluation for DAC HYP was supplemented by a secondary supplementary clinical evaluation which concentrated on efficacy, particularly the post hoc analyses and safety. The secondary evaluation was requested because it appeared that efficacy was insufficient to justify the safety risks observed by the Delegate.

Pharmacology

Pharmacokinetics

DAC HYP is a humanised, MAb product intended for SC administration. Following SC injection of DAC HYP time to peak plasma concentration (t_{max}) is achieved in approximately 7 days. Absolute bioavailability for the 100 mg to 300 mg SC dose is approximately 90%. The elimination half-life ($t_{1/2}$) was approximately 15 days. Consistent with the long elimination half-life, steady state is achieved after about 16 weeks with dosing of 150 mg SC injection every 4 weeks. At steady state the DAC HYP accumulation ratio is approximately 2.5. The estimated volume of distribution is small and ranges from 8.8 to 13.4 litres. The primary routes of elimination are likely to be proteolytic degradation, similar to that of physiological antibodies, and receptor mediated clearance.

The PFS and PFP contain the same formulation and are bioequivalent. In single dose PK studies following SC administration of doses ranging from 50 mg to 300 mg DAC HYP was slightly more than dose proportional in the 50 mg to 100 mg SC dose range and dose proportional from 100mg to 300 mg SC.

Therapeutic MAb that modulate cytokine activities can indirectly influence the expression of CYP isoenzymes. The effect of multiple dosing of DAC HYP 150 mg on CYP substrates was assessed in Study 302. Twenty subjects underwent serial PK sampling for DAC HYP and probe drugs for CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A during 2 sequential treatment periods. The probe-drug cocktail consisted of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg. Oral vitamin K 10 mg was used to counteract warfarin's anticoagulant effect prophylactically. No effect on the PK of the various substrates was seen.

Pharmacodynamics

DAC HYP binds CD25, the alpha subunit of the high-affinity IL-2R, and prevents binding of CD25 to its ligand, IL-2. PD markers were assessed in healthy subjects in Phase I studies and in patients with MS in Phase II and Phase III studies. PD parameters, including lymphocyte subsets in peripheral blood and soluble markers of inflammation, were assessed in DAC HYP MS studies based on their relationship to IL-2 signalling modulation. The proposed dose regimen of 150 mg SC every 4 weeks was associated with sustained CD25 saturation on peripheral T cells, a decrease in T_{reg} cells and an increase in serum IL-2 and CD56_{bright} NK cells. T cell and B cell counts decreased to $\leq 10\%$ from baseline during the first year of DAC HYP treatment, while total NK cell counts increased approximately

1.5 fold as a result of the change in CD56^{bright} NK cells. No effect on cell mediated immunity as measured by the Cylex ImmuKnow assay was detected.

Immunogenicity was evaluated in 4 Phase I studies in healthy subjects as well as in the Phase III studies in patients with MS. Study 205MS302 is an ongoing open Phase III study primarily to assess immunogenicity. Subjects received 150 mg DAC HYP every 4 weeks. Data to Week 44 was reported in the interim analysis. Post-baseline anti-DAC-antibody (ADA) reactivity was seen in 15 (13%) subjects in the main study which included 3 (3%) subjects who had pre-existing ADA reactivity at baseline. All subjects were negative at baseline for NABs and post-baseline NABs were observed in 4 (4%) subjects in the main study.

The rate of initial ADA response to single-dose DAC HYP treatment was higher in Phase I studies compared with that following multiple-dose treatment in Phase II and Phase III studies. In the Phase I studies, the incidence of immunogenicity responses appeared to be inversely correlated with the DAC HYP dose and was further elevated as the drug washed out. In the pivotal studies treatment-emergent ADAs to DAC HYP 150 mg were observed in 4% and 19% of evaluable subjects in Study 205MS201 (52 weeks treatment phase) and Study 205MS301 (144 week treatment phase), respectively.

Treatment-emergent NABs to DAC HYP 150 mg were observed in 3% and 8% of evaluable subjects in Studies 205MS201 and 205MS301, respectively. The sponsor attributed differences in the incidences of immunogenicity between these studies primarily to more frequent immunogenicity testing at early time-points and more sensitive assay used in Study 205MS301 compared with Study 205MS201.

Time-varying NAB status increased DAC HYP clearance by 19% on average. No effect of ADA status on efficacy, safety, or PD profile of DAC HYP was detected. There was no apparent impact of immunogenicity status (ADA or NAB) on the evaluated PD markers, including CD25 saturation, the increase in CD56^{bright} NK cells, and the decrease in T_{reg} cells in Studies 205MS301 or 205MS302, an ongoing open safety/immunogenicity study.

Study 205MS203 was a single arm, open-label extension study following Study 205MS202 and allowed for optional administration of trivalent 2013-2014 influenza vaccine (Influvac, surface antigen; inactivated vaccine) and assessment of subsequent immune response to that vaccine. This study enrolled 90 subjects. Overall sero-conversion (percentage (95% CI)), defined as the percentage of subjects with a pre-vaccination haemagglutinin (HI) titre < 10 and post-vaccination HI titre ≥ 40 or a pre-vaccination HI titre ≥ 10 and a 4-fold increase in HI titre post-vaccination, was observed for 69% (58% to 78%), 69% (58% to 78%), and 44% (34% to 55%) for the A/H1N1, A/H3N2, and B strains, respectively. Sero-protection, defined as a post-vaccination HI titre ≥ 40, was observed for 92% (85% to 97%), 91% (83% to 96%), and 67% (56% to 76%) of subjects for the A/H1N1, A/H3N2, and B strains, respectively.

Efficacy

Two studies were considered to be pivotal for efficacy and safety. These studies were evaluated in the first CER and in the supplementary CER (for extracts of both reports please see Attachment 2 and Attachment 3).

Study 205MS201

Study 205MS201 was a multi-centre, double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of DAC HYP as a monotherapy treatment in patients with RRMS. 621 subjects were randomised in a 1:1:1 ratio to receive placebo, 150 mg DAC HYP, or 300 mg DAC HYP SC every 4 weeks (13 total doses) over the 52 week treatment period.

The primary objective was to determine whether DAC HYP, when compared to placebo, is effective in reducing the rate of relapses between baseline and Week 52. The primary endpoint was the annualised relapse rate between baseline and Week 52. Secondary efficacy endpoints were:

- the number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects;
- the number of new or newly enlarging T2 hyperintense lesions at Week 52;
- the proportion of relapsing subjects between baseline and Week 52;
- the change in MSIS-29 physical score at Week 52 compared to baseline.

Assessment of disability progression was a tertiary endpoint.

The major inclusion criteria were: age from 18 to 55 years; diagnosis of RRMS according to McDonald criteria; baseline EDSS between 0.0 (normal neurological exam) and 5.0 (ambulatory without aid for about 200 m; disability impairs full daily activities) inclusive; and either had experienced at least 1 relapse within the 12 months prior to randomisation with a cranial MRI demonstrating lesions consistent with MS or had shown evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to randomisation. Patients with primary progressive, secondary progressive or progressive relapsing MS were excluded from the study.

Statistical testing for efficacy endpoints was performed between the DAC HYP 300 mg group and placebo and the DAC HYP 150 mg group and placebo separately. A sequential, closed testing procedure was used to control the overall type I error rate that might result from multiple comparisons.

If the first comparison (300 mg versus placebo) was statistically significant ($p = 0.05$), then the second comparison (150 mg versus placebo) was tested at the 0.05 significance level. However, if the first comparison was not statistically significant, then the second comparison was not considered statistically significant. The same procedure was used to control for a type I error for the secondary endpoints, with the endpoints in rank order as listed above.

A total of 621 patients were randomised, 204 to placebo, 208 to DAC HYP 150 mg, and 209 to DAC HYP 300 mg. Median age was 35 years and 65% of the population were female. The mean EDSS score at baseline was 2.7 (median 2.5) and the mean number of relapses in the last 3 years was 2.4. Over 90% of patients in each treatment group completed the 52 week double-blinded treatment period.

In the Intent-to-treat (ITT) population there were 88 relapses in the placebo group, 43 in the 150 mg DAC HYP group and 47 in the 300 mg DAC HYP group. The annualised relapse rates were 0.462 in the placebo group, 0.222 in the 150 mg DAC HYP group and 0.238 in the 300 mg DAC HYP group. DAC HYP 150 mg and 300 mg reduced the annualised relapse rate by 54% ($p < 0.0001$) and 50% ($p = 0.0002$), respectively, compared to placebo. Various sensitivity analyses for the primary endpoint also showed a statistically significant difference in annualised relapse rates. The first CER (Attachment 2) tabulates results and provides statistical comparisons.

Secondary endpoint results are discussed in the first CER. DAC HYP 150 mg and 300 mg reduced the number of new Gd-enhancing lesions between Weeks 8 and 24 by 69% ($p < 0.0001$) and 78% ($p < 0.0001$) respectively, compared to placebo. The adjusted mean number of new or newly enlarging T2 hyper-intense lesions at Week 52 was 8.13 (95% CI: 6.65 to 9.94) in the placebo group, 2.42 (95% CI: 1.96 to 2.99; $p < 0.0001$) in the DAC HYP 150 mg group, and 1.73 (95% CI: 1.39 to 2.15; $p < 0.0001$) in the DAC HYP 300 mg group. The proportion of relapsing subjects was reduced by 55% in the DAC HYP 150 mg group ($p < 0.0001$) and 51% ($p = 0.0003$) in the DAC HYP 300 mg group, compared to placebo.

There was no statistically significant difference in quality of life measures. Although not statistically assessable, the proportion of subjects with 12 week confirmed disability progression was 13.3% in the placebo group, 5.9% in the DAC HYP 150 mg group, and 7.8% in the DAC HYP 300 mg group.

Assessment of efficacy in patients with high and low disease activity prior to study entry was performed as a post hoc analysis. This showed similar reductions in relapse rates in these two groups. The absolute benefit, in terms of number of relapses prevented, is expected to be higher in subjects with high disease activity.

Study 205MS202

Study 205MS202 was a 12 month double-blind extension of Study 205MS201. It primarily assessed safety and immunogenicity of DAC HYP when administered after a 6-month washout period. Patients were randomised to 6 treatment groups based on treatments received in Study 205MS201. These were:

- Placebo:
 - DAC HYP 150 mg SC every 4 weeks for a total of 13 doses; or
 - DAC HYP 300 mg SC every 4 weeks for a total of 13 doses.
- DAC HYP 150 mg:
 - Placebo SC every 4 weeks for a total of 5 doses followed by DAC HYP 150 mg SC every 4 weeks for a total of 8 doses; or
 - DAC HYP 150 mg SC every 4 weeks for a total of 13 doses.
- DAC HYP 300 mg:
 - Placebo SC every 4 weeks for a total of 5 doses followed by DAC HYP 300 mg SC every 4 weeks for a total of 8 doses; or
 - DAC HYP 300 mg SC every 4 weeks for a total of 13 doses.

The clinical endpoints examined included ARR, 3-month confirmed disability progression, MRI endpoints and quality of life. A total of 517 subjects were randomised. The mean, SD time on study treatment was similar across the 6 treatment groups. Reporting of measures of MS activity combined the DAC HYP 300 mg and 150 mg treatment groups and compared continuous treatment with interrupted treatment and initial placebo treatment in Study 201 with clinical response when given continuous active treatment with either dose of DAC HYP.

Statistical analysis of the efficacy results is very uncertain given the multiple endpoints and that these were not primary endpoints. For patients continuing active treatment through Year 2 (as in Study 205MS202) the ARR was 0.165 compared with 0.148 in Year 1. For patients who had a 6 month washout period then recommenced DAC HYP treatment the ARR was 0.212. For patients given placebo in Study 205MS201 then 12 months of DAC HYP at either 300 mg or 150 mg the ARR in Study 205MS202 was 0.432. The confirmed 3-month sustained disability by treatment group is shown in Table 11 (below).

Table 11. Summary of time to sustained progression of disability for 3 months measured by an increase in EDSS from baseline (Year 1); Study 205MS201

	Placebo + DAC HYP 150 mg	Placebo + DAC HYP 300 mg	DAC HYP 150 mg +Washout	DAC HYP 150 mg for 2 Years	DAC HYP 300 mg +Washout	DAC HYP 300 mg for 2 Years
Number of subjects in per protocol population	84 (100)	79 (100)	64 (100)	65 (100)	68 (100)	64 (100)
Number of subjects progressed	8 (10)	10 (13)	2 (3)	3 (5)	3 (4)	5 (8)
Time(weeks) to progression(a) 25th percentile	NA	NA	NA	NA	NA	NA
Median	NA	NA	NA	NA	NA	NA
Estimated proportion of subjects with progression at year 1 (a)	0.10	0.13	0.03	0.05	0.04	0.08

NOTE: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a 205MS201 baseline EDSS ≥ 1.0 sustained for 3 months or at least a 1.5 point increase on the EDSS from a 205MS201 baseline EDSS of 0 sustained for 3 months. A cutoff of 74 days is used to determine sustained progression for 3 months.

(a) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.

Study 205MS301

Study 205MS301 was a multicentre, double-blind, parallel group, monotherapy active-control study to determine the efficacy and safety of DAC HYP versus INF β -1a (tradename: Avonex) in patients with RRMS. The primary objective was to test the superiority of DAC HYP compared to IFN β -1a in preventing MS relapse in patients with RRMS. The secondary objectives were to test the superiority of DAC HYP compared with IFN β -1a in slowing functional decline and disability progression and maintaining quality of life in this population.

The study had a 4 week randomisation period followed by a 144 week treatment period. Patients received DAC HYP 150 mg SC once every 4 weeks or IFN β -1a 30 μ g intramuscularly (IM) once weekly. Both groups received matching placebos and blinded treatment continued for 96 to 144 weeks.

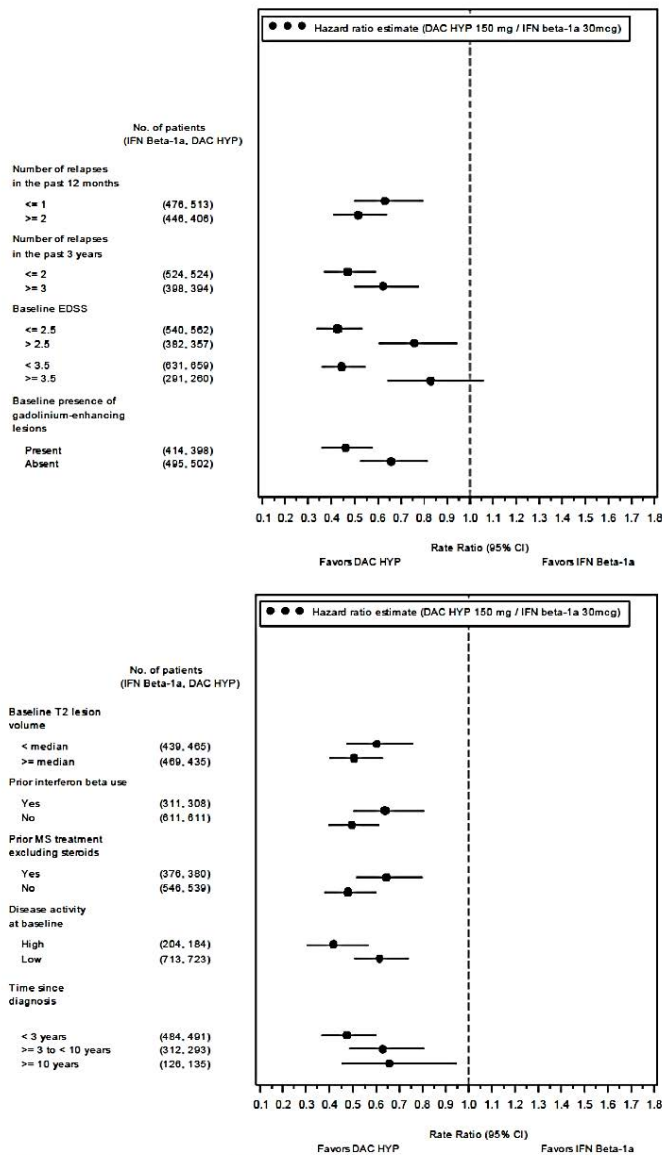
The major inclusion criteria were: either a diagnosis of RRMS; 2 or more clinical relapses within the previous 3 years with at least 1 clinical relapse in the 12 months prior to randomisation; or 1 or more clinical relapses and 1 or more new MRI lesions (Gd-enhancing and/or T2 hyper-intense lesion) within the previous 2 years, with at least one of these events in the 12 months prior to randomisation; and an EDSS score between 0.0 and 5.0, inclusive.

As in Study 205MS201 the primary efficacy endpoint was the ARR. Disability progression was a second secondary efficacy endpoint, following the MRI endpoint of newly or newly enlarging T2-hyperintense lesions at Week 96. Confirmed disability progression was defined by at least a 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 that was sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks. The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS (EDSS ≤ 2.5 versus EDSS > 2.5), history of prior IFN β use, and baseline age (age ≤ 35 versus age > 35 years). The proportion of patients who were relapse free and the proportion of patients with a ≥ 7.5 -point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks were lower ranked secondary endpoints.

In order to control for inflation of the type I error due to multiple secondary endpoints, a sequential closed testing procedure was employed with the secondary endpoints ranked in the order of importance. If the first secondary is statistically significant then the second comparison was tested at the 0.05 significance level.

There were multiple subgroup analysis performed based on various measures of severity of disease including: baseline EDSS (≤ 2.5 vs. > 2.5); baseline presence of Gd-enhancing lesions (present or absent); number of relapses in the past 12 months (≤ 1 versus ≥ 2); number of relapses in the past 3 years (≤ 2 versus ≥ 3); prior immunomodulatory MS treatment excluding steroids (yes versus no); disease activity (high was ≥ 2 relapses in the year prior to randomisation and ≥ 1 Gd lesion at baseline MRI. Results are shown in Figure 2 below.

Figure 2. Subgroup analyses by baseline disease characteristics for ARR, Study 205MS301



NOTE: Rate ratios and 95% CI based on negative binomial regression model adjusted for the following covariates (excluding covariates defining the subgroup): baseline relapse rate, history of prior IFN beta use, baseline EDSS (≤ 2.5 vs > 2.5) and baseline age (≤ 35 vs > 35).

A total of 1841 subjects were randomised and received at least 1 dose of study treatment, 922 subjects received IFN β -1a and 919 received DAC HYP, with about 70% of patients completing their assigned study treatments. Mean (SD) age was 36.2 years (9.32) in the IFN β -1a treatment group and 36.4 years (9.36) in the DAC HYP treatment group About two-thirds of patients were female. Baseline EDSS scores (mean, median) were similar in the IFN β -1a (2.54, 2.25) and DAC HYP (2.48, 2.00) treatment groups with 70% of baseline scores < 3.5 and 30% ≥ 3.5 . Patients had a mean (median) of 1.6 (1.0) relapses in the 12 months prior to the study and 2.7 (2.0) relapses in the 3 years prior to the study.

There was a 45% reduction in ARR in the DAC HYP group compared to the IFN β -1a group. The adjusted ARRs were 0.393 (95% CI: 0.353 to 0.438) in the IFN β -1a treatment group and 0.216 (95% CI: 0.191 to 0.244) in the DAC HYP treatment group. The ARR ratio was 0.550 ($p < 0.0001$).

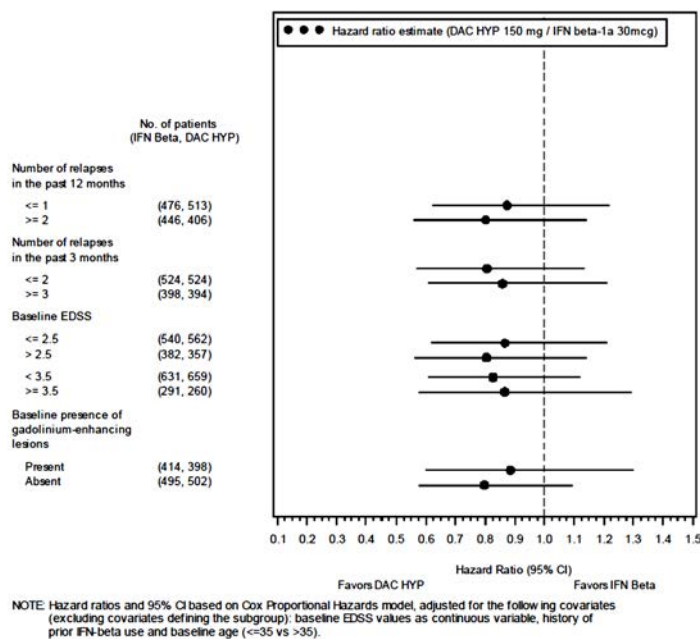
The adjusted mean number of new or newly enlarging T2 hyper-intense lesions at Week 96 was 9.44 (95% CI: 8.46 to 10.54) in the IFN β -1a treatment group and 4.31 (95% CI: 3.85 to 4.81) in the DAC HYP treatment group. Relative to IFN β -1a, DAC HYP reduced the number of new or newly enlarging T2 lesions by 54.4% (95% CI: 46.9% to 60.8%; $p < 0.0001$) at Week 96.

The endpoint for confirmed disability progression was not met. The hazard ratio for DAC HYP/IFN β -1a was 0.84 (95% CI: 0.66 to 1.07). It was estimated that at Week 144 20.3% of subjects given DAC HYP and 16.2% given INF β -1a had confirmed 12-week disability progression, an absolute reduction of 4.1% and a relative risk reduction of 16% ($p = 0.1575$) compared with IFN β -1a.

Although not able to be considered from a statistical viewpoint, at 96 weeks, 213 subjects (23%) in the IFN β -1a group had a ≥ 7.5 -point worsening from baseline MSIS-29 Physical Impact scores compared with 171 subjects (19%) in the DAC HYP treatment group. 7.5 points on this scale is considered to be clinically meaningful. Figure 2 (above) shows a forest plot of results for ARR stratified by disease severity subgroups and Figure 3 (below) from the study report shows a similar plot of confirmed 3-month disability progression. There is no clear pattern in either of these to suggest that patients with more severe disease at baseline are likely to receive more benefit than those with less severe disease.

A number of post hoc and sensitivity analyses were performed, including an analysis purporting to show a group in which disability progression was reduced. The supplementary evaluation report (Attachment 3) includes commentary on these analyses. The conclusions of the sponsor regarding disability progression are not accepted.

Figure 3. 3-month sustained disability progression measured by increase in EDSS by baseline disease characteristics



Safety

The dataset submitted contained safety data on 1785 patients with MS given DAC HYP, 204 given placebo and 922 given INF- β -1a. A further 127 healthy subjects had received

DAC HYP in Phase I studies. In the overall safety population mean (SD) exposure to DAC HYP (any dose) was 31.9 months (range: 0 to 71 months).

A total of 778 patients were treated with DAC HYP (any dose) for > 30 months in all studies.

Safety data from the pivotal studies were not pooled due to the use of different comparators (placebo or INF β -1a) and the different duration of exposure in the two pivotal studies. In the dose-finding pivotal study (Study 205MS201) DAC HYP was associated with a dose-related increase in the incidence of the following: pyrexia (< 1% placebo versus 3% DAC HYP 150 mg and 7% DAC HYP 300 mg), Infections and infestations SOC (44% placebo versus 50% DAC HYP 150 mg and 54% DAC HYP 300 mg) and the Skin and subcutaneous tissue disorders SOC (13% placebo versus 18% DAC HYP 150 mg and 22% DAC HYP 300 mg).

In Study 205MS301, the comparative study with INF β -1, there was a higher incidence of events for DAC HYP in the Infections and Infestations System Organ Class (SOC) (57% IFN β -1a versus 65% DAC HYP) and the Skin and Subcutaneous Tissue Disorders SOC (19% versus 37%). The incidence of events was higher in the IFN β -1a group for the Nervous System disorders SOC (63% IFN β -1a versus 54% DAC HYP) and the General Disorders and Administration Site Conditions SOC (59% IFN β -1a versus 39% DAC HYP). The most common AEs that occurred at an incidence \geq 2% higher in the DAC HYP group than in the IFN β -1a group were nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain, rash, and lymphadenopathy. The most common AEs that occurred at an incidence \geq 2% higher in the IFN β -1a group than in the DAC HYP group were MS relapse, influenza-like illness, pyrexia, chills, and hypertension.

Ten deaths had been reported, 5 in patients given INF β -1a and 5 given DAC HYP. The deaths in patients given INF were: acute myocardial infarction, peritonitis, suicide, pancreatic cancer and progressive relapsing MS. Investigators considered none of the above events related to treatment. In the DAC HYP group the deaths were attributed to ischaemic colitis and psoas abscess (related), autoimmune hepatitis (unrelated), MS with aspiration pneumonia, decubitus ulcer, sepsis, cardiorespiratory arrest (not related), acute respiratory distress with septic shock (unrelated), subdural haematoma/intracranial haemorrhage after a fall (unrelated). The patient who died with a psoas abscess initially presented with a maculopapular rash which was desquamating. Skin biopsy was consistent with a drug reaction. She then developed Staphylococcus aureus sepsis and the psoas abscess and died 94 days after discontinuing study medication. The basis for investigators determining relatedness of these deaths is not clear.

SAEs occurring in 5 or more subjects were MS relapse, pneumonia, urinary tract infection, lymphadenopathy, bronchitis, colitis ulcerative, hepatic enzyme increased, MS, and ovarian cyst. These are shown below in Table 12.

Table 12. Serious AEs occurring in 3 or more patients

	DAC HYP 150 mg	DAC HYP 300 mg	Total DAC HYP
Number of subjects in the pooled safety population	1492 (100)	293 (100)	1785 (100)
Number of subjects with a serious event	345 (23)	102 (35)	447 (25)
MULTIPLE SCLEROSIS RELAPSE	155 (10)	54 (18)	209 (12)
PNEUMONIA	10 (<1)	2 (<1)	12 (<1)
URINARY TRACT INFECTION	11 (<1)	1 (<1)	12 (<1)
LYMPHADENOPATHY	5 (<1)	3 (1)	8 (<1)
BRONCHITIS	1 (<1)	4 (1)	5 (<1)
COLITIS ULCERATIVE	4 (<1)	1 (<1)	5 (<1)
HEPATIC ENZYME INCREASED	3 (<1)	2 (<1)	5 (<1)
MULTIPLE SCLEROSIS	4 (<1)	1 (<1)	5 (<1)
OVARIAN CYST	3 (<1)	2 (<1)	5 (<1)
APPENDICITIS	4 (<1)	0	4 (<1)
CONVULSION	4 (<1)	0	4 (<1)
FALL	4 (<1)	0	4 (<1)
HEPATITIS TOXIC	4 (<1)	0	4 (<1)
LYMPHADENITIS	4 (<1)	0	4 (<1)
NEPHROLITHIASIS	3 (<1)	1 (<1)	4 (<1)
ABORTION SPONTANEOUS	3 (<1)	0	3 (<1)
ADENOMYOSIS	2 (<1)	1 (<1)	3 (<1)
AUTOIMMUNE HEPATITIS	1 (<1)	2 (<1)	3 (<1)
CELLULITIS	3 (<1)	0	3 (<1)
DEPRESSION	3 (<1)	0	3 (<1)
DERMATITIS	3 (<1)	0	3 (<1)
DRUG HYPERSENSITIVITY	2 (<1)	1 (<1)	3 (<1)
ENDOMETRIOSIS	3 (<1)	0	3 (<1)
PULMONARY EMBOLISM	2 (<1)	1 (<1)	3 (<1)
URTICARIA	2 (<1)	1 (<1)	3 (<1)
UTERINE LEIOMYOMA	3 (<1)	0	3 (<1)
VIRAL INFECTION	3 (<1)	0	3 (<1)

NOTE 1: Numbers in parentheses are percentages.

2: A subject was counted only once within each preferred term.

3: Preferred terms are presented by decreasing incidence in the total column.

Of particular note are the 3 cases of autoimmune hepatitis and the 4 reports of 'toxic hepatitis'. Serious GI events in ≥ 2 subjects given DAC HYP included colitis ulcerative (5 subjects), and Crohn's disease (2 subjects), diarrhoea, gastritis, and inguinal hernia (2 subjects each). The sponsor's Safety Summary also stated that the inflammatory bowel disease cases tended to have a late onset, occurring after approximately 1 to 3.5 years of exposure to DAC HYP.

Four cases of tuberculosis were reported in subjects given DAC HYP and none in the placebo of INF β -1a groups. The sponsor noted that affected patients lived in areas with endemic tuberculosis and that one case was not confirmed. Within the Skin and Subcutaneous Tissue Disorders the most frequently reported AEs were rash, dermatitis and eczema. 2% of subjects given DAC HYP had severe skin AEs, including one case reported as (SJS) and 2 cases reported as drug reaction with eosinophilia and systemic symptoms (DRESS).

These cases did not meet the standard criteria for SJS or DRESS and on review by a dermatologist were considered most likely to be delayed-type hypersensitivity rashes. 4% of subjects given DAC HYP discontinued due to skin and subcutaneous tissue AEs.

There was an increased incidence of hepatic events and transaminase elevations in subjects treated with DAC HYP. Discontinuation of treatment due to hepatic events was 4% in the IFN β -1a group versus 5% in the DAC HYP 150 mg group in the active controlled study. There was an imbalance of cases with ALT or AST ≥ 3 x upper limit of normal (ULN) and concurrent total bilirubin ≥ 2 x ULN in the DAC HYP group compared with the IFN β 1a group. In the clinical development program, 19 subjects had an elevation of ALT or AST ≥ 3 x ULN and concurrent elevation of total bilirubin ≥ 2 x ULN: 1 subject received placebo, 1 subject received IFN β -1a and 17 subjects received DAC HYP.

As noted in the FDA guidance document '*Guidance for Industry Drug-induced Liver Injury (DILI): Premarketing Clinical Evaluation (2009)*' finding one Hy's Law case in the clinical

trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe drug induced liver injury (DILI) when given to a larger population. In the Safety Summary for the submission, the sponsor stated that overall, 2 cases in the DAC HYP group were considered Hy's Law cases based on a causality assessment of 'probable' with 1 subject in the DAC HYP 300 mg/washout/300 mg group with autoimmune hepatitis who died, and 1 subject with acute hepatic failure who had also received treatment with valproic acid, carbamazepine, and who was taking Herbalife products. In the IFN β -1a group, there was 1 Hy's Law case with a causality assessment of 'highly likely' in a subject with autoimmune hepatitis. For the remaining 15 subjects in the DAC HYP group, other factors such as treatment with hepatotoxic agents, viral hepatitis, biliary disease, and infections, were considered more likely to have contributed to the event than DAC HYP. Except for the case of fatal autoimmune hepatitis, all other subjects with ALT > 3 x ULN and total bilirubin > 2 x ULN had resolution of their event.

Serious cases of colitis, some of which were reported as ulcerative colitis (5 cases) or Crohn's disease (2 cases), were often characterised by prolonged diarrhoea and other symptoms, such as fever and abdominal pain. These cases were evaluated by an independent gastroenterologist specialising in inflammatory bowel disease. In the expert report, the cases are described as ranging from mild to severe and from microscopic to frank colitis. The gastroenterologist considered that none of these cases were consistent with Crohn's disease or ulcerative colitis. There was no evidence of fistula or abscess formation or sequelae of chronic perforation. None of the events progressed to perforation or required surgery, including those in subjects that remained on DAC HYP. Based on information to date, these events appeared to be self-limited and were controlled with oral anti-inflammatory agents and corticosteroids, and none of the subjects required treatment with biologics.

Potentially significant abnormalities in white cell count were seen in about 4% of subjects. For all DAC HYP-treated subjects, the majority of abnormalities in white blood cell (WBC), lymphocyte, and neutrophil counts were Grade 1 or Grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria. For WBC counts, 3 out of 1706 subjects (< 1%) group had Grade 3 abnormalities and 0 subjects had Grade 4 abnormalities. For lymphocyte counts, 15 subjects (< 1%) had Grade 3 abnormalities and 0 subjects had Grade 4 abnormalities. For neutrophil counts, 11 subjects (< 1%) had Grade 3 abnormalities. One subject in Study 205MS301 had a Grade 4 neutropenia this subject developed Reiter's syndrome with agranulocytosis and lymphopenia and thrombocytopenia. These were attributed to concomitant medications that included: omeprazole, sulfasalazine and triamcinolone. The investigator did not consider these to be related to study medication.

The incidence of decreased CD4+ and CD8+ counts in the total DAC HYP group were similar at baseline. In the total DAC HYP experience, the incidence of decreased post-baseline CD4+ (< 400 cells/ μ L, < 200 cells/ μ L) was 29% and 3%, respectively, and the incidence of decreased CD8+ counts (< 200 cells/mm³, < 100 cells/mm³) was 34% and 4%, respectively.

RMP evaluation

The RMP evaluator has noted that the safety concerns of colitis, severe skin reactions, and infections have been amended in the safety specification however the safety concern of autoimmune hepatitis has not been included. In ongoing negotiations the RMP evaluator has requested that this as an important potential risk be added to the ASA of the RMP.

To mitigate the risks from use of DAC HYP the RMP evaluator has recommended the following post-market activities:

- A patient alert card.
- A risk management guide for prescribers to mitigate the risk of hepatic injury.
- The inclusion of advice on the risk of opportunistic infections, in particular PML, in educational materials.

The RMP evaluator requested the sponsor provide the TGA with the following:

- a distribution plan to the TGA for the additional educational materials including the patient alert card
- the quantity of educational materials to be distributed
- identify the healthcare professionals to be targeted for education, and
- the time frame for provision of these activities.

The RMP evaluator had requested that Australia be included in Study 205MS401 which is intended to measure the outcome indicators for the effectiveness of the additional risk minimisation activities. Rather than include Australia in the above study, the sponsor proposes to conduct a physician survey in Australia. The RMP evaluator accepted the survey proposal and recommended it be conducted within two years of the supply of Zinbryta in Australia, regardless of PBS listing. The sponsor should provide a draft of the physician survey and a study plan to the TGA for review. The study plan should include the objectives of the survey and quantitative targets for relevant indicators to be measured, the number of the survey participants to be included, practice specialties of the participants, the target participation rate, relevant time frames, the methods of survey distribution, evaluation of the survey results, and plans for alternative measures if the targets are not achieved. Negotiation of this proposal is ongoing.

Suggested wording for the RMP condition of registration will be provided once the ASA is revised as required and agreed by the TGA.

Risk-benefit analysis

Delegate's considerations

A revised guideline for the development of medicinal products for the treatment of MS was adopted by the TGA in October 2015. Important new information relevant to this submission in that revised guideline includes:

- Acknowledgement that disease modifying treatments act mainly by suppressing or modulating the immune responses involved in MS pathogenesis. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options that is, treatment is restricted to patients with rapidly evolving multiple sclerosis or those who had a suboptimal response to prior therapies.
- A recommendation for large-scale long-term parallel group trials to support claims for reducing disability progression with study duration dependant on the population studied, and should be sufficient to show a reliable and relevant effect on disability. Such a study may need to last approximately 3 years.
- The expected benefit of treatment in consideration of disease activity and life expectancy of patients with multiple sclerosis, should be weighed against the

anticipated risk for opportunistic infections, malignancies and other potential serious safety issues.

- If a development aims at RMS as the intended indication, it should provide for separate conclusions at the time of the risk-benefit assessment on the efficacy and safety in patients both with low and highly active multiple sclerosis. The recommended approach will be that data on efficacy and safety are generated for both populations. In any case it has to be made possible to conclude that any efficacy as observed in the patients with low disease activity also translates into efficacy in the population with more active disease.
- Add-on study designs may be considered as an alternative as long as there are no synergistic drug effects leading to increased safety concerns, for example: a synergistic immunosuppressive effect.
- Time to relapse is acceptable as a primary endpoint provided that data are generated to show maintenance of effect. Time to second or third relapse may be useful for this.
- The effect of withdrawal of the test drug should be systematically monitored. At the time for application for a marketing authorisation, it is expected that comprehensive data on clinical and/or Magnetic resonance imaging (MRI) activity after discontinuation are available.
- For biological products whether antibodies develop against the administered products or related molecules has to be evaluated as well as the impact of this on the long term efficacy and safety.
- In trials intended to evaluate the relapse rate, it is recommended not to include SPMS subjects with superimposed relapses as this might complicate trial design and hamper the interpretation of the effect on relapses and disability. It is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS. However, extrapolation of the effect on disability will not be considered appropriate as pathophysiology is different.

The development program for DAC HYP was largely completed prior to finalisation of the above guideline and does not adhere to its recommendations in a number of areas. Firstly, DAC HYP is a new biological treatment. The original molecule, DAC was approved in the prophylaxis of acute organ rejection. The pivotal efficacy and safety studies were conducted in an MS population that did not yet have moderate to severe disability with EDSS scores up to 6, though the EDSS score cut-off was 5. Mean EDSS scores in the 2 pivotal studies were between 2 and 3. In the largest study (205MS301) 70% of patients had EDSS scores below 3.5 equating to fully ambulatory but with moderate disability in 1 Functional System (FS) and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS. For this group there are a number of approved disease modifying agents with known safety profiles that have been demonstrated to reduce disability.

DAC HYP has demonstrated a reduction in absolute risk reduction (ARR) of around 54% compared with placebo (Study 205MS301) and 45% compared to IFN β -1a group. A statistically significant reduction in confirmed sustained 3-month disability progression has not been demonstrated.

Additionally a trend towards reduction in 12 week sustained disability progression suggested the difference from INF- β -1a for this endpoint was quite small, in the region of 4% absolute difference over 3 years and did not reach statistical significance. Various sensitivity analyses suggested the trend is real and there is a small difference between the two treatments over 3 years even though the primary analysis did not show statistical significance. In the supplementary CER there is a discussion on cross study comparisons of various MS treatments for reduction in relapse rates. These comparisons are limited by

the variability in relapse rates across studies however the comparisons did show relapse rates in the placebo arms of these studies and the relapse rates for Zinbryta were similar to those of fingolimod and dimethyl fumarate and higher than glatiramer and beta interferon.

No additional benefit from use of the 300 mg dose compared to the 150 mg dose of Zinbryta was seen.

Unfortunately the major pivotal study was not designed primarily to identify the extent of difference between INF β -1a and DAC HYP for 12 week disability progression. This was the second ranked, secondary endpoint in the major pivotal study whereas ideally it would have been the primary or co-primary endpoint. However as both the primary endpoint and the first secondary endpoint were statistically significant 12 week disability progression was able to be considered. The absolute difference in 12 week disability progression was quite small, estimated to be 4.1% over 144 weeks with the relative difference at week 144 being 25%. Subgroup analyses did not suggest a greater effect in individuals with more or less active disease or more or less baseline disability (see Figures 2 and 3 above).

As noted by the clinical evaluators, only 358 patients have received DAC HYP for more than 24 months. The extent of exposure is sufficient to pick up adverse events that occur at a frequency of about 1/1000 this is not sufficient to pick up cases of PML that have been associated with the use of other highly active immunomodulators in MS including natalizumab, alemtuzumab and dimethyl fumarate. Nor is it sufficient when those events are more frequent with increasing duration of use of the product, as appears to be the case for other medicines associated with PML. This is a particularly important issue given that DAC as Zenepax has been associated with PML, though the post renal transplant patients in whom it was indicated are likely to have been exposed to other immunosuppressants concomitantly.

Adverse events of major concern are the signal for hepatic and skin hypersensitivity reactions, colitis and serious infections, which have also been associated with deaths during the clinical development program. While there was no clear indication of overall reduction in lymphocytes or neutrophils there was a significant reduction in CD4+ and CD8+ cells and that may have contributed to the increased infection rate.

Liver injury appears to be of particular concern. There were 2 Hy's law cases, however in total there were 17 cases of elevated total bilirubin and transaminases in patients given DAC HYP which would have met the criteria for Hy's law though there were other possible explanations for the elevations. This compares with only one similar case in patients given INF β -1a.

Hypersensitivity reactions affecting the skin and gut also appear to be major concerns. While independent expert reviewers amended the initial very serious diagnoses (SJS, DRESS, ulcerative colitis, Crohn's disease) in these SOCs it is clear that serious hypersensitivity reactions are associated with DAC HYP.

There was an imbalance in deaths and the basis for attribution of deaths as possibly related/ unrelated appears not to be consistent with the known effects of either daclizumab or INF β -1a, for example deaths due to infection considered unrelated.

There was an imbalance in the number of cases of tuberculosis reported with 4 in patients given DAC HYP versus none in patients given INF β -1a.

There were very substantial reductions in CD4+ and CD8+ cells in patients given DAC HYP.

Only 358 patients have received DAC HYP for more than 24 months. This is not sufficient to identify the risk of PML which has been associated with other highly active immunomodulators in MS including natalizumab, alemtuzumab and dimethyl fumarate. Nor is it sufficient when those events are more frequent with increasing duration of use of

the product, as appears to be the case for other medicines associated with PML. This is a particularly important issue given that DAC (Zenapax) has been associated with PML, though the post renal transplant patients in whom it was identified are likely to have been exposed to other immunosuppressants concomitantly. It is possible the very low CD4+ cell counts may predispose patients to PML as occurs in HIV infection.

The supplementary clinical evaluator considered that the difference in benefit from DAC HYP against more effective interferon regimens is likely to be minor. The supplementary clinical evaluator also noted that DAC HYP reduces relapse rate by at least 50% and that a large proportion of disability progression is known to come from incomplete recovery from relapses, suggesting that DAC HYP could have a useful role in subjects with a high risk of relapses. The supplementary clinical evaluator also considered that the risks and benefits should be made clear to patients and clinicians and that they are in the best position to decide what risk they are prepared to accept to achieve a 50% reduction in relapse rate, and whether DAC HYP is an appropriate choice compared to other available agents. None of the new agents is without some significant safety concerns, and some patients show poor tolerability of other new agents, such as dimethylfumarate, so it is expected that DAC HYP will find a use in some patients.

At this stage the Delegate is proposing to approve Zinbryta provided that the indication restricts use to third line treatment and that treatment is commenced only on the advice of a neurologist. A comprehensive risk management plan is also required given the risks, including the potential risk of PML associated with this product. Amendments to the PI were recommended by both clinical evaluators. The PI will be further considered after the advice of the TGA's Advisory Committee has been considered.

The Delegate notes that in the USA patients are provided with a 'Zinbryta Patient Wallet Card' and are advised they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation. Patients are also advised to show the Zinbryta Patient Wallet Card to other treating health care providers. At this stage there appears to be no agreement on a similar alert card for Australian patients of Zinbryta. The Delegate considers such a card is necessary if this product is to be registered.

Proposed action

At the time of pre-ACPM assessment, the Delegate had no reason to say that the application for Zinbryta should not be approved for registration; subject to successful negotiation of the indications and access restrictions which should apply to prescribers and patients.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The supplementary clinical evaluator considered that extrapolation to SPMS should not occur given the pivotal study population had RRMS. Given the new guideline recommendations regarding extrapolation of results for relapse prevention but not disability progression, the Delegate proposes to allow for use of Zinbryta in all forms of relapsing MS.
2. A specific claim for reduction in disability progression is not proposed for any subgroup of patients with MS. Does the committee have concerns with this approach?
3. Restricting the indication to third line treatment and limiting initial prescribing to neurologists have been considered as strategies to mitigate the risk of serious adverse effects while allowing access to what appears to be an effective medication for relapsing forms of MS. Does the committee consider that further restrictions on

access should apply to daclizumab? If so what additional restrictions are recommended?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Biological and non-clinical evaluations

The sponsor acknowledges the Delegate's summary of the quality and non-clinical evaluations and has no further comments. In relation to the non-clinical evaluator's comments, the proposed PI does include the CNS findings of microglial aggregates, and micro-haemorrhage in a small subset of aggregates.

Has a delay in progression of disability been demonstrated?

The evaluation of daclizumab in Australia consisted of an initial CER and a SCER allowing TGA evaluation of post hoc analyses of efficacy and safety reviewed by the CHMP. This information was offered to address initial concerns raised by the Delegate concerning safety risks versus efficacy. The sponsor appreciates the opportunity to have these data assessed and believes that there is robust evidence that daclizumab 150mg/mL provides a clinically meaningful treatment option for prescribers and patients with relapsing forms of MS in Australia. The sponsor acknowledges the first round clinical evaluator's conclusions on efficacy benefits. Whilst some concerns were raised by the evaluator regarding the robustness of statistical analyses of the endpoints concerning delay in progression of disability, evidence to support an effect on disability progression was acknowledged by the supplementary clinical evaluator. The supplementary evaluator also acknowledged that the placebo controlled results for daclizumab compare favourably with other active treatments in placebo-controlled studies and that no approved agent has demonstrated a consistent benefit over an active comparator agent, leading to a final conclusion that 'the evidence that [daclizumab] reduced progression is inconclusive, from a statistical perspective, but the absolute magnitude of the observed trends is favourable when compared to other new agents'.

The sponsor believes that a clinically relevant benefit of delay to progression of disability has been established. In the placebo-controlled trial, there was a 57% reduction in the risk of 12 week confirmed disability progression ($p = 0.021$) and a 76% reduction in 24 week confirmed disability progression ($p = 0.0037$) in patients treated with daclizumab 150mg compared to placebo. While disability progression was a tertiary endpoint in this trial and therefore these p-values are not adjusted for multiple hypothesis testing, the magnitude and consistency of the treatment effect was compelling. Furthermore, despite failing to reach statistical significance at 12 weeks in the primary analysis (against IFN β -1a), the pre-specified analyses of disability progression confirmed at 24 weeks indicated a clear benefit of daclizumab over IFN β -1a (27% reduction in risk; $p = 0.03$). The sponsor believes these data provide a compelling argument in support of a clinically relevant effect on disability progression being established in favour of daclizumab treatment over placebo or IFN β -1a.

In line with guideline CPMP/EWP/908/99: Points to consider on multiplicity issues in clinical trials: '*additional claims on statistically significant and clinically relevant findings based on secondary variables or on subgroups are possible only after the primary objective of the clinical trial has been achieved, and if the respective questions were pre-specified, and were part of an appropriately planned statistical analysis strategy*'. The sponsor reiterates that the analyses of the confirmed progression of disability endpoints were pre-specified and were part of the appropriately planned statistical analysis strategy for Study 205MS201 (12 week only) and Study 205MS301 (both 12 week and 24 week). The results of the primary trial objective were met and the results of both studies showed nominally

statistically significant benefit in 24 week disease progression versus placebo or IFN β -1a, respectively.

This was further reinforced by the SCER comments:

‘Despite the fact that the supplementary evaluator and the sponsor have drawn different conclusions about the statistical robustness of the progression data, these efficacy results are considered satisfactory. The supplementary evaluator does not believe that a clear benefit on progression endpoints should be an absolute requirement for a new disease-modifying agent in MS. In subjects with RRMS, a large proportion of disability progression is due to damage sustained during relapses, and preventing relapses is a worthwhile achievement in its own right, provided that there is at least no adverse effect on progression. Although the data do not provide robust confirmation of a benefit for progression endpoints, there is a consistency across multiple different analyses that, in aggregate, strongly suggests that [daclizumab] has a favourable effect on progression, and at least [daclizumab] appears highly unlikely to have an adverse effect on progression. Coupled with strong evidence of a reduced relapse rate, this is sufficient to support the claim of efficacy in RRMS.’

It is also notable that these clinically relevant tertiary endpoints were included in the peer reviewed publication of Study 205MS301 in the New England Journal of Medicine:¹⁶

‘On the basis of the pre-specified hierarchical testing plan, the results of the analyses of the third and fourth pre-specified secondary endpoints were not considered to be significant.’

‘The Kaplan–Meier estimate of the percentage of patients with disability progression confirmed at 24 weeks was 9% versus 12% at week 96 and 13% versus 18% at week 144 in the daclizumab HYP versus IFN β -1a groups, which represent a 27% lower risk of disability progression confirmed at 24 weeks (a tertiary endpoint) for daclizumab HYP compared with IFN β -1a ($p = 0.03$)’

The following conclusion stated:

‘Overall, the pre-specified additional analyses of disability progression confirmed at 12 weeks and both the pre-specified primary and additional analyses of the (tertiary) endpoint of disability progression confirmed at 24 weeks indicated a benefit of daclizumab HYP over IFN β -1a except when it was assumed that disability progression did not occur in any patient who was censored after a tentative disability progression.’

The sponsor acknowledges that the proposed ITT population meets the definition of relapsing forms of MS as per the latest MS clinical guideline (EMA/CHMP/771815/2011 Rev. 2), the definition of relapsing forms of MS includes:

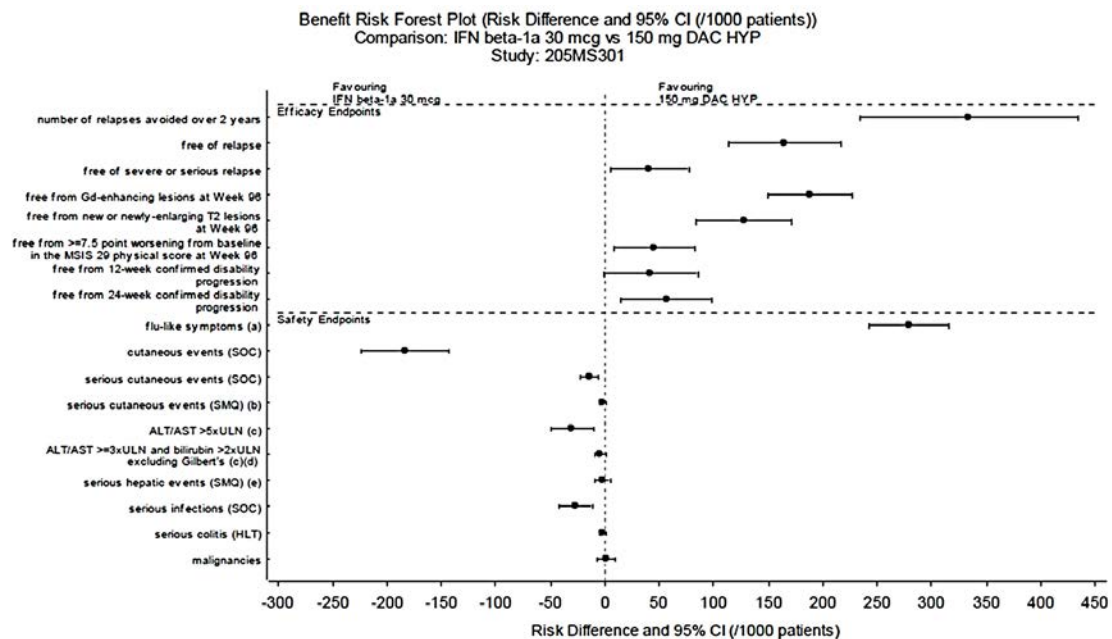
1. patients with RRMS (relapsing remitting MS);
2. patients with SPMS (secondary progressive MS) and superimposed relapses; and
3. patients with a clinically isolated demyelination event and evidence of dissemination of lesions in time and space on MRI.

Overall, the totality of the disability data from the development program and its consistency across studies and multiple sensitivity analyses supports that DAC HYP 150 mg reduces the risk of confirmed disability progression in patients with relapsing forms of MS. The sponsor believes restricting daclizumab use to patients who have failed initial treatment is inappropriate as the focus on a single endpoint of disease progression fails to encompass the clear advantages of daclizumab over IFN β -1a as summarised in the

¹⁶ Kappos, L et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. N. Engl. J. Med. 2015; 373:1418–1428.

SCER and as shown in the forest plot of both the benefits and risks of daclizumab versus IFN β -1a (see Figure 4 below).

Figure 4. Benefit/risk forest plot (risk difference and CI 95% (per 1000 patients) comparison: IFN β -1a 30 μ g versus DAC HYP 150 mg, Study 205MS301)



Can the risks of daclizumab be appropriately managed?

The sponsor acknowledges the assessment of risks summary in the SCER. Safety assessments by both the sponsor and TGA agree that the majority of treatment related AEs were mild to moderate and were manageable with standard treatment or as clinically appropriate, interruption or discontinuation of treatment.

The sponsor has developed a comprehensive RMP Safety Specification and has submitted the RMP in the required format, consisting of EU RMP v3.0 and ASA version 2.0. Within this RMP the important identified risks are transaminase elevations and serious hepatic injury, serious skin reactions, infections and serious infections, colitis, depression and serious lymphadenopathy. Acute hypersensitivity reactions, opportunistic infections (including PML), malignancies and sustained severe lymphopenia are important potential risks. These issues are described in the RMP and addressed in the proposed PI, as appropriate. The planned implementation of the RMP in Australia is closely aligned with that in the EU. The risk mitigation activities planned for implementation in Australia involve mandatory education of Health care professionals and patients on signs and symptoms of serious hepatic injury and the need for monthly liver function monitoring during treatment and for 4 months after. Educational components consist of a Hepatic Risk Management Guide for HCPs and a Patient Alert Card. This Patient Alert Card will fulfil the role of the 'Zinbryta Patient Wallet Card' described by the Delegate.

The sponsor has carefully evaluated the Delegate's considerations on the potential risk of PML given the reduction in CD4+ and CD8+ cells observed during the clinical program and that the risk of PML has emerged in the post-marketing setting of some other immunomodulatory agents in the context of sustained severe lymphopenia. Sustained severe lymphopenia was not observed during daclizumab clinical trials.

The majority of decreased lymphocyte counts during treatment were mild or moderate, and the majority of moderate decreases in lymphocyte counts were observed at a single time point only. Decreases in lymphocyte counts were not associated with an increased risk of infection or opportunistic infections compared to those without decreased

lymphocyte counts. There is currently no evidence to support an association between the duration or level of reduction of CD4+ and CD8+ cells observed with an increased risk of PML or other opportunistic infections, or that there was any association of these cell count reductions with an increased risk of serious infections. The RMP to be adopted in Australia includes sustained severe lymphopenia, and opportunistic infections (including PML), as important potential risks, and these will be monitored as part of the pharmacovigilance activities post-marketing.

The sponsor wishes to clarify the extent of subject exposure to daclizumab in the clinical development program. The daclizumab clinical program provides a robust safety database, including 2133 patients with relapsing MS. In the placebo-controlled, active comparator-controlled and other studies, 1785 patients with relapsing MS evaluable for safety have been treated for periods up to 6 years with an overall exposure of approximately 4100 person-years. Of these, 1215 patients have received more than 2 years and 573 patients more than 3 years of treatment clearly meeting the current TGA adopted 'Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95)' and which allowed for the detection of rare adverse events. Rare is defined as an incidence of ≥ 1 in 10,000 but <1 in 1000 person years.

Has a clear place in therapy been established?

In order to further assess the benefit risk balance of daclizumab in the context of Australian clinical practice, the sponsor approached three neurologists specializing in the treatment of MS in Australia for independent advice on place in therapy for daclizumab.

The individual reports are provided and can be summarised into the following key points:

- Treatment choice is done on an individual basis, dependent on patient clinical presentation and disease activity on MRI.
- There is a clear need for further novel treatments of MS in Australia (patients are continuing to relapse). This can be further summarised as follows:
 - Response to treatment varies on an individual level.
 - All current therapies have tolerability and safety concerns (sometimes serious).
 - The majority of patients will still have disease activity irrespective of treatment (clinically or radiologically).
 - A unique mode of action may provide benefit in MS patients as the disease is heterogeneous in aetiology.
- Difficulties comparing medications across studies noted but comparisons based on pivotal trial results and clinical practice are possible.
- Medication choices are classified into low potency (interferons and glatiramer acetate), low to medium potency (teriflunomide), medium potency (fingolimod, dimethyl fumarate) and high potency (natalizumab and alemtuzumab) disease-modifying therapies. Daclizumab can be classified as a medium to high potency disease-modifying therapy on this basis.
- Given the superiority daclizumab has demonstrated over IFN β -1a in DECIDE, in line with head to head trials for fingolimod (TRANSFORMS), dimethyl fumarate (CONFIRM) and alemtuzumab (MS CARE II), it is shown to have medium to high efficacy.
- While, daclizumab does not seem as potent as natalizumab or alemtuzumab in some efficacy analyses, it provides patients with an alternative when these products do not offer a favourable benefit-risk profile.

- A trend towards higher efficacy therapies also carries a higher safety burden.
- Neurologists are familiar with additional safety monitoring of disease modifying therapies, including medium to higher potency products.
- All modern DMTs used in MS have risks and benefits. With the advent of medium to higher potency products the discussion of benefit and risk involves active engagement and understanding of prescribers and patients of the benefits and risks on an individual basis. This has evolved over time to become a valuable asset in treatment decisions and management of adherence and compliance. Prescribing and management of patients on a given treatment is appropriately informed via the PI and RMP tools. Even with 10 treatment choices in Australia, a proportion of patients continue to relapse. Having new therapies with different modes of action offers alternative treatment choices to prescribers and patients.

Sponsor's conclusion

The sponsor considers that the efficacy of daclizumab in the treatment of relapsing forms of MS, in terms of both relapses and disability progression, has been adequately established in accordance with the relevant guideline. The sponsor acknowledges and agrees with the Delegate's to allow for use of daclizumab in all forms of relapsing MS. Further, the sponsor believes that the key risks of treatment with daclizumab are well understood and that appropriate tools will be in place to minimise and manage such risks by the proposed labelling, physician educational materials, and patient alert card. The sponsor believes that the benefit risk profile of daclizumab for the proposed indication:

'Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the risk of relapse'

is positive, a view that is supported by independent Australian expert clinical opinion.

The sponsor disagrees with the Delegate's proposal that the indication should be restricted to third line treatment of MS or that additional restrictions on access should be applied. The primary goal of treatment of MS is to prevent accumulation of disability that occurs as a result of relapses. All MS therapies in Australia, regardless of their potency, have broadly similar indications. All MS therapies have risks that require consideration in patient care. The sponsor contends that the identified risks with daclizumab are well understood and can be managed within clinical practice, and do not justify additional restrictions on access that exceed those applied to other approved MS therapies in Australia. As patients in Australia with MS continue to experience relapses despite the availability of multiple therapies, there continues to be an unmet need for effective therapies, especially those that utilise novel mechanisms of action. The sponsor acknowledges the Delegate's intent to further consider the PI after the Advisory Committee's advice has been considered and welcomes the opportunity to finalise the PI at that time.

Advisory committee considerations

The Advisory Committee on Prescription medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Zinbryta solution for injection Prefilled Pen and solution for injection Pre-filled Syringe containing 150 mg/mL of daclizumab to have an overall positive benefit-risk profile. The ACPM agreed that the indication should be as proposed by the sponsor:

Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse.

In making this recommendation the ACPM:

- was of the view that initial prescription of daclizumab should be restricted to neurologists.
- recommended the following RMP post-market activities: a patient alert card Zinbryta Patient Wallet Card and a risk management guide for prescribers to mitigate the risk of hepatic injury.
- advised the inclusion of a boxed warning regarding the risk of hepatic disease/impairment.
- noted to include advice on the risk of opportunistic infections, in particular PML, in the Precautions section of PI.
- advised to provide patients with a 'Zinbryta Patient Wallet Card' to be carried at all times and to be shown to other treating health care providers. This patient card should describe symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the *Precautions* section of the PI and relevant sections of the CMI to ensure the restriction of the initial prescription to neurologists.
- a statement in the *Precautions* section of the PI and relevant sections of the CMI to advise on the risk of opportunistic infections, in particular PML, and screening for JC virus.
- A boxed warning stating the risk of hepatic disease or impairment, including autoimmune hepatitis.

Specific advice

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

1. *The supplementary clinical evaluator considered that extrapolation to SPMS should not occur given the pivotal study population had RRMS. Given the new guideline recommendations regarding extrapolation of results for relapse prevention, but not disability progression, the Delegate proposes to allow for use of Zinbryta in all forms of relapsing MS.*

The ACPM agrees with the Delegate and the secondary [supplementary] clinical evaluator to include all relapsing forms of MS as part in the proposed indication and that provided evidence does not support the exclusion of patients with SPMS.

2. *A specific claim for reduction in disability progression is not proposed for any subgroup of patients with MS. Does the committee have concerns with this approach?*

The ACPM did not express any concerns with the sponsor's approach and noted that the first pivotal study showed a statistically significant reduction in improvement of disability progression compared to placebo over 12 months.

3. *Restricting the indication to third line treatment and limiting initial prescribing to neurologists have been considered as strategies to mitigate the risk of serious adverse effects while allowing access to what appears to be an effective medication for relapsing forms of MS. Does the committee consider that further restrictions on access should apply to daclizumab? If so what additional restrictions are recommended?*

The ACPM agrees with limiting initial prescription to a neurologist to enhance appropriate prescription without disadvantaging patients, which is consistent with other agents with similar indications and risk benefit profile. No further restrictions on prescribing are required other than those agreed to in the RMP.

- *The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zinbryta daclizumab 150 mg/mL solution for injection pre-filled syringe and Zinbryta daclizumab 150 mg/mL solution for injection pre-filled pen indicated for:

'Zinbryta is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to delay the progression of physical disability and to reduce the frequency of relapse.'

Specific conditions of registration applying to these goods

- The Zinbryta (daclizumab) EU-RMP version 4.1 dated June 2016 with Australian Specific Annex version 2.0 dated February 2016 and any future updates as agreed with the TGA will be implemented in Australia.
- Batch release testing and compliance with Certified Product Details (CPD):
 - It is a condition of registration that all batches of Zinbryta (daclizumab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
 - It is a condition of registration that each batch of Zinbryta (daclizumab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
 - The sponsor must supply: Certificates of Analysis of all active ingredient (drug substance) and final product.
 - Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
 - Evidence of the maintenance of registered storage conditions during transport to Australia.
 - Five (5) syringes/pens of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI for Zinbryta 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>.

Attachment 2. Extract from the Clinical Evaluation Report

Attachment 3. Extract from the Supplementary Clinical Evaluation Report

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